19 September 2024
EMA/465276/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dupixent

International non-proprietary name: Dupilumab

Procedure No. EMEA/H/C/004390/II/0081

Note

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

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List of abbreviations

AD	Atopic dermatitis
ADA	Anti-drug antibody
ADR	Adverse drug reactions
AE	Adverse event
AESI	Adverse events of special interest
AUC	Area under the concentration-time curve
CI	Confidence intervals
Cmax	Maximum concentration
Ctrough	Trough concentration at the end of the selected dosing interval
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CSR	Clinical study report
DSQ	Dysphagia Symptom Questionnaire
EGD	Esophagogastroduodenoscopy
ELISA	Enzyme linked immunosorbent assay
EoE	Eosinophilic esophagitis
EoE-HSS	Eosinophilic Esophagitis Histology Scoring System
EU	European Union
FAS	Full analysis set
HLT	High-level term
Ig	Immunoglobulin
IL	Interleukin
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
PBRER	Periodic benefit-risk evaluation report
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PEESS	Peadiatric Eosinophilic Esophagitis Symptom Score
PEIS-C	Pediatric EoE Impact Scale-Caregiver version
PEIS-P	Pediatric EoE Impact Scale-Patient version
PESQ-C	Paediatric EoE Sign/Symptom Questionnaire-Caregiver version
PESQ-P	Paediatric EoE Sign/Symptom Questionnaire-Patient version
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PPI	Proton pump inhibitor
PT	Preferred term
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QoL	Quality of life
QW	Once weekly
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SMQ	Standardized MedDRA query
SOC	System organ class
STC	Swallowed topical corticosteroid
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
Th2	T helper 2
URTI	Upper respiratory tract infection
WBC	White blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Winthrop Industrie submitted to the European Medicines Agency on 28 November 2023 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 children aged 1 year and older to the already approved eosinophilic esophagitis (EoE) indication in adults and children above 12 years of age for Dupixent based on final results from study R668-EE-1877 (Part A, Part B, and Part A Addendum) - A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Dupilumab in Paediatric Patients with Active Eosinophilic Esophagitis. 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.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0541/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0541/2022 was completed.

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 did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	28 November 2023
Start of procedure:	23 December 2023
CHMP Rapporteur Assessment Report	19 February 2024
CHMP members comments	11 March 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 March 2024
Request for supplementary information (RSI)	21 March 2024
CHMP Rapporteur Assessment Report	02 July 2024
CHMP members comments	15 July 2024
Updated CHMP Rapporteur Assessment Report	18 July 2024
Request for supplementary information (RSI)	25 July 2024
CHMP Rapporteur Assessment Report	4 September 2024
CHMP members comments	9 September 2024
Updated CHMP Rapporteur Assessment Report	13 September 2024
Opinion	19 September 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Eosinophilic esophagitis (EoE) is a serious, rare, chronic, type 2 inflammatory, allergic/immune-mediated disease of the esophagus. The disease is characterized by local eosinophilic inflammation of the esophagus leading to symptoms of esophageal dysfunction (Furuta, 2017) (Liacouras, 2011). EoE has been reported in all ages. However, most cases are in children and adults younger than 50 years (Dellon, 2014a) (Dellon, 2014b) (Dellon, 2007) (Kapel, 2008) (Liacouras, 2011) (Spergel, 2009).

Clinical, histological, and molecular evidence also suggests that EoE has the same underlying pathogenesis in different age groups (Straumann, 2012). Histologic, biomarker, and genetic studies have demonstrated a generally similar pattern of inflammation and genetic abnormalities across age groups. Thus, the differences observed in the presentation of EoE symptomatology and endoscopic findings between pediatric and adult patients (eg, less dysphagia and fewer remodelling features in pediatric patients) likely reflect different durations of disease.

The proposed indication for this application is as follows: *DUPIXENT is indicated for the treatment of eosinophilic esophagitis in adults, adolescents, and children aged 1 year and older who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.*

Epidemiology and risk factors

The current prevalence of EoE is estimated at 22.7 per 100,000 worldwide and 19.1 per 100,000 among children (Arias, 2016) and appears to be increasing (Dellon, 2014a). Gender differences in EoE have been consistently reported, with a predominance in male patients versus females (Veerappan, 2009) (Dellon, 2014a), but there are no known gender-related differences in disease biology, clinical manifestations, severity, or natural history of the disease (Ally, 2015) (Lucendo, 2017) (DeBrosse, 2011) (Falk, 2014). In the EU, a Danish study found that the prevalence of EoE was 15 per 100,000 among boys aged 10 to 19 years old and 10 per 100,000 in boys aged 9 years and under, with a lower prevalence in girls of 3 per 100,000 among girls aged 10 to 19 years old and 4 per 100,000 in girls aged 9 years and under (Dellon, 2015). EoE is predominantly diagnosed in young Caucasians, although the incidence is increasing in other racial groups (Dellon, 2014a).

Atopic/type 2 inflammatory comorbidities such as food allergy, allergic rhinitis, asthma, and atopic dermatitis (AD) are significantly more common in EoE patients compared to the general population in adults and children with as many as 90% of patients with EoE having a comorbid atopic disease (González-Cervera, 2017) (Straumann, 2012) (Assa'ad, 2007) (Davis, 2013). There are reports of concomitant asthma in 26% to 50% of patients with EoE, and 19% to 55% of patients with EoE may have AD (Cianferoni, 2016). It has been postulated that EoE is a late manifestation of the atopic march (Blanchard, 2010).

Aetiology and pathogenesis

The disease is characterized by type 2 inflammation with esophageal eosinophilia leading to symptoms of esophageal dysfunction (Straumann, 2008).

Despite differences in symptom presentation between age groups, the pathological hallmark of the disease across all ages is eosinophil-predominant inflammation of the mucosa. Patients with EoE have increased levels of esophageal inflammatory infiltrates, including eosinophils, T-lymphocytes, mast cells, and basophils, as well as increased expression of type 2-associated chemokines and cytokines, such as eotaxin-3, IL-4, IL-5, and IL-13 in esophageal biopsies (Abonia, 2012) (Blanchard, 2007) (Blanchard, 2006) (Bullock, 2007) (Mishra, 2009) (O'Shea, 2018) (Sherrill, 2014) (Straumann, 2001) (Wen, 2013).

Clinical presentation, diagnosis

Clinical features in young children are generally non-specific and heterogenous in nature (depending on the patient's age and their ability to describe salient symptoms) and consequently may be more difficult to recognize (especially relevant for caregivers) or attribute to EoE by physicians. Infants and toddlers are more likely to present with feeding difficulties, vomiting, regurgitation, refusal to eat meals with the potential for suboptimal weight gain, and failure to thrive, while school-age pediatric children experience heterogeneous symptoms such as abdominal pain, vomiting, and gastroesophageal reflux (Cianferoni, 2016) (Hirano, 2017) (Iuliano, 2018) (Liacouras, 2014) (Miehlke, 2015) (Schoepfer, 2014) (Spergel, 2009) (Taft, 2011). Children can also infrequently experience dysphagia but may be more likely to describe this experience using simpler terms such as 'trouble swallowing' or 'food getting stuck'. Children with symptomatic EoE frequently learn coping strategies to modify their dietary and eating behavior by taking small bites, eating slowly with excessive chewing, drinking copious amounts of fluids, and avoiding food consistencies that can trigger symptoms (Furuta, 2015) (Barni, 2021), therefore impacting their symptom presentation and increasing the difficulty of symptom detection. EoE symptoms, dietary modifications and compensatory behaviors can cause psychosocial issues and

lead to substantially impaired QoL for patients and their caregivers (DeBrosse, 2011) (Falk, 2014) (Straumann, 2008).

Diagnostic criteria in both adults and pediatric patients include ≥15 eos/hpf (400x) in mucosal esophageal biopsies, regardless of age. As a consequence of this inflammation, a large number of patients (up to 90%) have associated endoscopic findings. Adults may have more fibrostenotic features. These include fixed or transient concentric rings, longitudinal furrows, white plaques, edema (as evidenced by reduced visual mucosal vascularity), fragile or crepe-like mucosa, and/or stricture. Edema, rings, and furrows are common endoscopic features, seen in at least half of patients (Singla, 2016). The severity of esophageal rings scored using the EoE-EREFS is correlated with the risk of food impaction (Mishra, 2009).

Endoscopic findings in EoE appear to vary by age, with more inflammatory features such as erythema and plaques seen in younger patients and more fibrotic findings (strictures and rings) at older ages (Dellon, 2009). These age-related differences are thought to reflect the time from diagnosis, and not a different pathophysiologic process (Gonsalves, 2014), and may provide insight into the natural history of the disease. If EoE remains untreated, it often progresses to the development of esophageal fibrosis and strictures resulting in food impactions and associated significant morbidities (DeBrosse, 2011) (Falk, 2014) (Keles, 2022) (Straumann, 2003) (Straumann, 2008), exemplifying the need to intervene early to prevent the development of fibrostenotic changes.

Management

Given the common underlying pathophysiology, current treatment paradigms for both adults and pediatric patients with EoE consists of food elimination diets, use of STCs, and high-dose (Proton pump inhibitor) PPI therapy. The combination of diet modification and approved or unapproved pharmacologic therapies can be effective in the management of some patients with EoE, such as Jorveza (budesonide orodispersible tablets) which has been approved in the EU, Canada, and Australia for the treatment of EoE in adults. About 25% of patients may have significant ongoing symptoms, despite treatment with dietary modification and corticosteroids (Book, 2012). Additionally, a significant proportion of patients do not respond to STCs and those that do may not have sustained benefit (Eluri, 2017) (DeBrosse, 2011) (Falk, 2014) (Keles, 2022) (Straumann, 2003) (Straumann, 2008).

Dupilumab 300 mg SC QW has been approved in several countries for the treatment of adult and pediatric patients aged 12 years and older, weighing at least 40 kg, with EoE.

Unmet medical need

Eosinophilic esophagitis is a chronic, type 2 inflammatory, immune-mediated disease of the esophagus which results in fibrostenosis of the esophagus if left untreated. No approved medicinal product is available for the treatment of EoE in children <12 years of age or for adolescents <40 kg.

2.1.2. About the product

Dupilumab is a human monoclonal IgG4 antibody that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes.

Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide, and IgE, therefore, broadly suppressing Type 2 inflammation. Dupilumab belongs to the pharmacological class of immunomodulators, IL inhibitors.

Dupilumab (DUPIXENT) has been approved in multiple regions or countries for the treatment of type 2 inflammatory diseases including AD, asthma, chronic CRSwNP, EoE, COPD, and PN. The current approved indications in the EU (DUPIXENT (Dupilumab) [Summary of Product Characteristics], 2023) are:

- **AD:**

  Adults and adolescents: "for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy."

  Children 6 months to 11 years of age: "for the treatment of severe atopic dermatitis in children 6 months to 11 years old who are candidates for systemic therapy."

- **Asthma:**

  Adults and adolescents: "indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment."

  Children 6 months to 11 years of age: "indicated in children 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with medium to high dose ICS plus another medicinal product for maintenance treatment."

- **CRSwNP:** "as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control."

- **EoE:** "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."

- **PN:** "for the treatment of adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy."

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

At the time of this submission, dupilumab is currently approved at a recommended dose of 300 mg QW for adults and adolescents 12 years and older with EoE weighing at least 40 kg in the EU. The primary support for the efficacy and safety of dupilumab in children ≥1 to <12 years of age with EoE is provided by Study R668-EE-1877, which assessed the safety and efficacy of dupilumab over a 16-week randomized, double-blind, placebo-controlled treatment period (Part A) and a 36-week extended active treatment period (Part B) in children ≥1 to <12 years of age with EoE.

Given that EoE in adult and pediatric patients is pathophysiologically identical both histologically and molecularly, results from Study R668-EE-1774, which demonstrated both histologic and symptomatic benefit of dupilumab 300 mg QW in adults and adolescents with EoE, can be considered supportive for the pediatric indication being sought in this application.

2.1.4. General comments on compliance with GCP

The MAH states that the clinical studies provided for this application 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 and Non-clinical aspects

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

The applicant provided in section 3.2.R the Justification for no need of Notified Body Opinion - MDR Article 117.

2.2.1. Ecotoxicity/environmental risk assessment

Dupilumab is a monoclonal antibody consisting of linked naturally occurring amino acids. As per the ERA Guideline (EMEA/CHMP/SWP/4447/00 Rev1, 2006), 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.

2.2.2. Conclusion on the non-clinical aspects

The applicant sufficiently outlined that there are no changes to the design or intended purpose of the device (200mg and 300mg PFS presentations), nor is there a new medical device being introduced. The justification for not providing the notified body opinion is acceptable. As there is no self-administration for the age 1 to 11 years, the usability of the PFS-S in the new EoE paediatric population is supported by existing usability data for the authorized presentations. Therefore, it can be agreed that an additional usability study is not required.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of dupilumab. Considering the above data, dupilumab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. 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 / Report Location/ Study Status	Study Population/Analysis Sets	PK-Related Objective	Study Design and Duration	Treatment: Dose, Route of Administration, Frequency (number of participants in Safety Analysis Set)
Eosinophilic Esophagitis in Children (≥1 to <12 years of age) – SC Administration (Phase 3)				
R668-EE-1877 Study ongoing[1] R668-EE-1877 Part A CSR Module 5.3.5.1 Part A completed; CSR for final analysis of Part A completed R668-EE-1877 Part B CSR Module 5.3.5.1 Part B completed; CSR for final analysis of Part B completed	Children (≥1 to <12 years of age) with EoE. Parts A and B 98 participants were included in PK analysis.	To describe the relationship between systemic dupilumab concentrations and clinical responses in pediatric participants (≥1 to <12 years of age) with EoE. To describe the concentration-time profile of functional dupilumab in serum over time. To characterize the ADA and NAb response to dupilumab. Dupilumab trough concentrations and immunogenicity were assessed.	Randomized, double-blind, multicenter, phase 3 study consisting of 3 parts (Parts A, B, and C) and follow-up period.[1] Part A (16-week double-blind treatment period) Sparse sampling for C_{trough} at day 1, week 4, and week 16 and ADA at day 1 and week 16 Treatment duration: 16 weeks. Follow-up: 12 weeks for participants who did not enter Part B. Part B (36-week extended active treatment period) Sparse sampling for C_{trough} and ADA at week 32 and week 52 Treatment duration: 36 weeks. Follow-up: 12 weeks for participants who did not enter Part C.	Higher exposure dupilumab (Parts A and B): 100 mg Q2W (≥5 to <15 kg), or 200 mg Q2W (≥15 to 30 kg), or 300 mg Q2W (≥30 to <60 kg), or 300 mg QW (≥60 kg; Part B only). Lower exposure dupilumab (Parts A and B): 200 mg Q4W (≥5 to <15 kg), or 300 mg Q4W (≥15 to <30 kg), or 200 mg Q2W (≥30 to <60 kg), or 300 mg Q2W (≥60 kg; Part B only). Part A • 34 participants received placebo • 28 participants received lower exposure dupilumab SC • 36 participants received higher exposure dupilumab SC Part B • 14 participants received placebo in Part A and lower exposure dupilumab SC in Part B • 18 participants received placebo in Part A and higher exposure dupilumab SC in Part B • 29 participants received lower exposure dupilumab SC in Part A and lower exposure dupilumab SC in Part B • 37 participants received higher exposure dupilumab SC in Part A

Study / Report Location/ Study Status	Study Population/Analysis Sets	PK-Related Objective	Study Design and Duration	Treatment: Dose, Route of Administration, Frequency (number of participants in Safety Analysis Set)
				and higher exposure dupilumab SC in Part B

Abbreviations: ADA=anti-drug antibodies; CSR=clinical study report; C_{trough}= trough concentration at the end of the dosing interval; EoE=eosinophilic esophagitis; PK=pharmacokinetics; Q2W=every 2 weeks; Q4W=every 4 weeks; QW=once weekly; SC=subcutaneous.

[1] An open-label extension (Part C) of Study R668-EE-1877 evaluating treatment with dupilumab for up to an additional 108 weeks is ongoing and not included in this application. In Part C, all participants receive weight-tiered higher exposure dupilumab consistent with the proposed posology for registration (200 mg Q3W [≥5 to <15 kg], 200 mg Q2W [≥15 to <30 kg], 300 mg Q2W [≥30 to <40 kg], or 300 mg QW [≥40 kg]).

2.3.2. Pharmacokinetics

Dupilumab 300 mg SC QW is currently approved for the treatment of adult and adolescent patients aged 12 years and older, weighing at least 40 kg, with EoE. In the framework of the latter authorization application, the pharmacokinetics (PK) of functional dupilumab in serum has been described in adults and adolescents with EoE. Previously, PK was also described in healthy participants, adults and pediatric (≥6 months to <18 years) patients with AD, adult and pediatric (≥6 to <18 years) patients with asthma, adults with CRSwNP, and adults with PN. The purpose of this application is to extend the current indication for the treatment of EoE to include children ≥1 to <12 years of age with EoE, and patients 12 years and older weighing <40 kg with EoE.

EoE Studies with pharmacological data

The proposed indication expansion is based on the principle of exposure bridging to adult and adolescent data. It is supported by data from the completed phase 3 Study R668-EE-1877 Parts A and B in children ≥1 to <12 years of age with EoE. Under the assumption of similarity of the adult and pediatric EoE populations, the PK, PD, and E-R data from children (≥1 to <12 years) are compared to data from adults and adolescents with EoE in Study R668-EE-1774.

Study R668-EE-1877

Phase 3 Study R668-EE-1877 assessed primarily the safety and efficacy of dupilumab over a 16-week randomized, double-blind, placebo-controlled treatment period (Part A) and a 36-week extended active treatment period (Part B). An open-label extension evaluating treatment with dupilumab for up to 108 additional weeks (ie, up to 2 additional years) in children ≥1 to <12 years of age is ongoing (R668-EE-1877 Part C). Therefore, full data from Part C of Study R668-EE-1877 are not presented but only interim data with a cut-date of 17 Jan 2024 have been provided during the procedure.

In Study R668-EE-1877, functional dupilumab concentrations and PD data as measured by plasma eotaxin-3 for dupilumab in the treatment of participants with EoE have been collected. Dosing is summarized in the Table 1 below.

Table 1. Dupilumab Weight-tiered Dosing Regimens in Study R668-EE-1877 by Study Part (Parts A, B, and C) and Proposed Regimen for Registration

R668-EE-1877 Part A (Completed)[a]	R668-EE-1877 Part B (Completed)	R668-EE-1877 Part C (Ongoing)[b]
Higher exposure dupilumab:[c] • ≥5 to <15 kg: 100 mg Q2W • ≥15 to <30 kg: 200 mg Q2W • ≥30 to <60 kg: 300 mg Q2W	Higher exposure dupilumab:[c] • ≥5 to <15 kg: 100 mg Q2W • ≥15 to <30 kg: 200 mg Q2W • ≥30 to <60 kg: 300 mg Q2W • ≥60 kg: 300 mg QW (Part B only)	Higher exposure dupilumab (proposed regimen):[c,d] • ≥5 to <15 kg: 200 mg Q3W • ≥15 to <30 kg: 200 mg Q2W • ≥30 to <40 kg: 300 mg Q2W • ≥40 kg: 300 mg QW
Lower exposure dupilumab: • ≥5 to <15 kg: 200 mg Q4W • ≥15 to <30 kg: 300 mg Q4W • ≥30 to <60 kg: 200 mg Q2W	Lower exposure dupilumab:[c] • ≥5 to <15 kg: 200 mg Q4W • ≥15 to <30 kg: 300 mg Q4W • ≥30 to <60 kg: 200 mg Q2W • ≥60 kg: 300 mg Q2W (Part B only)	Not applicable

Abbreviations: Q2W=every 2 weeks; Q3W=every 3 weeks; Q4W=every 4 weeks; QW=once weekly.

[a] Placebo arm included in Part A is not shown.

[b] While data from Part C are not part of this application, all participants who continued into Part C were assigned to the higher exposure dupilumab regimens shown in this table.

[c] Weight-tiered doses were assigned for the double-blind treatment period (Part A) based on body weight at the Part A baseline. Individual weight-tiered doses within each regimen were adjusted to a heavier weight tier, if appropriate, based on body weight measured at week 16 (the start of Part B), week 32, week 52 (the start of Part C), and each subsequent in-clinic visit in Part C.

[d] Weight-tiered dupilumab regimens being evaluated in Study R668-EE-1877 Part C are the proposed posology for registration.

- **Study R668-EE-1877 Part A (completed).**

  During Part A, eligible children (≥1 to <12 years), weighing ≥5 to <60 kg, with EoE were randomized in a 2:2:1:1 ratio to receive either higher exposure dupilumab, lower exposure dupilumab, higher exposure-matched placebo, or lower exposure-matched placebo SC throughout a 16-week treatment period. Following completion of the 16-week double-blind treatment period, eligible participants continued into Part B of the study. Participants who did not enter Part B entered a 12-week post-treatment follow-up period.

- **Study R668-EE-1877 Part B (completed).**

  Participants randomized to higher exposure dupilumab or lower exposure dupilumab in Part A received the same dupilumab exposure regimen for 36 weeks during Part B. Participants who were randomized to placebo in Part A received higher exposure dupilumab or lower exposure dupilumab for 36 weeks during Part B according to the exposure regimen assigned at randomization. Higher exposure or lower exposure dupilumab regimens were the same as those for Part A. However, if the participant's weight tier had increased at week 16 or at week 32, doses were adjusted to the corresponding weight-tiered dose in the same dupilumab

exposure group. Participants weighing ≥60 kg at either visit received 300 mg QW (higher exposure dupilumab) or 300 mg Q2W (lower exposure dupilumab).

After implementation of protocol amendment 4, eligible participants who completed the 36-week Part B treatment period continued directly into the open-label extension period (Part C) of the study. Participants who completed their end-of-study visit prior to amendment 4 were evaluated for Part C eligibility at a re-entry visit. Inclusive of Parts A and B, the study treatment duration was 52 weeks. Participants who did not directly enter Part C entered a 12-week post-treatment follow-up period.

- **Study R668-EE-1877 Part C (ongoing).**

  All participants in Part C are administered weight-tiered higher exposure dupilumab for up to an additional 108 weeks or until participant is eligible to receive commercially available dupilumab, whichever is sooner.

  ≥40 kg (300 mg QW)

  ≥30 to <40 kg (300 mg Q2W)

  ≥15 to <30 kg (200 mg Q2W)

  ≥5 to <15 kg (200 mg Q3W)

The dupilumab weight-tiered regimens being evaluated in Part C, which include modifications from the weight-tiered regimens evaluated in Parts A and B (Table 1), are the proposed posology for registration.

Study R668-EE-1774 (adults and adolescents >40 kg)

Study R668-EE-1774 was a randomized, 3-part, double-blind, multicenter, phase 3 study in adults (≥ 18 years) and adolescents (≥12 to <18 years) with EoE who weighed ≥40 kg. This study consisted of Parts A and B (each consisting of a 24-week double-blind treatment period), Part C (a 28-week extended active treatment period after completing Part A or B), and a 12-week follow-up period. Participants who prematurely discontinued study intervention or did not continue into the next period of the study entered a 12-week post-treatment follow-up period.

- **Study R668-EE-1774 Part A (completed).**

  During Part A participants received either dupilumab **300 mg QW** or placebo in a 1:1 ratio throughout a 24-week treatment period. Participants who did not enter Part A/C entered a 12-week post-treatment follow-up period.

- **Study R668-EE-1774 Part B (completed).**

  Participants who participated in Part A were not eligible to participate in Part B. During Part B participants received either dupilumab 300 mg SC QW, dupilumab **300 mg SC Q2W** (and matching placebo on alternate weeks), or placebo in a 1:1:1 ratio throughout a 24-week treatment period. Participants who did not enter Part B/C entered a 12-week post-treatment follow-up period.

- **Study R668-EE-1774 Part C (completed).**

  After completing the end of treatment visit in either Part A or Part B of the study, participants were eligible to continue into Part C. Participants who received either dupilumab 300 mg SC QW or placebo in Part A were administered dupilumab 300 mg SC QW for 28 weeks during Part A/C. Participants who were randomized to dupilumab 300 mg QW or 300 mg Q2W in Part B

received the same dosing regimen of dupilumab for 28 weeks during Part B/C. Participants who were randomized to placebo in Part B were re-randomized 1:1 to receive dupilumab 300 mg QW or 300 mg Q2W for 28 weeks during Part B/C. Inclusive of Part A or B plus Part A/C or B/C, the total study treatment duration was 52 weeks. After the end-of-treatment visit in Parts A/C and B/C, participants entered a 12-week follow-up period.

The co-primary endpoints for both Parts A and B were the proportion of participants achieving peak oesophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 and absolute change in DSQ score from baseline to week 24. The key secondary endpoints for both Parts A and B of the study were the absolute change in EoE-EREFS from baseline to week 24, percent change in peak oesophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 24, and absolute change in EoE grade and stage scores from the EoEHSS from baseline to week 24. These endpoints were also secondary efficacy endpoints in Parts A/C and B/C. In Parts A and B, potential relationships between concentrations of functional dupilumab and peak oesophageal intraepithelial eosinophil counts, DSQ total score, EoE-EREFS, EoEHSS grade score, and EoEHSS stage score were assessed.

PK Data and Analysis

Comparisons of dupilumab PK and PD data in children, adolescents, and adults with EoE focus on the phase 3 studies R668-EE-1877 and R668-EE-1774 (adults/adolescents), which utilized similar study designs. Comparisons of observed concentrations of dupilumab focus on week 16 (end of double-blind treatment period for Study R668-EE-1877 Part A), week 24 (end of double-blind treatment period for Study R668-EE-1774 Parts A and B), and week 52 (end of extended active treatment period for Study R668-EE-1877 Part B and Study R668-EE-1774 Parts A/C and B/C) and represent steady-state concentrations of dupilumab at each corresponding time point.

The PKAS includes all participants in Studies R668-EE-1877 (Parts A and B) and R668-EE-1774 (Parts A, B, A/C, and B/C) who received any study intervention and who had at least 1 non-missing drug concentration result following the first dose of study intervention. The PKAS is based on the actual treatment received. Samples for the analysis of dupilumab concentrations in serum were collected according to a protocol-specified sparse collection schedule, which included a baseline sample, Ctrough samples collected at the end of various dosing intervals across each study (R668-EE-1877: week 4 and 16 [Part A] and weeks 32 and 52 [Part B]; R668-EE-1774: weeks 12 and 24 [Parts A and B] and weeks 32 and 52 [Parts A/C and B/C]). Additional samples may have been collected at early termination visits or during the follow-up period for participants completing the study or not immediately continuing into the next study part.

Descriptive summaries and concentration-time profiles per Study parts are provided in the following Table 2.

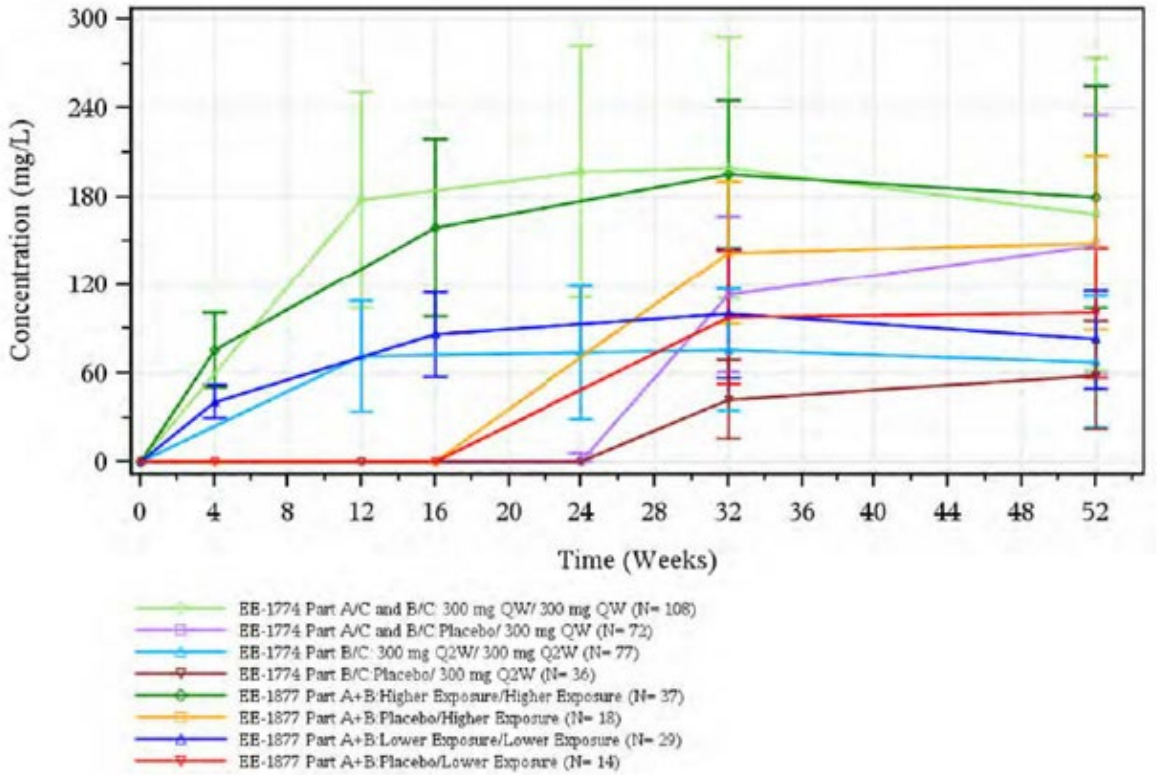
Table 2. Summary of Trough Concentrations of Functional Dupilumab in Serum by Study for Participants with EoE Receiving Dupilumab in Study R668-EE-1877 or Study R668-EE-1774 (PKAS)

		Week 16 (N=60)		Week 24 (N=175)		Week 52 (N=358)	
Dupilumab Treatment Group or Dose Regimen	Population	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Dupilumab 300 mg QW	Adult/adolescent EoE, ≥40 kg	0		101	196 (86.3)	170	159 (99.4)
Dupilumab 300 mg Q2W	Adult/adolescent EoE, ≥40 kg	0		74	73.6 (46.0)	106	65.7 (43.1)
Higher Exposure Dupilumab	1 to <12 years, 5 to <60 kg	33	159 (60.3)	0		45	169 (71.2)
100 mg Q2W	1 to <12 years, 5 to <15 kg	3	135 (34.9)	0		3	132 (26.9)
200 mg Q2W	1 to <12 years, 15 kg to <30 kg	17	164 (73.9)	0		20	179 (84.7)
300 mg Q2W	1 to <12 years, 30 kg to <60 kg	13	157 (44.9)	0		22	166 (61.3)
Lower Exposure Dupilumab	1 to <12 years, 5 to <60 kg	27	86.6 (28.8)	0		37	89.2 (37.9)
200 mg Q4W	1 to <12 years, 5 to <15 kg	4	86.3 (31.4)	0		2	61.0 (31.7)
300 mg Q4W	1 to <12 years, 15 kg to <30 kg	16	85.2 (29.6)	0		21	87.1 (42.1)
200 mg Q2W	1 to <12 years, 30 kg to <60 kg	7	89.8 (29.7)	0		14	96.4 (31.3)

Abbreviations: BLQ=below limit of quantitation; EoE=eosinophilic esophagitis; N=number of participants; PKAS=pharmacokinetic analysis set; Q2W=every 2 weeks; Q4W=every 4 weeks; QW=once weekly; SD=standard deviation.

Note: BLQ concentrations were set to 0. Study R668-EE-1877 included children ≥1 to <12 years of age and Study R668-EE-1774 included adults and adolescents ≥12 years of age. Adult and adolescent concentrations at week 24 in R668-EE-1774 Part A (300 mg QW) or Part B (300 mg QW and Q2W) and week 52 concentrations in R668-EE-1774 Part A/C (300 mg QW), R668-EE-1774 Part B/C (300 mg QW and Q2W). Pediatric participants ≥1 to <12 years at week 16 in R668-EE-1877 Part A or week 52 in R668-EE-1877 Part B. Concentrations at week 52 include participants who received active drug or placebo in R668-EE-1774 Part A and B or R668-EE-1877 Part A. Dose regimen at each time point correlates to the last administered dose.

Figure 1. Mean (SD) Concentrations of Functional Dupilumab in Serum by Time and Dose Regimen in Participants with EoE in Studies R668-EE-1877 and R668-EE-1774 (PKAS)



Abbreviations: BLQ=below limit of quantitation; EoE=eosinophilic esophagitis; N=number of participants; PKAS=pharmacokinetic analysis set; Q2W=every 2 weeks; QW=once weekly; SD=standard deviation.
Note: BLQ concentrations were set to 0. Study R668-EE-1877 included children ≥1 to <12 years of age and Study R668-EE-1774 included adults and adolescents ≥12 years of age. Participants in R668-EE-1774 Part A/C, R668-EE-1774 Part B/C, or R668-EE-1877 Part B PK analysis populations. Data for treatment period in R668-EE-1774 or R668-EE-1877.

Study R668-EE-1877 Part A (Double-Blind, Placebo-Controlled 16-week Treatment Period)

Table 3. Descriptive Statistics of Functional Dupilumab Concentrations in Serum by Time and Treatment Group in Pediatric Patients ≥1 to <12 Years with Eosinophilic Esophagitis Receiving Higher Exposure Dupilumab (Study R668-EE-1877, Part A)

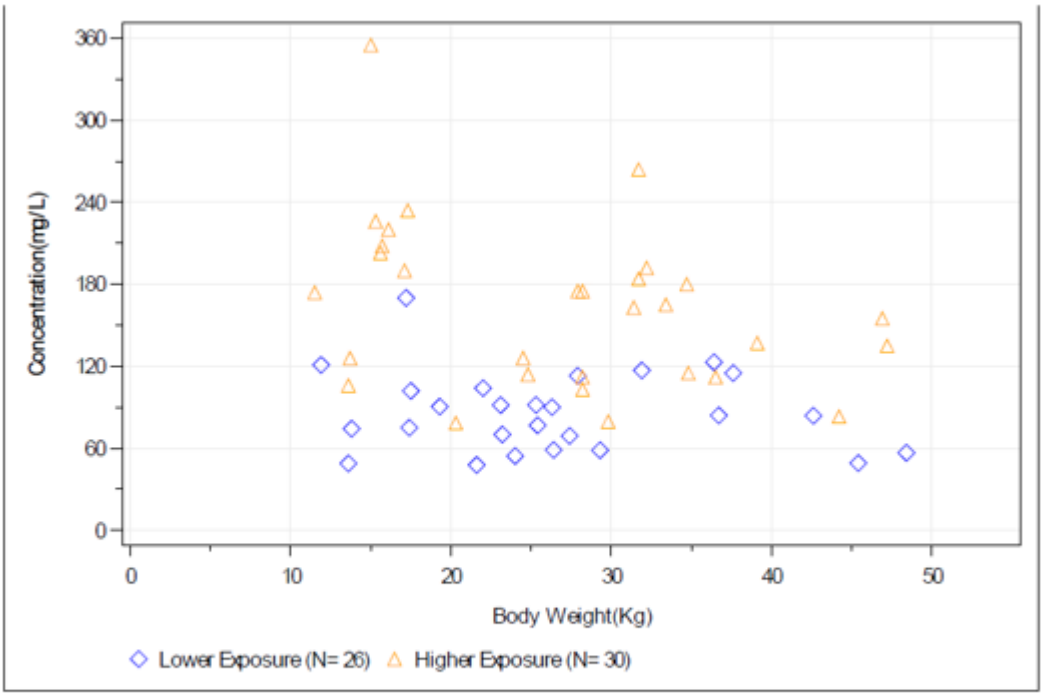
	Concentration of Functional Dupilumab in Serum (mg/L)										
Sampling Time Post First Dose (Week)	n	Mean	SD	SE	CV%	Min	Q1	Median	Q3	Max	Geometric Mean
Dupilumab 100 mg Q2W, >=5 kg to <15kg											
0	5	0	0	0	NA	0	0	0	0	0	NA
4	5	68.2	10.4	4.65	15.2	58.2	60.3	63.8	78.0	80.6	67.6
16	3	135	34.9	20.2	25.8	106	106	126	174	174	132
Dupilumab 200 mg Q2W, >=15kg to <30kg											
0	18	0	0	0	NA	0	0	0	0	0	NA
4	18	81.3	32.7	7.72	40.3	34.2	56.0	77.1	110	132	74.8
16	15	173	73.8	19.1	42.6	78.5	112	175	220	355	159
Dupilumab 300 mg Q2W, >=30kg to <60kg											
0	13	0	0	0	NA	0	0	0	0	0	NA
4	13	70.8	16.6	4.60	23.5	33.3	63.9	76.1	81.3	94.0	68.5
16	12	157	46.9	13.5	29.8	83.2	125	159	182	264	151

n = Number of patients; SD = Standard deviation; SE = Standard error; CV% = Coefficient of variation; Q = Quartile; NA = Not applicable
Note: Samples collected during Part A treatment period.
/home/prithvi.boggala/sasdata/Data/Production/PK/R668/R668-EE/R668-EE-1877/FirstStep/Analysis_CSR/Programs/Generated/T_PCSUMAP_AHE.sas (prithvi.boggala 11JUL2022 10:28 SAS Linux 9.4)

Exposure of dupilumab in Part A indicated that mean concentrations of dupilumab at week 16 for the higher exposure dupilumab treatment group were approximately 2-fold higher than the lower exposure dupilumab treatment group.

In the higher exposure dupilumab group, mean concentrations at week 16 in participants who received 100 mg Q2W (≥5 to <15 kg), 200 mg Q2W (≥15 to <30 kg), or 300 mg Q2W (≥30 to <60 kg) were 135 mg/L, 173 mg/L, and 157 mg/L, respectively. In Part A, dupilumab pharmacokinetics were investigated in 36 children 1 to 11 years of age with EoE receiving dupilumab [≥5 to <15 kg (100 mg Q2W), ≥15 to <30 kg (200 mg Q2W), and ≥30 to <60 kg (300 mg Q2W)], the mean ± SD steady-state trough concentration of dupilumab was 163±60.8 mcg/mL. In the lower exposure dupilumab group, concentrations of dupilumab were generally similar among the weight-based dose tiers. In the lower exposure dupilumab group, mean concentrations at week 16 were similar among weight-based dose tiers (81.4 to 89.8 mg/L).

Figure 2. Scatter Plot of Functional Dupilumab in Serum at Week 16 by Baseline Body Weight and Treatment Group in Pediatric Patients ≥ 1 to <12 Years with Eosinophilic Esophagitis (Study R668-EE-1877, Part A)



n = Number of patients
Note: BLQ concentrations were set to 0.
/home/prithvi.boggala/sasdata/Data/Production/PK/R668/R668-EE/R668-EE-1877/FirstStep/Analysis_CSR/Programs/TFL/Figures/F_PCSCATTERBWT_A.sas (prithvi.boggala 24JUN22:09:24 SAS Linux 9.4)

Study R668-EE-1877 Part B (36-week Extended Active Treatment Period)

For participants who received dupilumab in both Parts A and B, mean concentrations of dupilumab at week 52 in the higher exposure dupilumab/higher exposure dupilumab group were approximately 2-fold higher than the lower exposure dupilumab/lower exposure dupilumab group. Participants who received placebo in Part A reached steady-state trough concentrations of dupilumab by week 32 in Part B and were within the range of variability for participants treated with dupilumab for the entire study at week 52. Concentrations of dupilumab demonstrated overlapping distributions among the different weight-tiered dosing regimens throughout Part B.

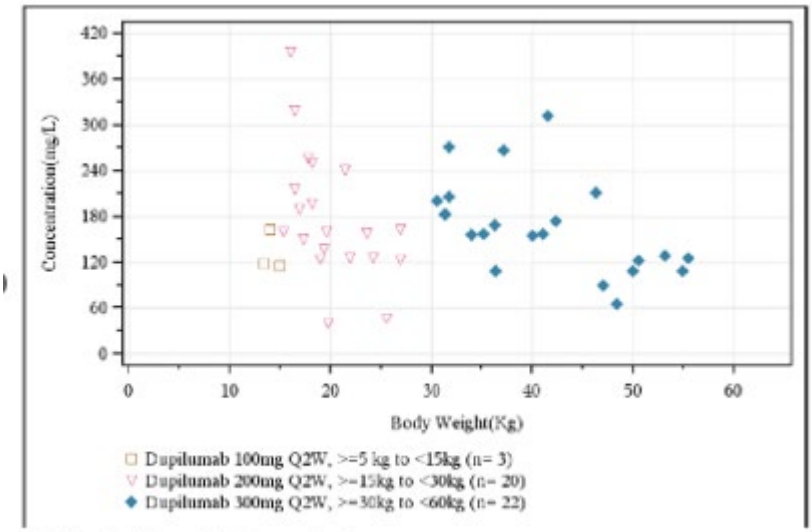
At week 52, mean concentrations of dupilumab in participants who received 100 mg Q2W (≥5 to <15 kg), 200 mg Q2W (≥15 to ≤30 kg), or 300 mg Q2W (≥30 to <60 kg) were 132 mg/L, 179 mg/L, and 166 mg/L, respectively. In the lower exposure dupilumab group, concentrations of dupilumab were generally similar among the weight-based dose tiers. At week 52, mean concentrations of dupilumab in participants who received 200 mg Q4W (≥5 to <15 kg), 300 mg Q4W (≥15 to <30 kg), or 200 mg Q2W (≥30 to <60 kg) were 61.0 mg/L, 87.1 mg/L, and 96.4 mg/L, respectively.

Table 4. Summary of Concentrations of Functional Dupilumab in Serum During the Treatment Period by Time and Treatment Group in Pediatric Participants ≥1 to <12 Years with EoE in Part B (Study R668-EE-1877, PKAS)

	Concentration of Functional Dupilumab in Serum (mg/L)							
	Higher Exposure Dupilumab/ Higher Exposure Dupilumab (N=37)		Placebo/ Higher Exposure Dupilumab (N=18)		Lower Exposure Dupilumab/ Lower Exposure Dupilumab (N=29)		Placebo/ Lower Exposure Dupilumab (N=14)	
Sampling Time Post First Dose (Week)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
16	33	159 (60.3)	18	0 (0)	27	86.6 (28.8)	12	0 (0)
32	36	186 (59.5)	17	142 (48.5)	28	99.0 (42.8)	13	105 (49.8)
52	30	179 (75.3)	15	149 (59.1)	24	83.0 (33.2)	13	101 (44.3)

N = Number of participants; n = Number of participants at each time point; SD = Standard deviation
Note: BLQ concentrations were set to 0. Samples were collected during the Part B treatment period.
Source: PTT 2.1
/sasdata/Data/Production/PK/R668/R668-EE/R668-EE-1877/WK52/Analysis_CSR/Programs/TFL/Tables/Generated/t_pcsum_b.sas (prithvi.boggala 27MAR2023 09:49 SAS Linux 9.4)

Figure 3. Scatter Plot of Concentrations of Functional Dupilumab in Serum at Week 52 by Body Weight and Dose Regimen in Pediatric Participants ≥1 to <12 Years with EoE Receiving Higher Exposure Dupilumab in Part B (Study R668-EE-1877, PKAS)



n = Number of participants; Q2W = Once every 2 weeks
Note: BLQ concentrations were set to 0. Dose regimens were based on last administered dose prior to week 52. Body weight corresponds to week 36 and was used to determine weight-tiered doses for weeks 36 to 52.

Study R668-EE-1877 Part C (ongoing 108-week Open-Label Extension Period)

Available PK data have been provided from the ongoing Study R668-EE-1877 Part C open-label extension period with a data cut-off date of 17 Jan 2024. All patients in Part C received higher exposure dupilumab regimens based on body weight, i.e.:

· 200 mg Q3W in patients who weigh ≥5 kg to <15 kg

· 200 mg Q2W in patients who weigh ≥15 kg to <30 kg

· 300 mg Q2W in patients who weigh ≥30 kg to <40 kg

· 300 mg QW in patients who weigh ≥40 kg

Of the 98 participants who entered Part B, 61 participants continued into Part C.

Available data for concentrations of functional dupilumab in serum from the ongoing Study R668-EE-1877 Part C are provided for the overall population in Table 5 and at Week 100 by the last administered weight-tiered dose in Table 6.

Observed trough concentrations at Week 100 in each weight-tiered dose group for which data is available collected in N=21 subjects are overall consistent with expectations based on the population PK analysis conducted in pediatric EoE patients (Quantitative Pharmacology Report R668-PK-23108-SR-01V1). No patients with drug concentration data available at Week 100 or later weighed <15 kg. PK data following 300 mg QW was only observed in one subject.

The predicted median (P5, P95) for Ctrough by dose in this population was 152 (76, 322) mg/L for 200 mg Q2W [15 to <30 kg], 147 (77, 269) mg/L for 300 mg Q2W [30 to <40 kg], and 261 (140, 452) mg/L for 300 mg QW [≥40 kg].

No ADA positive samples have been observed in Part C to date.

Table 5. Descriptive Statistics of Concentrations of Functional Dupilumab in Serum by Time in Pediatric Participants 1 to <12 Years with Eosinophilic Esophagitis (Study R668-EE-1877 Part C, 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	%BLQ
100	21	161	79.3	17.3	49.2	80.4	120	135	182	391	147	0
160	4	249	108	54.0	43.4	152	160	234	339	376	232	0
172	3	218	77.5	44.7	35.5	136	136	228	290	290	208	0

n = Number of participants contributing to the statistical results; SD = Standard deviation; SE = Standard error; CV = Coefficient of variation; Q = Quartile; BLQ = Below the lower limit of quantitation; %BLQ = the proportion of samples with concentrations <LLOQ

Table 6. Descriptive Statistics of Concentrations of Functional Dupilumab in Serum at Week 100 by Weight-Tiered Dose in Pediatric Participants 1 to <12 Years with Eosinophilic Esophagitis (Study R668-EE-1877 Part C, 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	%BLQ
Dupilumab 200mg Q2W, >=15kg to <30kg												
100	14	154	72.2	19.3	46.8	80.4	102	137	183	351	142	0
Dupilumab 300mg Q2W, >=30kg to <40kg												
100	6	138	16.7	6.81	12.1	126	128	133	139	171	138	0
Dupilumab 300mg QW, >=40kg												
100	1	391	--	--	--	391	--	--	--	391	--	0

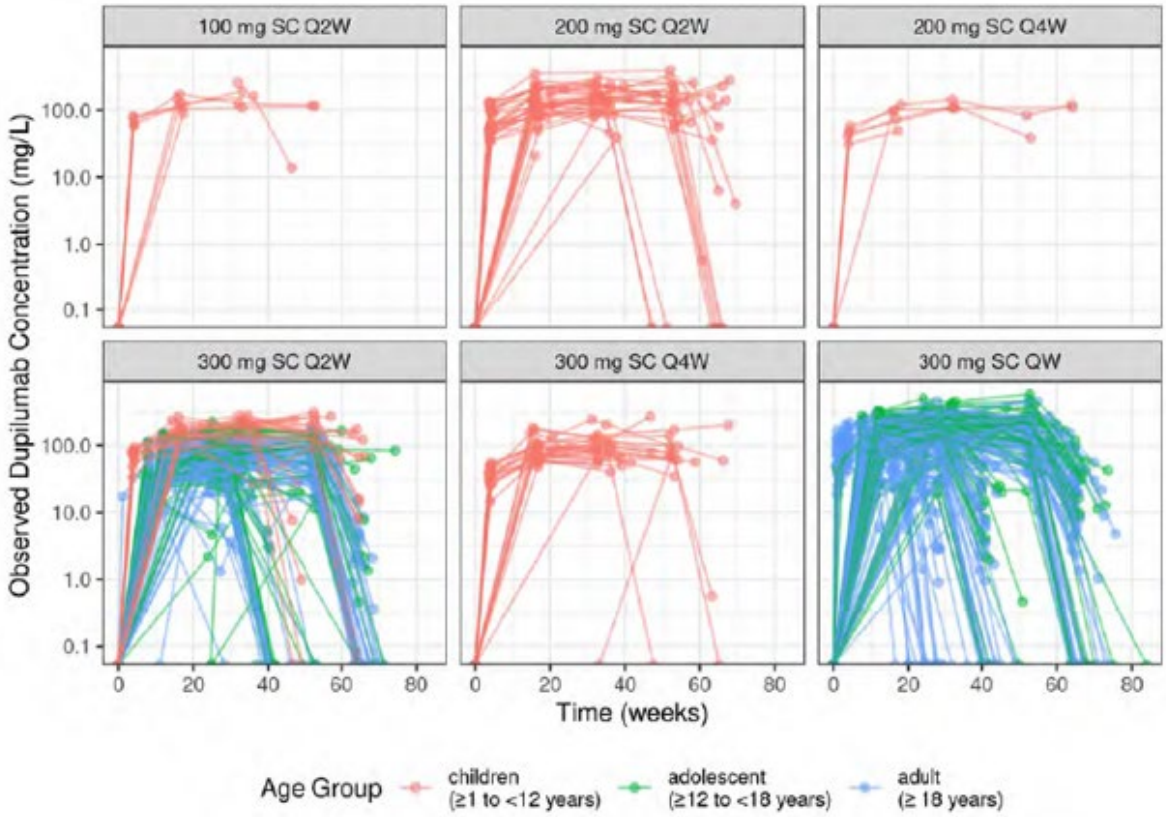
n = Number of participants contributing to the statistical results; SD = Standard deviation; SE = Standard error; CV = Coefficient of variation; Q = Quartile; BLQ = Below the lower limit of quantitation; %BLQ = the proportion of samples with concentrations <LLOQ

Note: Below LLOQ value is set to 0 except for geometric mean; Below LLOQ value is set to LLOQ/2 for geometric mean calculation, set to 0 if all values are below LLOQ for given timepoint.

Exploratory data analysis by dose

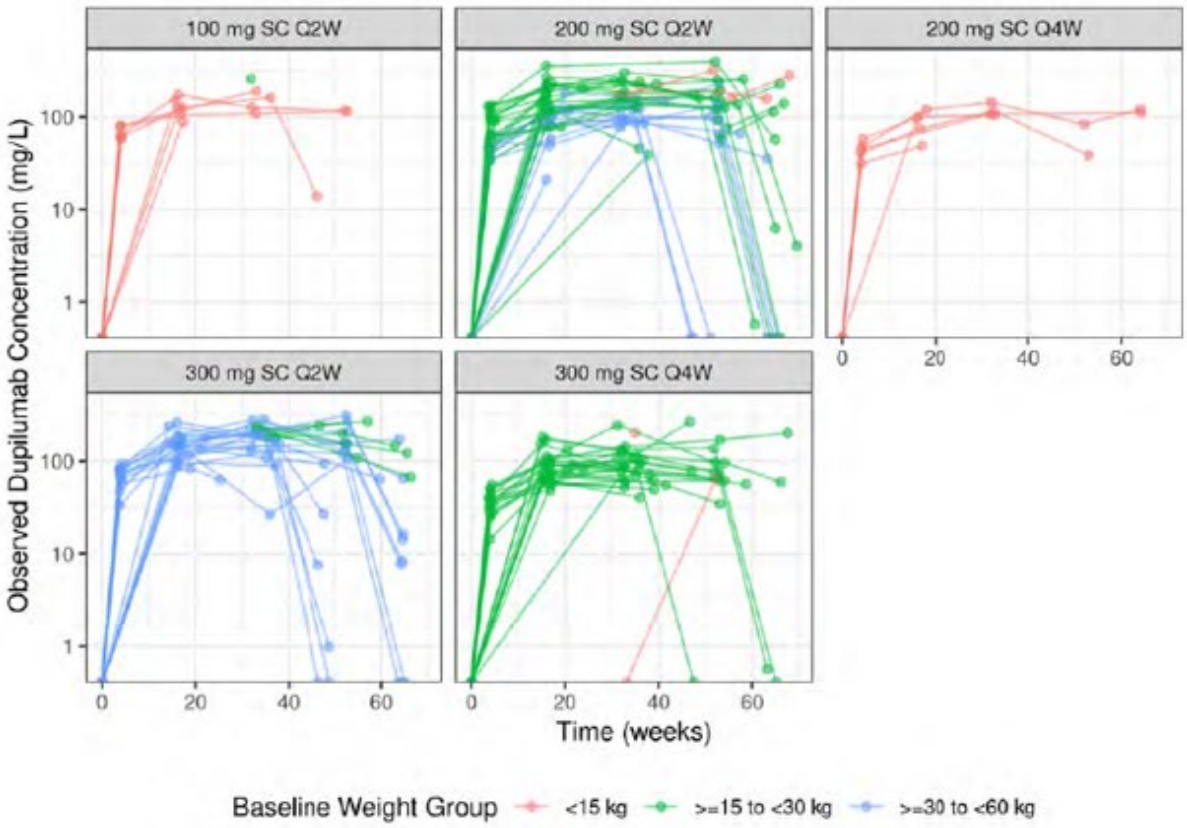
The observed concentration-time plots for dupilumab are presented below in the overall population and in the paediatric population by dose.

Figure 4. Observed Dupilumab Concentration vs Time Profiles by Dose in Patients with Eosinophilic Esophagitis



Lines do not represent time course of concentration, but rather link the measurements of individual subjects.

Figure 5. Observed Dupilumab Concentration vs Time Profiles by Dose in Children (≥1 to <12 Years of Age) with Eosinophilic Esophagitis



Lines do not represent time course of concentration, but rather link the measurements of individual subjects. As some patients experienced growth and therefore weight gain during the trial, dose adjustments were made in accordance with the defined weight-tiered, fixed doses and may appear as disconnected points within the plot.

Population PK Analysis

Aim and impact

The primary objectives of pop PK analysis were to characterize the population PK of dupilumab in children ≥1 to <12 years of age with EoE using a structural model built using data from paediatric and adult patients with EoE, as well as data from healthy adult volunteers. Exposure simulations based on the final pop PK model for EoE patients (≥1 to <12 years) were used to compare exposures with those from adults and adolescents (>40 kg) and to justify the proposed posology that has not been clinically tested.

Model development plan

Several population PK models have been developed to describe concentrations of dupilumab in various populations. Most of these models, including the prior analysis conducted in adult and adolescent participants with EoE (adult and adolescent EoE marketing authorization application), share the base model structure used in the initial analysis of healthy adult participants and adults with AD of a 2-compartment model with parallel linear and nonlinear (Michaelis-Menten) elimination, first-order SC absorption, and covariate effects for body weight and were assessed previously.
The overall model development plan was to construct a base model for EoE patients leveraging the information from the healthy participants who received either IV or SC doses of dupilumab and using a similar structural model to the initial analysis in healthy adult participants and adults with AD.

As the most informative data on the absorption and nonlinear elimination of dupilumab come from single dose studies with intense PK sampling conducted in healthy adult participants, model parameters were first estimated using the subset of data in healthy participants. Subsequently, a PK model was built with the goal of describing dupilumab PK specifically in the adult and paediatric EoE population.

The pooled dataset for pop PK development included a total of 632 unique subjects and 4459 drug concentration samples, with 3494 (78%) quantifiable samples and 965 (22%) post-dose samples that were BLQ. A total of 97 paediatric patients aged ≥1 to <12 years of age were included in the dataset, with 319 (95.2%) quantifiable samples and 16 (4.8%) post-dose BLQ samples.

Table 7. Summary of Subjects and PK Samples Included in the Population PK Analysis for Dupilumab by Indication and Age Group

Indication	Population	Number of Subjects With ≥1 Quantifiable* Samples	Total Number of Subjects	Number of Quantifiable* Samples	Number of Post-dose BLQ Samples	Percent of Post-dose BLQ Samples (%)
EoE patients	children (≥1 to <12 years)	97	98	319	16	4.78
	adolescent (≥12 to <18 years)	96	97	336	39	10.40
	adult (≥ 18 years)	233	235	890	115	11.44
Healthy subjects	adult (≥ 18 years)	202	202	1,949	795	28.97
Overall		628	632	3,494	965	21.64

BLQ = below the level of quantification; EoE = eosinophilic esophagitis.
* Quantifiable refers to observed non-BLQ values

The final pop PK parameters are detailed below.

Table 8. Population Pharmacokinetic Parameter Estimates for the Final Model

Parameter (Units)	Parameter Estimate (95% CI)	RSE %
CL: Clearance (L/day)*	0.145 (fixed)	—
Vc: Central Volume of Distribution (L)*	2.39 (fixed)	—
Q: Intercompartmental Clearance (L/day)*	0.511 (fixed)	—
V_P: Peripheral Volume of Distribution (L)*	1.47 (fixed)	—
V_{max}: Maximum Nonlinear Clearance Rate (mg/L/day)*	1.07 (fixed)	—
Km: Concentration of half-maximum nonlinear clearance (mg/L)*	0.134 (fixed)	—
Ka: Absorption Rate Constant (1/day)*	0.284 (fixed)	—
F_1: Bioavailability*	0.659 (fixed)	—
MTT: Mean Transit Time (Day)*	0.0726 (fixed)	—
Proportional Error in Healthy Volunteers [IV] (%)*	0.136 (fixed)	—
Proportional Error in Healthy Volunteers [SC] (%)*	0.179 (fixed)	—
Additive Error in Healthy Volunteers [SC] (mg/L)*	0.0284 (fixed)	—
Proportional Error in EoE Patients (%)	0.252 (0.25 — 0.254)	0.417
Additive Error in EoE Patients (mg/L)	11.6 (11.5 — 11.8)	0.747
Time-Varying Weight† on CL [REF: 70 kg]	1.08 (1.07 — 1.08)	0.307
Time-Varying Weight† on V_{ss} [REF: 70 kg]	0.71 (0.706 — 0.714)	0.29
Baseline Albumin on CL [REF: 45 g/L]	-1.16 (-1.17 — -1.15)	0.314
EoE Patient on CL [REF: Healthy Volunteers]	0.944 (0.944 — 0.944)	0.0184
EoE Patient on V_{max} [REF: Healthy Volunteers]	0.782 (0.78 — 0.783)	0.0725
EoE Patient on V_{ss} [REF: Healthy Volunteers]	1.3 (1.3 — 1.3)	0.0749
Time-Varying Weight† on Q [REF: 70 kg]	0.75 (fixed)	—
IIV†† on CL	0.097 (0.0969 — 0.0971)	0.065
IIV†† on V_{ss}	0.026 (0.026 — 0.0261)	0.0642

EoE = eosinophilic esophagitis; IIV = inter-individual variability; IV = intravenous; RSE = relative standard error; SC = subcutaneous; V_{ss} = Volume of distribution at steady-state ($V_{ss} = V_C + V_P$).

* Note: Parameters were fixed to the values obtained from the model with information from healthy volunteers only

† Note: Time-varying weights were used where available; otherwise, baseline weight values were used

†† Note: Conversion of values to coefficient of variation (CV%) is calculated by $CV(\%) = \sqrt{\exp(IIV) - 1} \times 100$, resulting in 31.9% for CL and 16.2% for V_{ss}. η-shrinkage values were 8.62% for CL and 64.9% for V_{ss}.

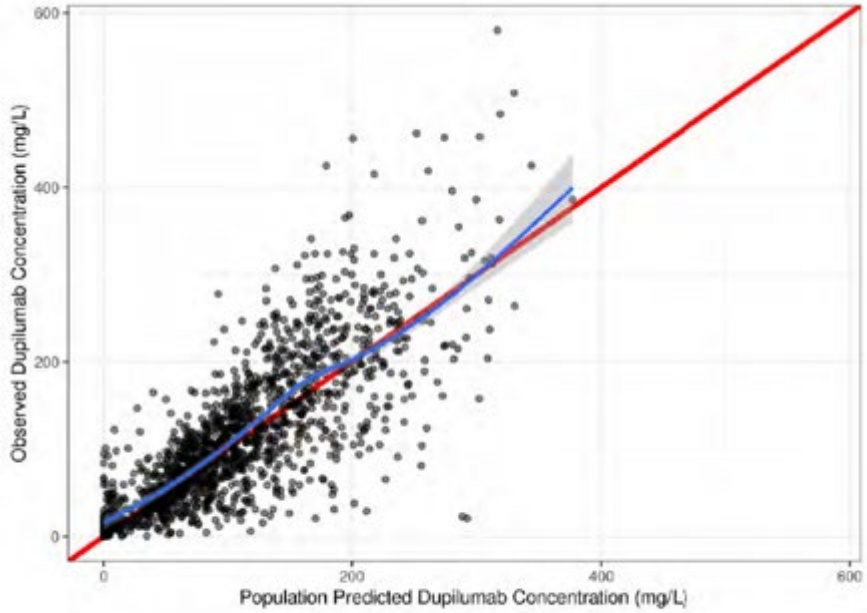
IIV was reported to be modest for CL (31.9%) and for Vss (16.2%). ETA shrinkage was low for CL (8.62%) and high for Vss (64.9%).

Model diagnostics and predictive performance

Goodness-of-fit plots (final model)

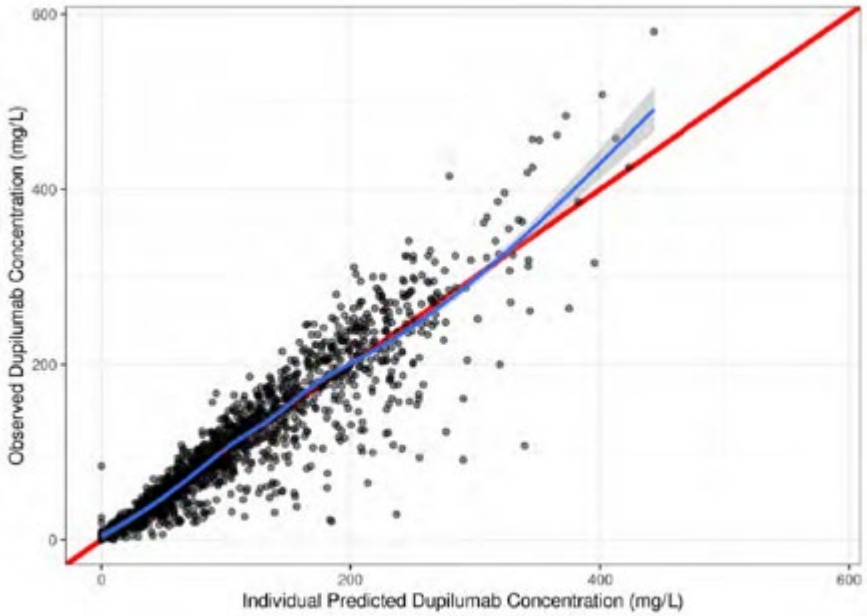
Observed vs Population/Individual Predicted Dupilumab Concentrations from the Final Model (Log Scale (bottom panels)) are provided below.

Figure 6. Observed vs Population Predicted Dupilumab Concentrations from the Final Model



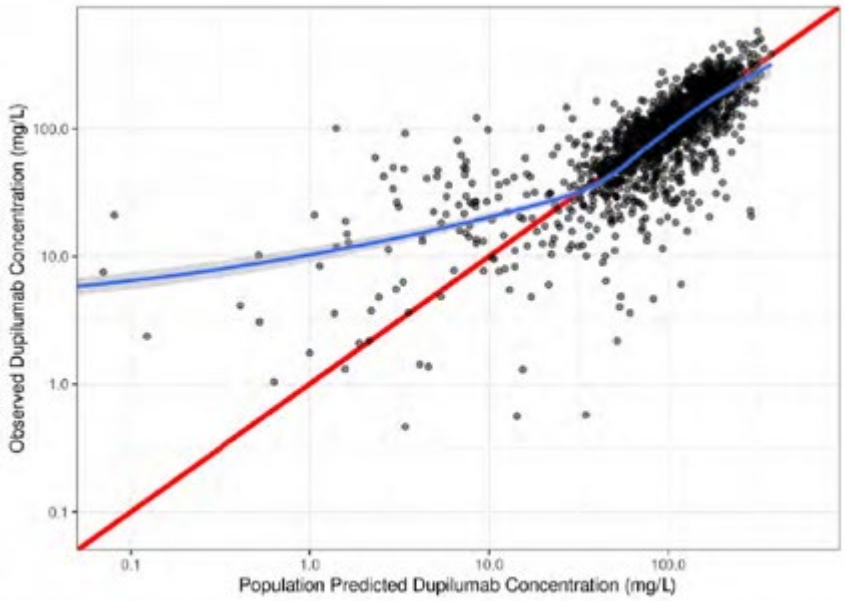
The solid red line is the line of unity. The blue line is the generalized additive model smoothing line, and the grey shaded region represents the 95% confidence interval of the line.

Figure 7. Observed vs Individual Predicted Dupilumab Concentrations from the Final Model



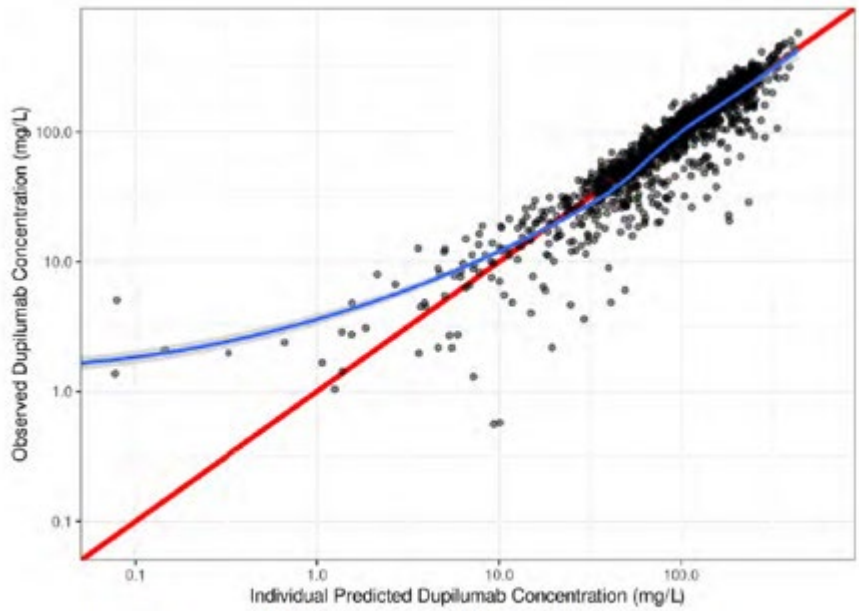
The solid red line is the line of unity. The blue line is the generalized additive model smoothing line, and the grey shaded region represents the 95% confidence interval of the line.

Figure 8. Observed vs Population Predicted Dupilumab Concentrations from the Final Model (Log Scale)



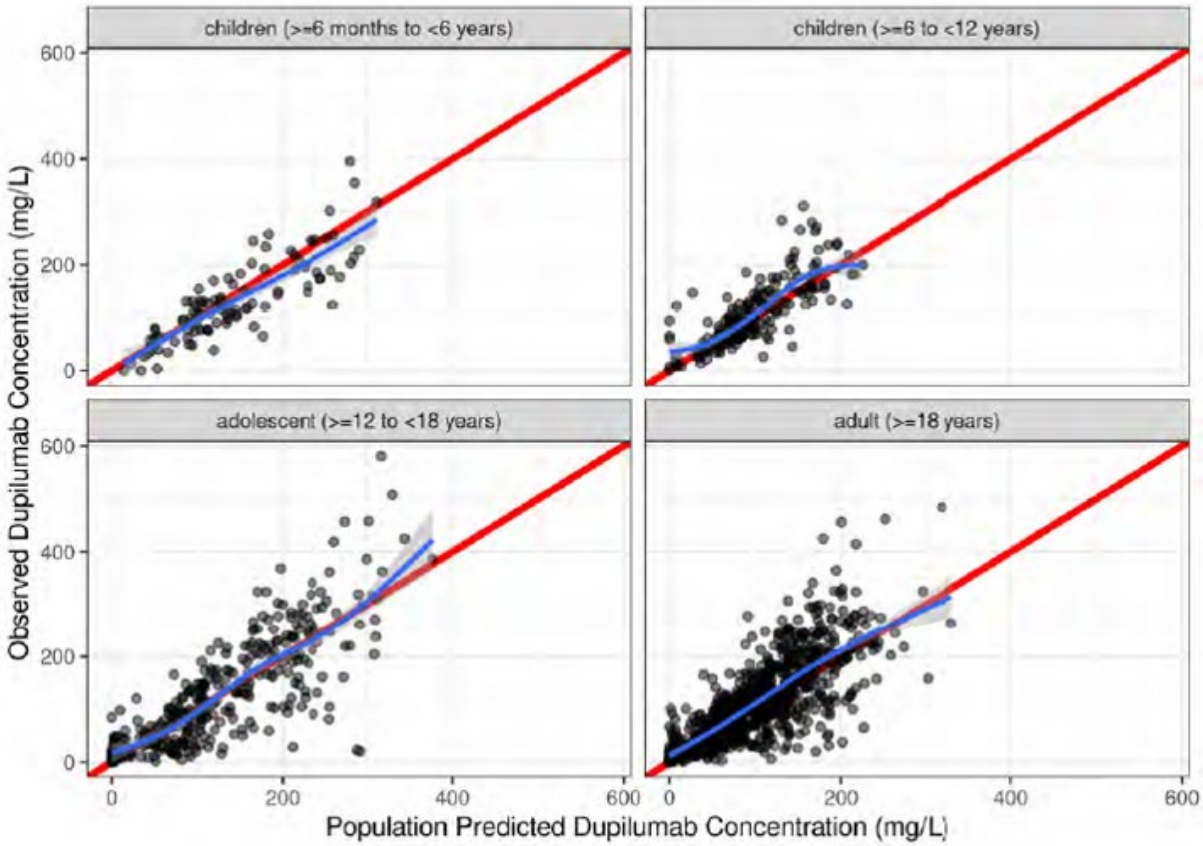
The solid red line is the line of unity. The blue line is the generalized additive model smoothing line, and the grey shaded region represents the 95% confidence interval of the line.

Figure 9. Observed vs Individual Predicted Dupilumab Concentrations from the Final Model (Log Scale)



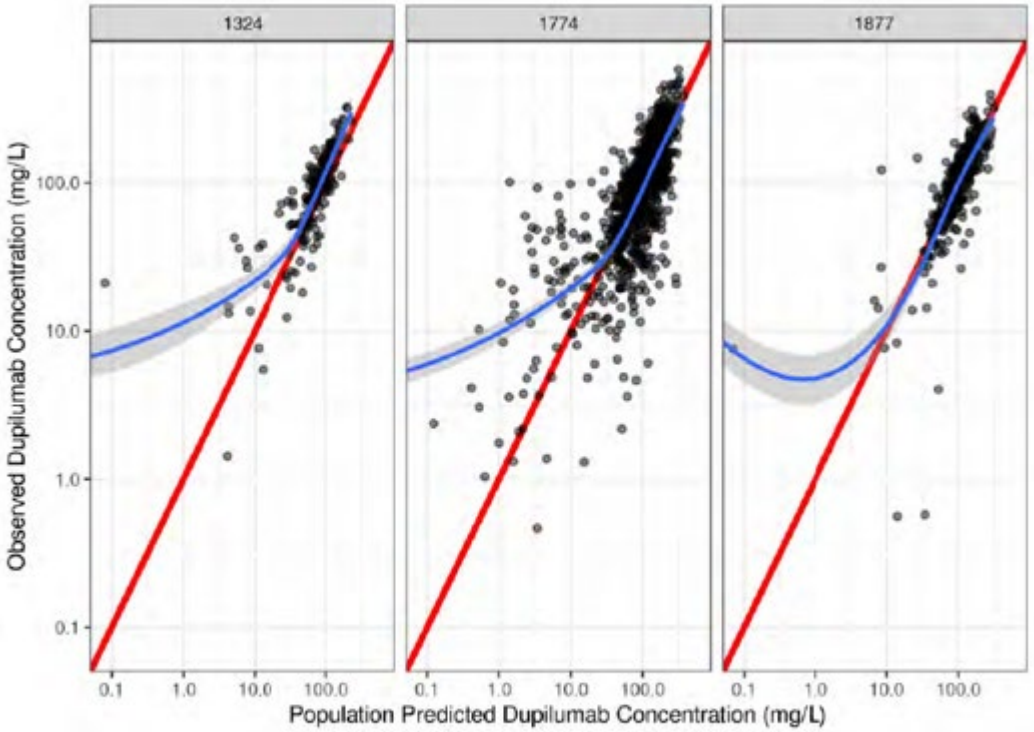
The solid red line is the line of unity. The blue line is the generalized additive model smoothing line, and the grey shaded region represents the 95% confidence interval of the line.

Figure 10. Observed vs Population Predicted Dupilumab Concentrations by Age Group from the Final Model



The solid red line is the line of unity. The blue line is the generalized additive model smoothing line, and the grey shaded region represents the 95% confidence interval of the line.

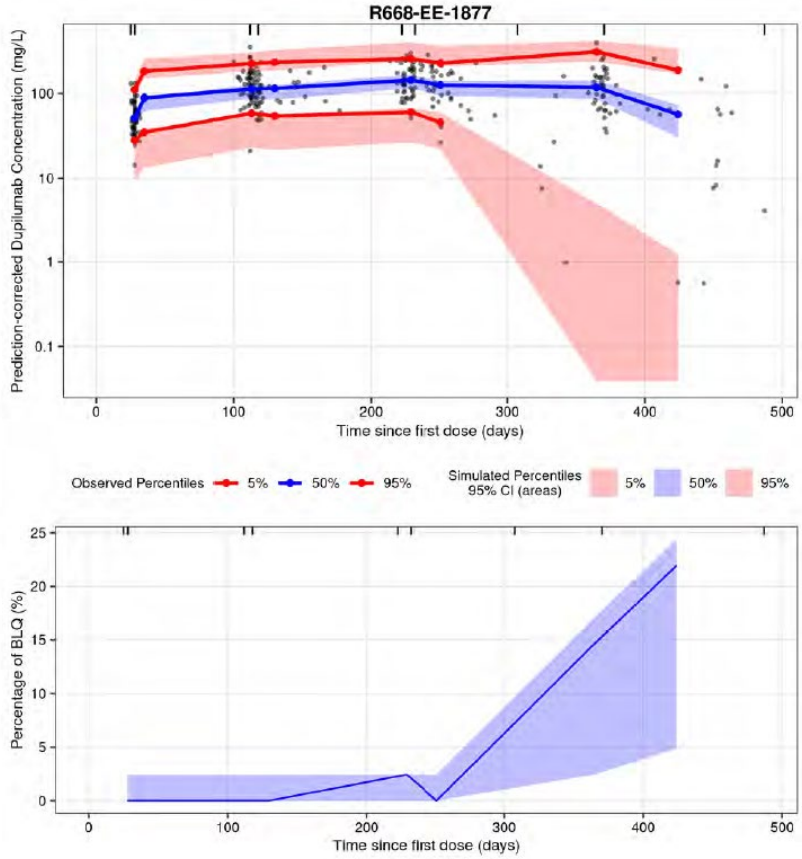
Figure 11. Observed vs Population Predicted Dupilumab Concentrations by Study from the final Model (Log Scale)



The solid red line is the line of unity. The blue line is the generalized additive model smoothing line, and the grey shaded region represents the 95% confidence interval of the line.

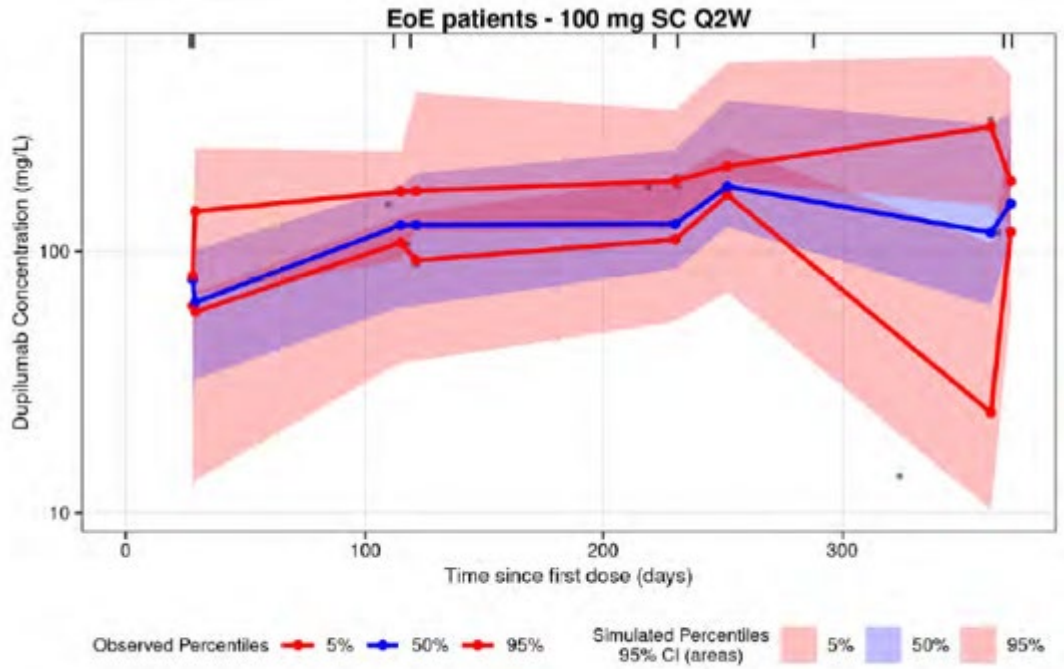
Visual predictive check plots (final model)

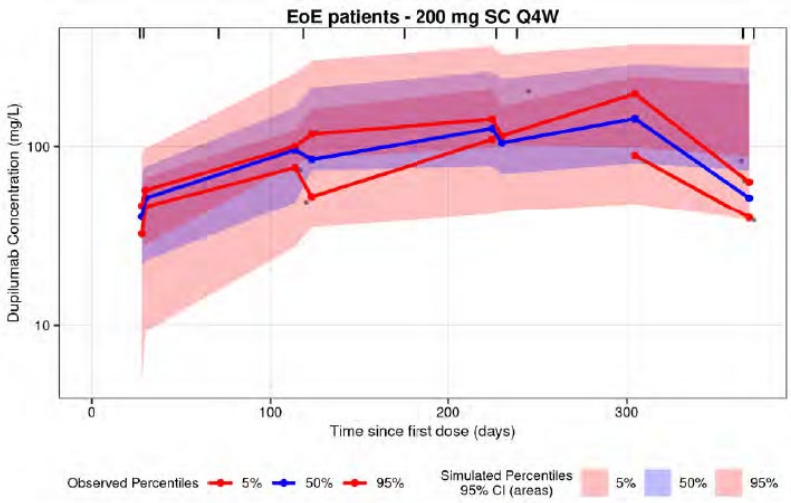
VPC plots also stratified by dose are provided below.

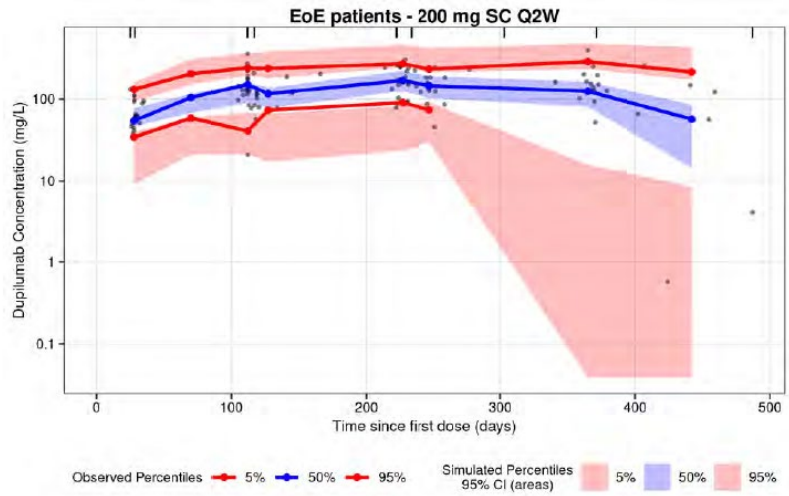


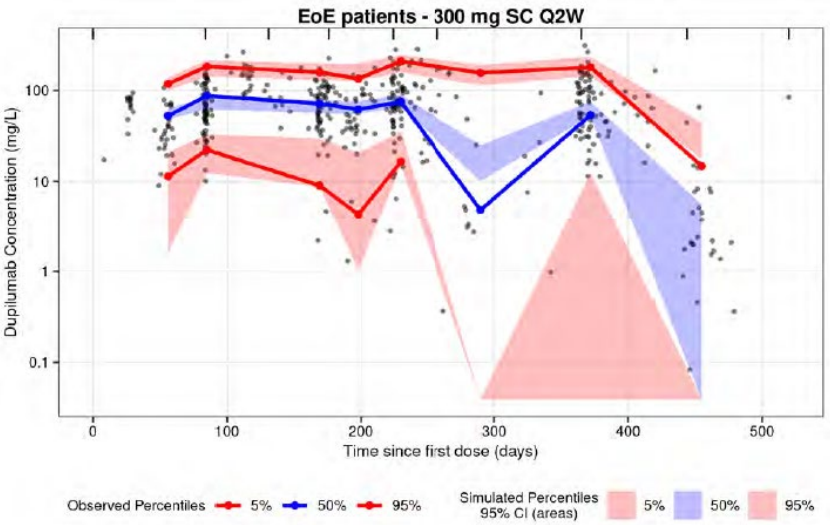
The population median is provided by the blue line, and the 5th and 95th percentiles are indicated by the red lines. The shaded bands represent the 95% confidence intervals of the median and percentiles generated from the model. The observed data is plotted using time since first dose and represented by the black points.

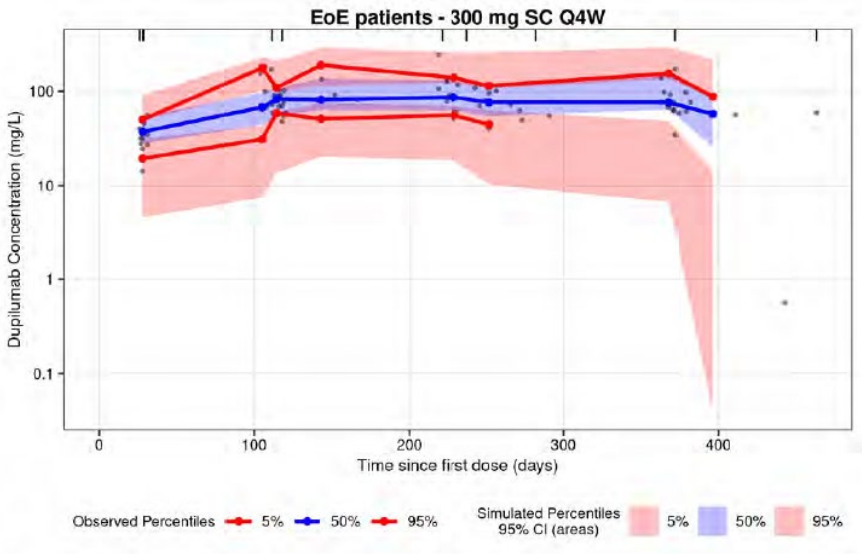
Figure 12. Visual Predictive Check by Treatment

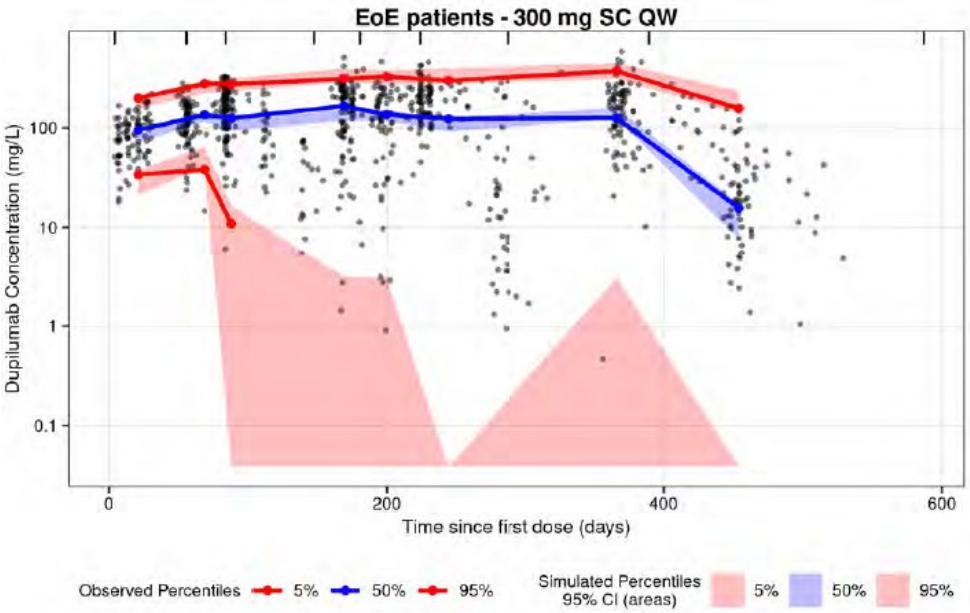





EoE patients - 200 mg SC Q2W
Dupilumab Concentration (mg/L)
100
10
1
0.1
0
100
200
300
400
500
Time since first dose (days)
Observed Percentiles 5% 50% 95%
Simulated Percentiles 95% CI (areas) 5% 50% 95%


EoE patients - 300 mg SC Q2W
Dupilumab Concentration (mg/L)
100
10
1
0.1
0
100
200
300
400
500
Time since first dose (days)
Observed Percentiles 5% 50% 95%
Simulated Percentiles 95% CI (areas) 5% 50% 95%


EoE patients - 300 mg SC Q4W
Dupilumab Concentration (mg/L)
100
10
1
0.1
0
100
200
300
400
Time since first dose (days)
Observed Percentiles 5% 50% 95%
Simulated Percentiles 95% CI (areas) 5% 50% 95%



Absorption

Based on population PK, SC bioavailability was determined to 66%, mainly informed by healthy volunteers.

Distribution

Based on population PK, Vss in the EoE population was 5.01 L, assuming a reference body weight of 70 kg for a typical patient. CV(%) was estimated to 16.2%

Elimination

Based on population PK, CL was determined to 0.145 L/day, mainly informed by healthy volunteers. CV(%) was estimated to 31.9%.

Dose proportionality and time dependencies

Dupilumab is characterized by nonlinear target-mediated kinetics.

Participants with EoE treated with dupilumab, including children (≥1 to <12 years) who received higher exposure or lower exposure dupilumab in Study R668-EE-1877 Parts A and B, achieved concentrations saturating the nonlinear clearance pathway throughout the duration of the dosing interval. Observed concentrations of functional dupilumab in children ≥1 to <12 years of age suggest dupilumab was at steady state within 16 weeks of starting higher exposure or lower exposure dupilumab.

Special populations

A descriptive summary of categorical and continuous data included in the PopPK analysis are summarized by their baseline values and provided in the Table 9 below.

Table 9. Summary of Covariates by Age Group in Patients with Eosinophilic Esophagitis

	Children (≥1 to <12 years) (N=98)	Adolescent (≥12 to <18 years) (N=97)	Adult (≥ 18 years) (N=235)	Overall (N=430)
Sex				
Female	23 (23.5%)	25 (25.8%)	98 (41.7%)	146 (34.0%)
Male	75 (76.5%)	72 (74.2%)	137 (58.3%)	284 (66.0%)
Race				
ASIAN	2 (2.0%)	2 (2.1%)	3 (1.3%)	7 (1.6%)
BLACK OR AFRICAN AMERICAN	10 (10.2%)	8 (8.2%)	2 (0.9%)	20 (4.7%)
OTHER	5 (5.1%)	6 (6.2%)	1 (0.4%)	12 (2.8%)
WHITE	81 (82.7%)	81 (83.5%)	226 (96.2%)	388 (90.2%)
NOT REPORTED	0 (0%)	0 (0%)	3 (1.3%)	3 (0.7%)
ADA Status / Maximum Titer Category				
ADA Negative	96 (98.0%)	93 (95.9%)	225 (95.7%)	414 (96.3%)
ADA Positive (Low Titer)	2 (2.0%)	3 (3.1%)	9 (3.8%)	14 (3.3%)
ADA Positive (Moderate Titer)	0 (0%)	1 (1.0%)	1 (0.4%)	2 (0.5%)
ADA Positive (High Titer)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Baseline Age (years)				
Mean (SD)	7.11 (3.09)	15.1 (1.62)	35.2 (11.5)	24.3 (15.0)
Median [5th, 95th]	8.00 [2.00, 11.3]	15.0 [12.0, 17.5]	36.0 [19.0, 55.6]	20.0 [4.00, 52.0]
(Min, Max)	(1.00, 11.4)	(12.0, 17.5)	(18.0, 68.0)	(1.00, 68.0)
Baseline Weight (kg)				
Mean (SD)	27.2 (11.2)	63.8 (16.5)	82.6 (20.1)	65.7 (28.4)
Median [5th, 95th]	25.4 [13.0, 47.2]	60.5 [45.9, 95.5]	80.4 [55.4, 121]	67.8 [16.9, 107]
(Min, Max)	(9.80, 59.9)	(40.0, 128)	(42.1, 172)	(9.80, 172)
Baseline Albumin (g/L)				
Mean (SD)	45.9 (2.40)	46.8 (3.04)	46.5 (3.07)	46.4 (2.93)
Median [5th, 95th]	46.0 [42.0, 50.0]	47.0 [41.8, 51.0]	47.0 [41.7, 51.0]	46.0 [42.0, 51.0]
(Min, Max)	(40.0, 56.0)	(37.0, 52.0)	(35.0, 55.0)	(35.0, 56.0)
Baseline peak esophageal intraepithelial eosinophil count (eos/hpf (400×))				
Mean (SD)	84.0 (40.4)	83.5 (46.6)	85.2 (50.0)	84.6 (47.1)
Median [5th, 95th]	81.0 [25.8, 154]	82.0 [24.7, 172]	78.0 [17.0, 192]	79.0 [20.2, 178]
(Min, Max)	(4.00, 209)	(3.00, 258)	(1.00, 253)	(1.00, 258)
Missing	1 (1.0%)	2 (2.1%)	2 (0.9%)	5 (1.2%)
Baseline eosinophilic esophagitis-endoscopic reference total score (Scale 0-18)				
Mean (SD)	6.97 (2.53)	6.34 (3.03)	6.91 (3.37)	6.79 (3.12)
Median [5th, 95th]	7.00 [2.00, 10.6]	6.00 [2.00, 10.9]	7.00 [2.00, 13.0]	7.00 [2.00, 12.0]
(Min, Max)	(0, 12.0)	(0, 14.0)	(0, 16.0)	(0, 16.0)
Missing	9 (9.2%)	5 (5.2%)	26 (11.1%)	40 (9.3%)
Baseline eosinophilic esophagitis-endoscopic reference total score (Scale 0-9)				
Mean (SD)			3.87 (1.87)	3.87 (1.87)
Median [5th, 95th]			4.00 [1.10, 7.00]	4.00 [1.10, 7.00]
(Min, Max)			(1.00, 7.00)	(1.00, 7.00)

	Children (≥1 to <12 years) (N=98)	Adolescent (≥12 to <18 years) (N=97)	Adult (≥ 18 years) (N=235)	Overall (N=430)
Missing	98 (100%)	97 (100%)	212 (90.2%)	407 (94.7%)
Baseline eosinophilic esophagitis histology scoring system mean grade score (Scale 0-3)				
Mean (SD)	1.27 (0.373)	1.29 (0.427)	1.21 (0.411)	1.24 (0.407)
Median [5th, 95th]	1.29 [0.613, 1.81]	1.25 [0.592, 1.96]	1.19 [0.552, 1.91]	1.24 [0.571, 1.91]
(Min, Max)	(0.321, 2.27)	(0.333, 2.24)	(0.0952, 2.38)	(0.0952, 2.38)
Missing	1 (1.0%)	2 (2.1%)	2 (0.9%)	5 (1.2%)
Baseline eosinophilic esophagitis histology scoring system mean stage score (Scale 0-3)				
Mean (SD)	1.28 (0.317)	1.31 (0.365)	1.22 (0.367)	1.25 (0.357)
Median [5th, 95th]	1.35 [0.693, 1.67]	1.38 [0.675, 1.83]	1.25 [0.512, 1.75]	1.29 [0.590, 1.76]
(Min, Max)	(0.315, 1.83)	(0.111, 2.04)	(0, 2.07)	(0, 2.07)
Missing	1 (1.0%)	2 (2.1%)	2 (0.9%)	5 (1.2%)
Baseline dysphagia symptom questionnaire (DSQ) total score (Scale (0-84)				
Mean (SD)		30.9 (17.1)	31.4 (15.4)	31.2 (15.9)
Median [5th, 95th]		35.5 [0, 53.6]	34.7 [1.10, 52.4]	35.0 [0, 53.2]
(Min, Max)		(0, 70.0)	(0, 70.0)	(0, 70.0)
Missing	98 (100%)	0 (0%)	23 (9.8%)	121 (28.1%)
Baseline proportion of days with ≥1 signs or symptoms as assessed by the pediatric EoE sign/symptom questionnaire caregiver version (PESQ-C)				
Mean (SD)	0.493 (0.395)			0.493 (0.395)
Median [5th, 95th]	0.500 [0, 1.00]			0.500 [0, 1.00]
(Min, Max)	(0, 1.00)			(0, 1.00)
Missing	2 (2.0%)	97 (100%)	235 (100%)	334 (77.7%)

ADA = anti-drug antibody; BLQ = below limit of quantification; eos/hpf = eosinophils per high-power field; N = number of patients; SD = standard deviation.

Note: Negative ADA status (ie, no treatment-emergent ADA) means that the subject did not exhibit ADA, pre-existing ADA levels were not treatment-boosted, or did not fall into the categories of low, moderate, or high, defined as: (1) 'low' >0 to <1000, (2) 'moderate' ≥1000 to <10000, and (3) 'high' ≥10000

Body weight

Body weight is the primary covariate affecting the PK of dupilumab in adult and pediatric participants with EoE, consistent with previous findings in other disease populations and age groups. Increasing body weight is associated with decreasing concentrations of dupilumab at a fixed dose (see Figure 19). The PK of dupilumab is indicated to be highly consistent across patients with AD, asthma, CRSwNP, EoE, PN, and healthy participants. While most models utilized baseline body weight as a covariate, time-varying body weight was implemented in the model to describe dupilumab PK for children ≥6 to <12 years with asthma treated for ≥1 year.

For the description of PK in EoE patients from 1 year of age (from 5 kg of weight) time-varying body weight effects have been implemented in the model-based description of PK, while additional maturation effects have not been accounted for.

Apparent increases in clearance with age, after accounting for the effects of baseline body weight, were described by a maturation function for clearance in paediatric participants ≥6 months to <6 years of age with AD.

Age

The population PK analysis demonstrated that in adult and pediatric (≥1 to <18 years) participants with EoE, after accounting for body weight, including changes in weight over time for pediatric participants, age was not a significant covariate on the PK of dupilumab in the final model.

Baseline Disease Activity

EoE disease severity, as assessed by peak esophageal intraepithelial eosinophil counts, was not observed to be a significant covariate on the PK of dupilumab. The median baseline peak esophageal intraepithelial eosinophil count for the youngest patients was similar to the count in the overall population (81.0 vs 79.0 eos/hpf, respectively). Median baseline EoE-endoscopic reference total scores, provided on a scale of 0-18, were similar across all age groups included in the PopPK analysis; this was also true for both the baseline EoE histology scoring system mean stage and grade scores.

PK in the target population

Simulations for paediatric patients 1 to 11 years of age were conducted with a population pharmacokinetic model to predict trough concentrations of dupilumab at steady-state as follows: ≥15 to <30 kg receiving 200 mg Q2W (170±78 mcg/mL); ≥30 to <40 kg receiving 300 mg Q2W (158±63 mcg/mL); or ≥40 kg receiving 300 mg QW (276±99 mcg/mL). Steady-state trough concentrations were also simulated for adult and paediatric patients 12 to 17 years of age and patients from ≥30 to <40 kg receiving 300 mg Q2W (159±61 mcg/mL).

Observed and predicted exposure based on the final pop PK model are presented below.
As the model is considered not adequate for application – in particular regarding the predictiveness of exposure in the paediatric weight group 5-15 kg – model-based results should be interpreted with caution.

Table 10. Summary Statistics of Steady-State Exposure Predictions of Dupilumab by Weight-Tiered Dose Regimen in Children (≥1 to <12 Years) or in Adults and Adolescents ≥40 kg, Median (P5, P95)

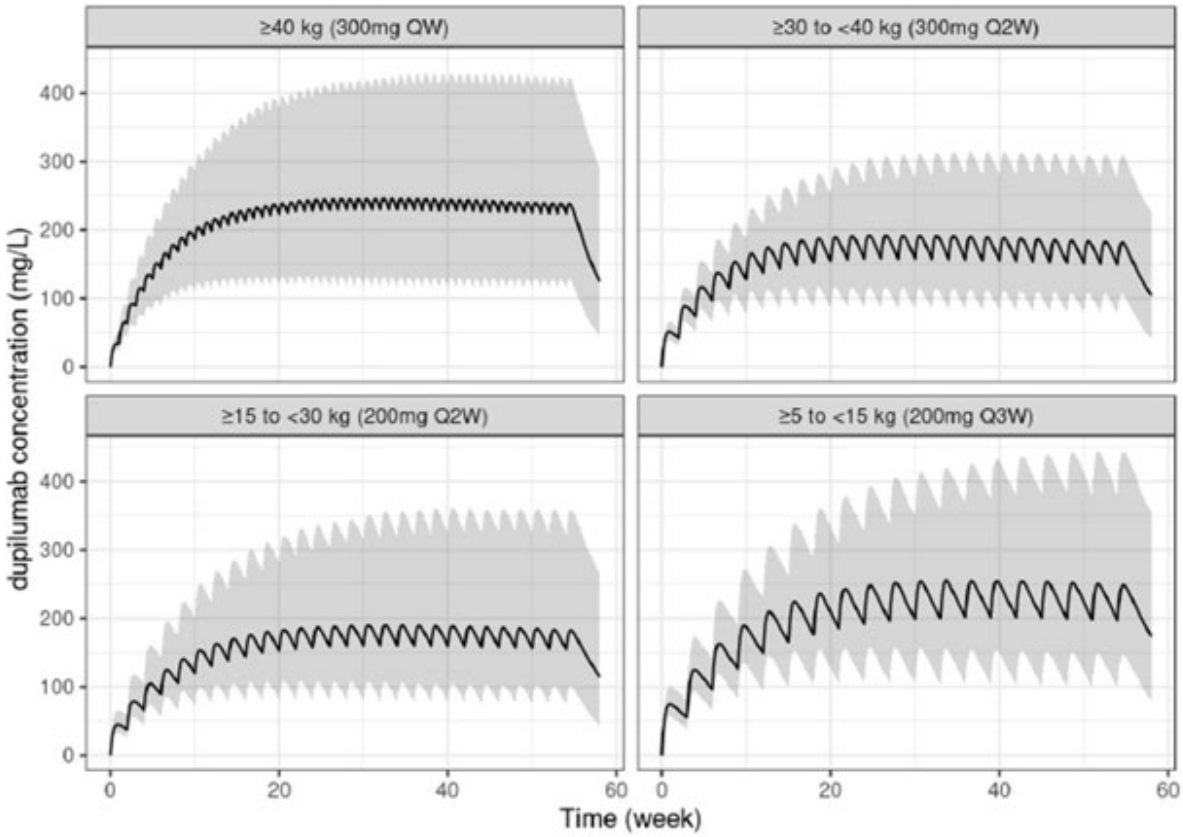
Dose and Weight	Group	$AUC_{4wks,ss}$ (mg*d/L)	$AUC_{tau,ss}$ (mg*d/L)	$C_{max,ss}$ (mg/L)	$C_{trough,ss}$ (mg/L)
300 mg QW, ≥40 kg	Adults and adolescents ≥12 years	6074 (3404, 10951)	1518 (851, 2738)	222 (126, 396)	207 (113, 383)

Table 11. Statistics of Steady-State Exposure Predictions by Weight-Tiered Dose Regimen in Children (≥1 to <12 Years) with EoE with Proposed Posoloy, Median (P5, P95)

Group	Treatment	$AUC_{4wks,ss}$ (mg*day/L)	$AUC_{tau,ss}$ (mg*day/L)	$C_{max,ss}$ (mg/L)	$C_{trough,ss}$ (mg/L)
≥40 kg	300 mg QW	7585 (4194, 12979)	1896 (1049, 3245)	277 (155, 470)	261 (140, 452)
≥30 to <40 kg	300 mg Q2W	4670 (2674, 8120)	2335 (1337, 4060)	180 (107, 304)	147 (77, 269)
≥15 to <30 kg	200 mg Q2W	4740 (2548, 9522)	2370 (1274, 4761)	180 (102, 352)	152 (76, 322)
≥5 to <15 kg	200 mg Q3W	6236 (3437, 11210)	4677 (2578, 8407)	246 (144, 425)	194 (96, 366)

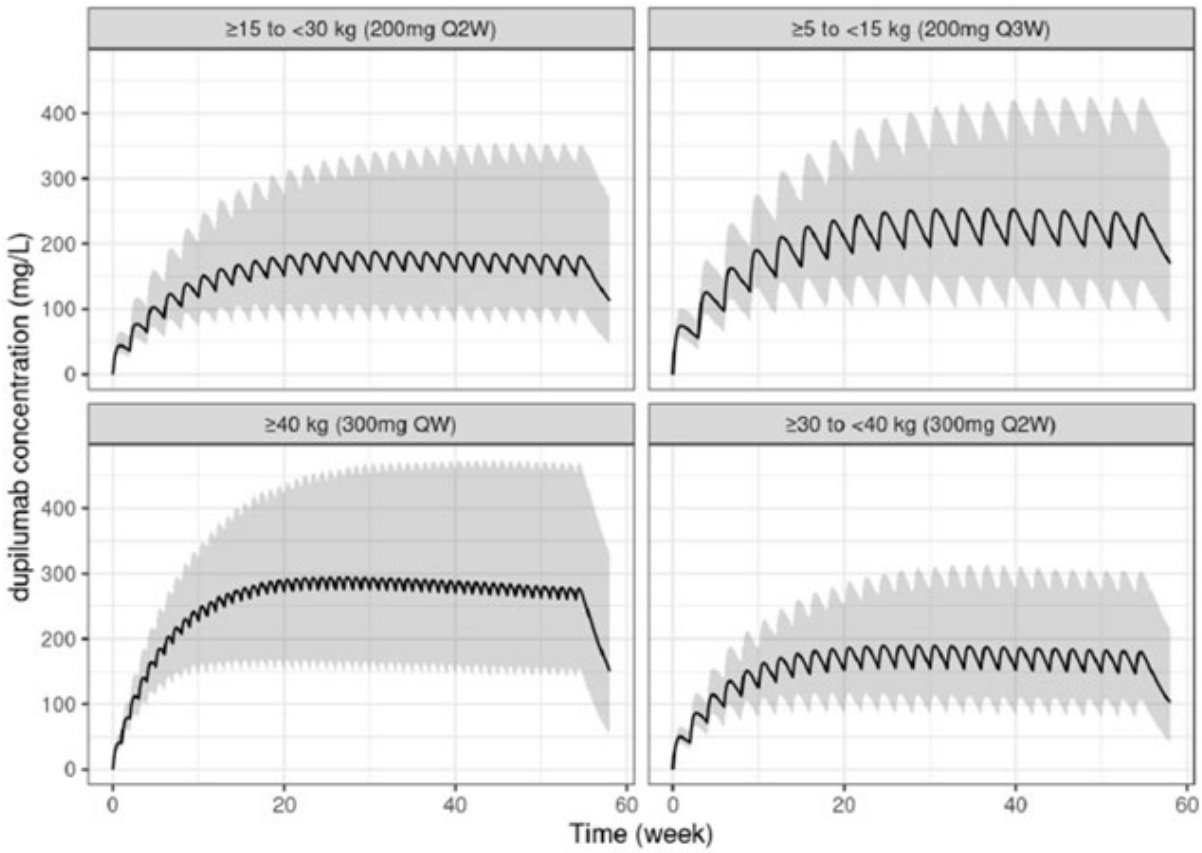
Abbreviations: AUC=area under the concentration-time curve; $AUC_{4wks,ss}$=AUC at steady-state over 4 weeks; $AUC_{tau,ss}$=AUC at steady-state over the dosing interval; $C_{max,ss}$=maximum concentration within the steady-state dosing interval; $C_{trough,ss}$=concentration at the end of steady-state dosing interval; P5=5th percentile; P95=95th percentile; QW=once weekly; Q2W=every 2 weeks; Q3W=every 3 weeks.
Note: For Q3W, $AUC_{4wk,ss} = AUC_{tau,ss} \times \frac{4}{3}$

Figure 13. Predicted Concentration by Weight-Tiered Dose Regimen in Adult and Pediatric Patients (≥1 Year of Age) with Eosinophilic Esophagitis with Proposed Posology



The population median is provided by the line, and the 5th and 95th percentiles are indicated by shaded region.

Figure 14. Predicted Concentration by Weight-Tiered Dose Regimen in Children (≥1 to <12 Years of Age) with Eosinophilic Esophagitis with Proposed Posology



The population median is provided by the line, and the 5th and 95th percentiles are indicated by shaded region.

Table 12. Summary Statistics of Steady-State Exposure Predictions by Weight-tiered Dose Regimen in Children (≥1 to <12 Years) with EoE to Support 200 mg Q3W for Participants ≥5 to <15 kg, Median (P5, P95)

Treatment Group	Bodyweight Group	Age	$AUC_{4wks,ss}$ (mg*day/L)[a]	$AUC_{tau,ss}$ (mg*day/L)	$C_{max,ss}$ (mg/L)	$C_{trough,ss}$ (mg/L)
100 mg Q2W	≥5 to <15 kg	≥1 to <12 yr	4528 (2431, 8259)	2264 (1215, 4130)	171 (95, 306)	149 (75, 278)
200 mg Q4W			4533 (2581, 8391)	4533 (2581, 8391)	189 (117, 327)	131 (64, 260)
200 mg Q3W			6236 (3437, 11210)	4677 (2578, 8407)	246 (144, 425)	194 (96, 366)

Abbreviations: AUC=area under the concentration-time curve; $AUC_{4wks,ss}$=AUC at steady-state over 4 weeks; $AUC_{tau,ss}$=AUC at steady-state over the dosing interval; $C_{max,ss}$=maximum concentration within the steady-state dosing interval; $C_{trough,ss}$=concentration at the end of steady-state dosing interval.
Note: For Q3W, $AUC_{4wks,ss}=AUC_{tau,ss}\times 4/3$

Table 13. Summary Statistics of Steady-State Exposure Predictions for Dupilumab 300 mg QW in Adults, Adolescents, and Children (≥1 to <12 Years) with EoE Weighting ≥40 to <60 kg by Age Group, Median (P5, P95)

Dose Regimen	Body Weight	Age Group	$AUC_{4wks,ss}$ (mg*day/L)	$AUC_{tau,ss}$ (mg*day/L)	$C_{max,ss}$ (mg/L)	$C_{trough,ss}$ (mg/L)
300 mg QW	≥40 kg to <60 kg	Adults and adolescents	7185 (4024, 12401)	1796 (1006, 3100)	262 (148, 449)	247 (135, 433)
		≥1 to <12 years	7775 (4304, 13809)	1944 (1076, 3452)	284 (159, 499)	267 (144, 482)

Abbreviations: AUC=area under the concentration-time curve; $AUC_{4wks,ss}$=AUC at steady-state over 4 weeks; $AUC_{tau,ss}$=AUC at steady-state over the dosing interval; $C_{max,ss}$=maximum concentration within the steady-state dosing interval; $C_{trough,ss}$=concentration at the end of steady-state dosing interval; QW=once weekly.

Table 14. Simulated Ctrough by Time Point and Weight Band in Pediatric Patients ≥1 to <18 Years of Age with EoE

Weight Group	Dupilumab Dose Regimen	Ctrough (mg/L), median (P5, P95)			
		Week 16*	Week 24	Week 32**	Week 52***
≥5 to <10 kg	200 mg Q3W	269 (177, 383)	301 (184, 454)	310 (179, 492)	302 (169, 517)
≥10 to <15 kg	200 mg Q3W	179 (105, 263)	197 (109, 311)	201 (108, 333)	196 (103, 345)
≥15 to <30 kg	200 mg Q2W	165 (91, 286)	178 (91, 321)	179 (90, 336)	175 (85, 340)

* For Q3W regimens, trough concentrations were determined following Week 15 dosing
** For Q3W regimens, trough concentrations were determined following Week 33 dosing
*** For Q3W regimens, trough concentrations were determined following Week 51 dosing

Comparison of Ctrough observed across studies

Table 15. Summary of Trough Concentrations of Functional Dupilumab in Serum by Study for Participants with EoE Receiving Dupilumab in Study R668-EE-1877 or Study R668-EE-1774 (PKAS)

		Week 16 (N=60)		Week 24 (N=175)		Week 52 (N=358)	
Dupilumab Treatment Group or Dose Regimen	Population	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Dupilumab 300 mg QW	Adult/adolescent EoE, ≥40 kg	0		101	196 (86.3)	170	159 (99.4)
Dupilumab 300 mg Q2W	Adult/adolescent EoE, ≥40 kg	0		74	73.6 (46.0)	106	65.7 (43.1)
Higher Exposure Dupilumab	1 to <12 years, 5 to <60 kg	33	159 (60.3)	0		45	169 (71.2)
100 mg Q2W	1 to <12 years, 5 to <15 kg	3	135 (34.9)	0		3	132 (26.9)
200 mg Q2W	1 to <12 years, 15 kg to <30 kg	17	164 (73.9)	0		20	179 (84.7)
300 mg Q2W	1 to <12 years, 30 kg to <60 kg	13	157 (44.9)	0		22	166 (61.3)
Lower Exposure Dupilumab	1 to <12 years, 5 to <60 kg	27	86.6 (28.8)	0		37	89.2 (37.9)
200 mg Q4W	1 to <12 years, 5 to <15 kg	4	86.3 (31.4)	0		2	61.0 (31.7)
300 mg Q4W	1 to <12 years, 15 kg to <30 kg	16	85.2 (29.6)	0		21	87.1 (42.1)
200 mg Q2W	1 to <12 years, 30 kg to <60 kg	7	89.8 (29.7)	0		14	96.4 (31.3)

Abbreviations: BLQ=below limit of quantitation; EoE=eosinophilic esophagitis; N=number of participants; PKAS=pharmacokinetic analysis set; Q2W=every 2 weeks; Q4W=every 4 weeks; QW=once weekly; SD=standard deviation.

2.3.3. Pharmacodynamics

Mechanism of action

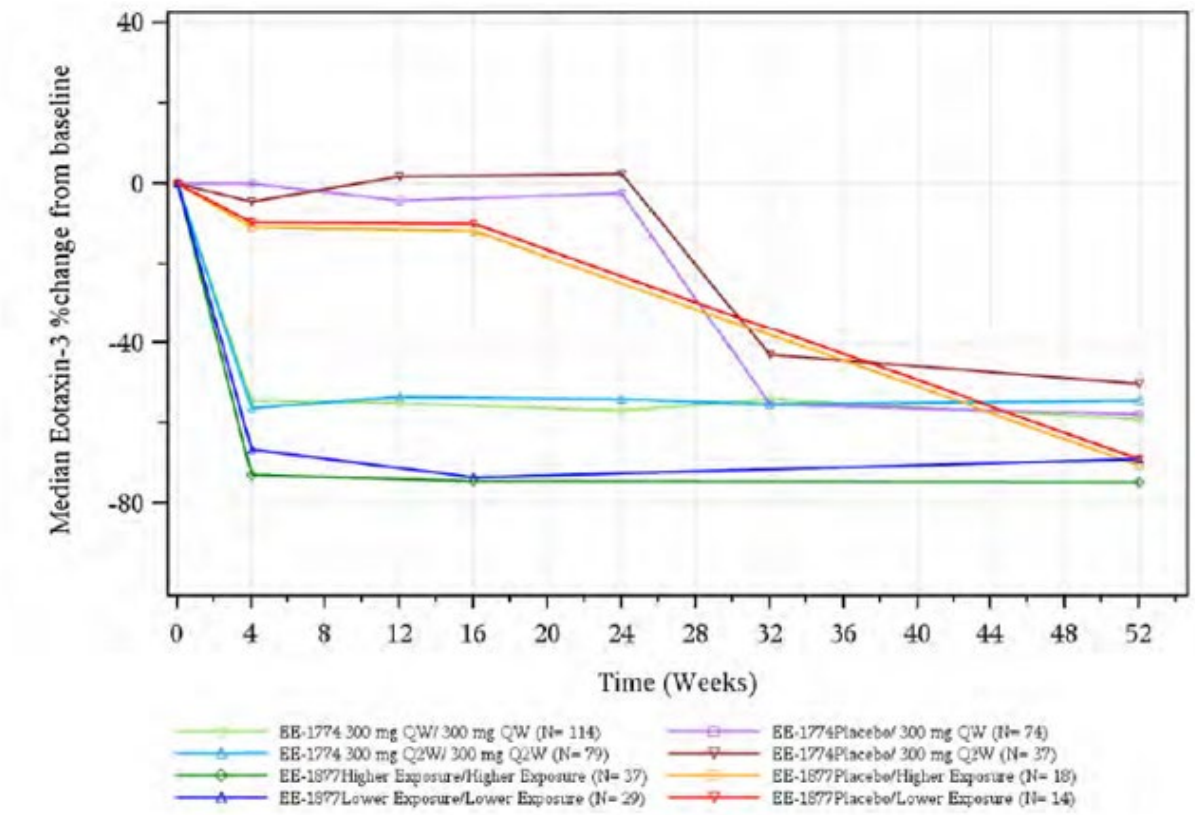
Dupilumab is a human monoclonal IgG4 antibody that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the type I receptor and both IL-4 and IL-13 signaling through the type II receptor. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide, and IgE, therefore, broadly suppressing type 2 inflammation.

Primary and secondary pharmacology

Plasma eotaxin-3

Concentrations of plasma eotaxin-3 were assessed as a biomarker of type-2 inflammation in children ≥ 1 to <12 years of age with EoE. Eotaxin-3 in plasma was measured at baseline and at weeks 4 and 16 (in Part A) and at week 52 (in Part B) in Study R668-EE-1877, and at baseline and weeks 4, 12, and 24 (in Parts A and B) and weeks 32 and 52 (in Part A/C or B/C) in Study R668-EE-1774 (see Figure 15 below).

Figure 15. Comparison of the Median Percent Change from Baseline in Plasma Eotaxin-3 by Treatment Group in Adult and Pediatric Participants ≥1 Year of Age with EoE (SAF)



Abbreviations: BLQ=below limit of quantitation; EoE=eosinophilic esophagitis; N=number of participants; Q2W=every 2 weeks; QW=once weekly; SAF=safety analysis set.

Eotaxin-3 concentrations in plasma reached a nadir within 4 weeks of starting treatment for participants who received dupilumab during the double-blind treatment period (ie, through week 16 in R668-EE-1877 and week 24 in R668-EE-1774), and remained suppressed throughout the treatment period (ie, through week 52). Dupilumab treatment provides a marked reduction in eotaxin-3, a chemokine associated with eosinophil recruitment, and reached a maximum effect within 4 weeks of starting treatment.

2.3.4. PK/PD modelling

Circulating Biomarkers

Treatment with higher exposure or lower exposure dupilumab in Part A and B of this study reduced biomarkers of type 2 inflammation (plasma eotaxin-3 and serum total IgE) relative to placebo treatment. No consistent association was observed between baseline total IgE or eotaxin-3 and treatment response (histological response). Median percent decreases in plasma eotaxin-3 were consistently greater for children ≥1 to <12 years of age with EoE than in adults and adolescents with EoE, even following the low dose regimen. Similar effect across low and high dupilumab treatment groups within each population (see Figure 15 above).

Exposure-Response Analysis for Efficacy

E-R for efficacy was evaluated for the peak esophageal intraepithelial eosinophil counts (proportion of participants achieving ≤6 eos/hpf [400×] and percent change from baseline, histology) in Study R668-EE-1877 (Parts A and B) and Study R668-EE-1774 (Parts A, B, A/C, and B/C), the proportion of days with 1 or more EoE signs by PESQ-C (change from baseline and percent change from baseline) in Study R668-EE-1877 (Parts A and B), and frequency and severity of EoE symptoms by PEESSv2.0-Caregiver (change from baseline) in Study R668-EE-1877 (Part A).

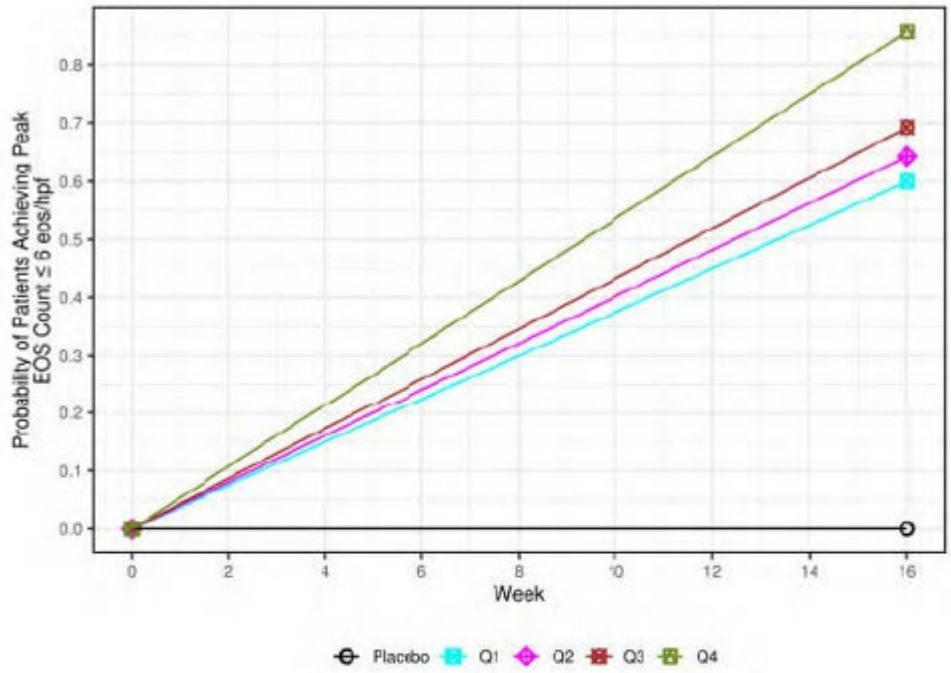
Peak esophageal intraepithelial eosinophil counts ≤6 eos/hpf (400×)

The proportion of participants achieving peak esophageal intraepithelial eosinophil counts ≤6 eos/hpf (400×) was assessed as the primary efficacy endpoint at week 16 in Study R668-EE-1877 Part A, a co-primary endpoint at week 24 in Study R668-EE-1774 Parts A and B, and as a secondary endpoint at week 52 in Studies R668-EE-1877 Part B and R668-EE-1774 Parts A/C and B/C. Logistic regression was performed on this binary endpoint to investigate the potential relationship between the probability of achieving peak esophageal intraepithelial eosinophil counts ≤6 eos/hpf (0 if >6 eos/hpf, 1 if ≤6 eos/hpf) and trough concentrations of dupilumab at corresponding timepoints. The continuous endpoint of percent change from baseline in peak esophageal intraepithelial eosinophil counts was assessed as a secondary endpoint in Study R668-EE-1877 Parts A and B and Study R668-EE-1774 Parts A, B, A/C, and B/C. Scatter plots were used to investigate the relationship between percent change from baseline in peak esophageal intraepithelial eosinophil counts and trough concentrations of dupilumab at corresponding timepoints for each population.

Study R668-EE-1877 Part A (Double-Blind, Placebo-Controlled 16-week Treatment Period)

Both the higher exposure and lower exposure dupilumab regimens significantly improved the proportion of participants achieving a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf (ie, histologic remission) relative to placebo at week 16.

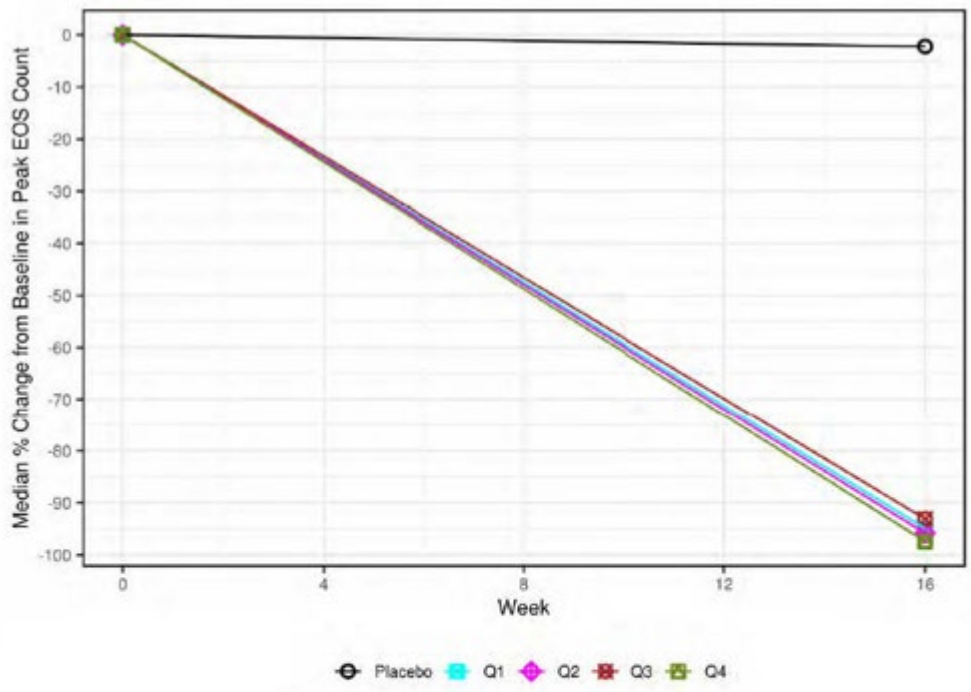
Figure 16. Proportion of Patients Achieving Eosophageal Intraepithelial Eosinophil Count ≤6 eos/hpf by Quartile of Functional Dupilumab Concentration in Serum at Week 16 in Pediatric Patients ≥1 to <12 Years with Eosinophilic Esophagitis (Study R688-EE-1877, Part A)



Quartile	Week 16
Placebo	0/26
Q1	9/15[0-83.2]
Q2	9/14[83.2<-114.0]
Q3	9/13[114.0<-170.0]
Q4	12/14[170.0<-355.0]

Note: BLQ concentrations were set to 0. The table shows the number of patients achieving a response over total number of patients in each concentration quartile at each time point, and the quartile range in parentheses. The primary imputation strategy was applied to clinical response endpoints; missing drug concentrations were not imputed.

Figure 17. Median Peak Esophageal Intraepithelial Eosinophil Count Percent Change from Baseline to Week 16 by Quartiles of Functional Dupilumab Trough Concentration in Serum at Week 16 in Pediatric Patients ≥1 to <12 Years with Eosinophilic Esophagitis (Study R668-EE-1877, Part A)

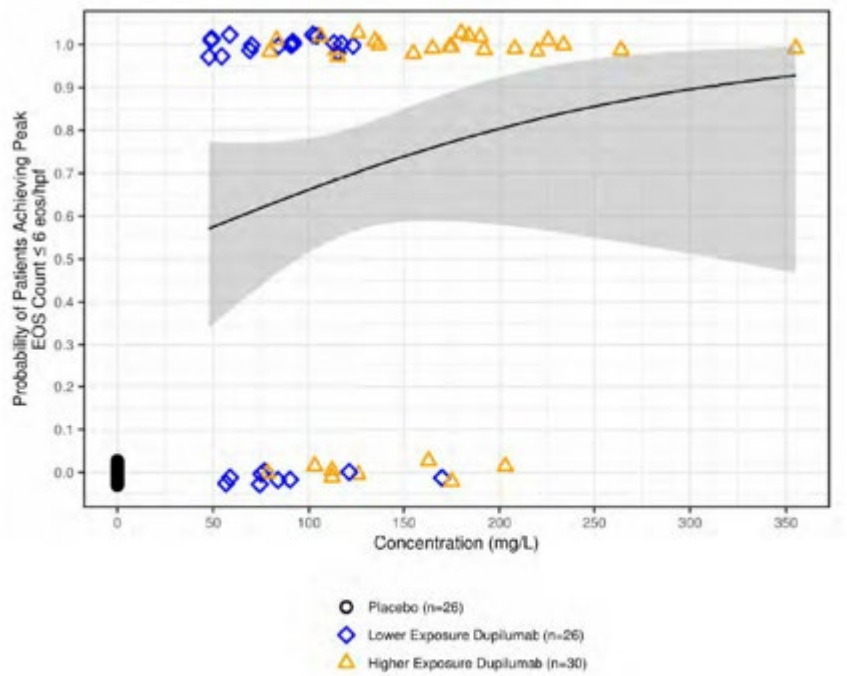


Quartile	Week 16
Placebo	26
Q1	15 [0-83.2]
Q2	14 [83.2<-114.0]
Q3	13 [114.0<-170.0]
Q4	14 [170.0<-355.0]

Note: BLQ concentrations were set to 0. The table shows the total number of patients in each concentration quartile at each time point, as well as the quartile range in parentheses. The primary imputation strategy was applied to clinical response endpoints; missing drug concentrations were not imputed.

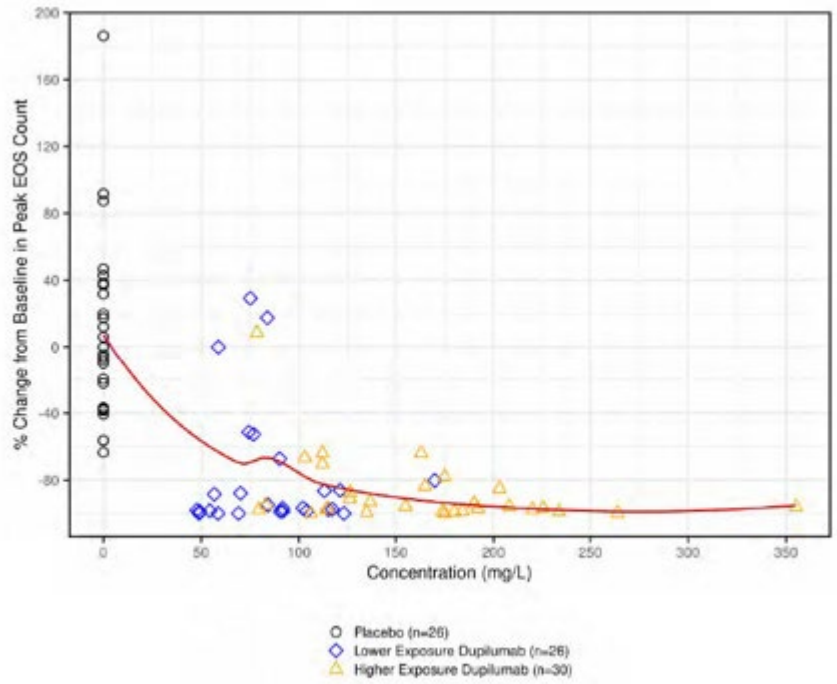
Based on a logistic regression analysis, a shallow, positive relationship was observed between increasing concentrations of dupilumab and a greater probability of achieving a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf (ie, histologic remission) at week 16.

Figure 18. Logistic Regression Relating Probability of Patients Achieving Histologic Response of Peak Esophageal Intraepithelial Eosinophil Count of <6 eos/hpf versus Trough Concentration of Functional Dupilumab at Week 16 in Pediatric Patients ≥1 to <12 Years with Eosinophilic Esophagitis (Study R668-EE-1877, Part A)



n = Number of patients
Note: BLQ concentrations were set to 0. The primary imputation strategy was applied to clinical response endpoints; missing drug concentrations were not imputed.

Figure 19. Plot of Peak Esophageal Intraepithelial Eosinophil Count Percent Change from Baseline versus Trough Concentration of Functional Dupilumab at Week 16 by Treatment Group in Pediatric Patients ≥1 to <12 Years with Eosinophilic Esophagitis (Study R668-EE-1877, Part A)

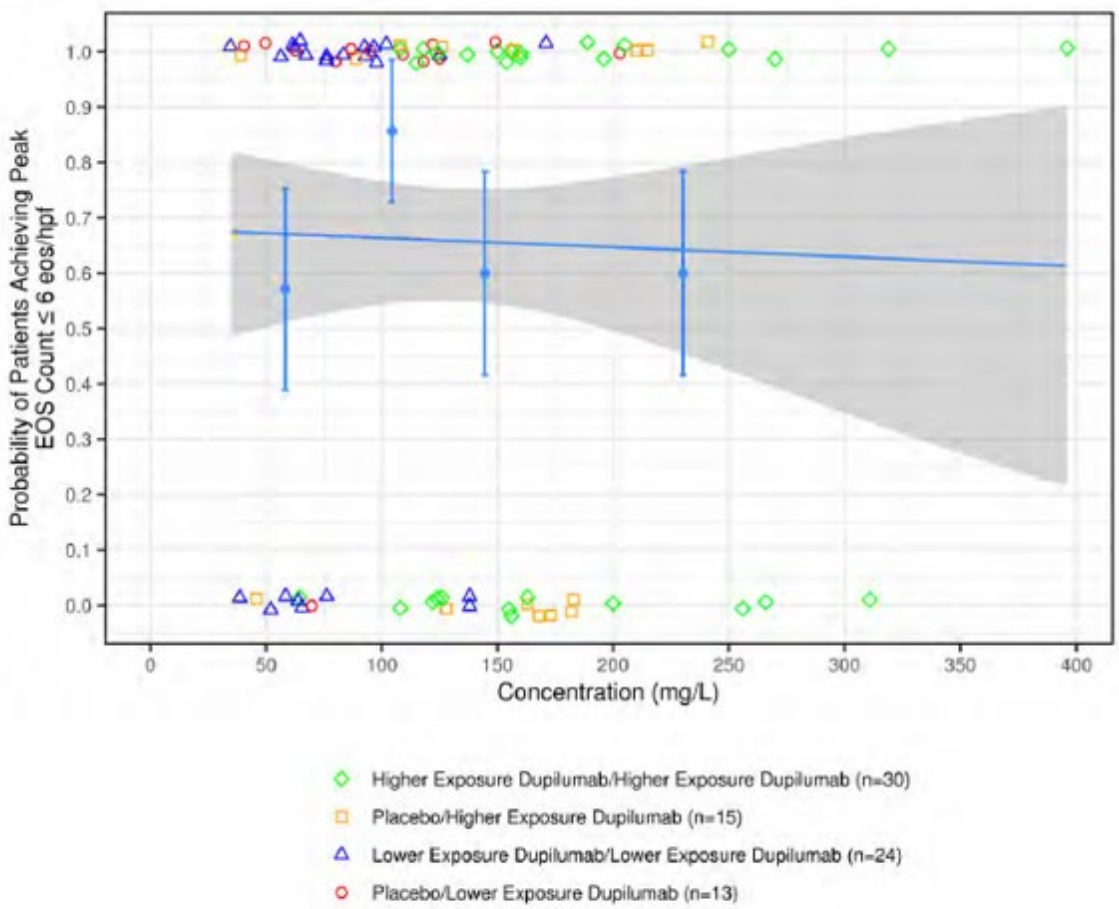


n = Number of patients
Note: BLQ concentrations were set to 0. Regression line LOESS (smooth 0.8). The primary imputation strategy was applied to clinical response endpoints; missing drug concentrations were not imputed.

Study R668-EE-1877 Part B (36-week Extended Active Treatment Period)

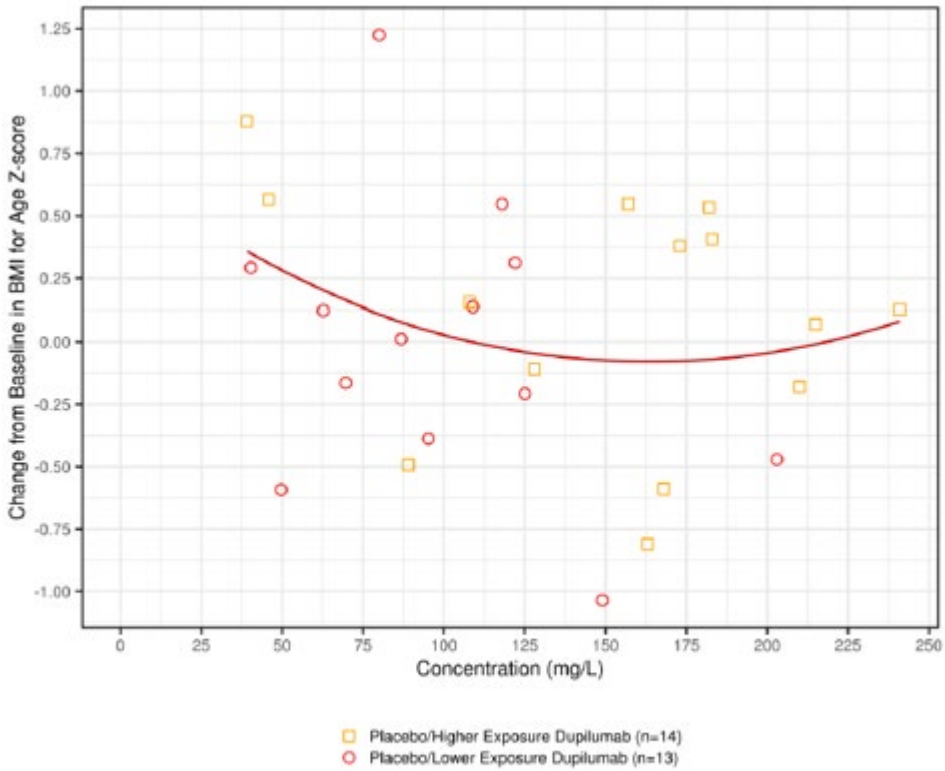
Logistic regressions for the probability of participants achieving a histologic response of peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf versus Ctrough of dupilumab at week 52 are presented by treatment group:

Figure 20. Logistic Regression Relating Probability of Participants Achieving Histologic Response of Peak Esophageal Intraepithelial Eosinophil Count of ≤6 eos/hpf versus Trough Concentration of Functional Dupilumab in Serum at Week 52 in Pediatric Participants ≥1 to <12 Years with EoE in Part B (Study R668-EE-1877, CRAS)



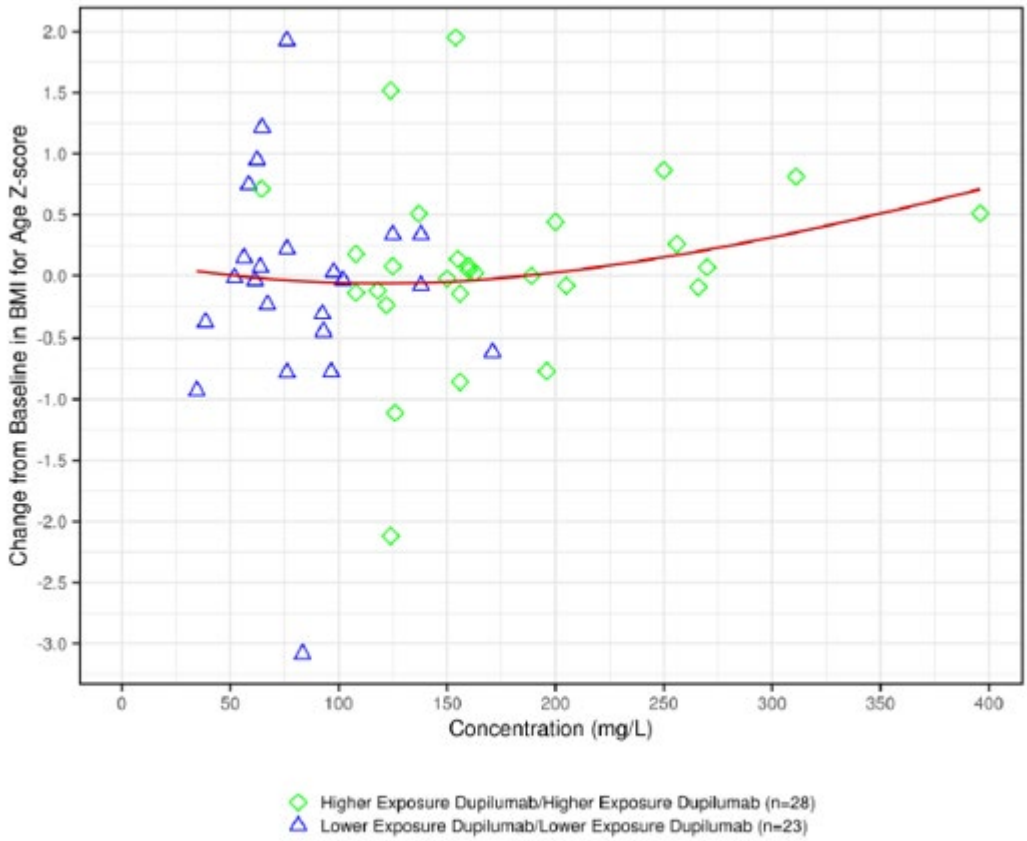
n = Number of participants
Note: BLQ concentrations were set to 0. The mean regression line is black. The confidence area around regression line is grey. Non-responders (0) and responders (1) individual concentration values are jittered and represented at the bottom and top of the figure respectively. Means of response and 90% confidence intervals (blue vertical lines) are presented in the figures for each exposure concentration quartile and are placed at the means of each concentration interquartile ranges on the x-axis.

Figure 21. Plot of Change from Baseline in BMI for Age Z-score vs. Trough Concentration of Functional Dupilumab at Week 52 by Treatment Group in Pediatric Patients 1 to <12 Years with Eosinophilic Esophagitis Receiving Placebo in Part A and dupilumab in Part B (Study R668-EE-1867, Part B)



N = Number of patients. BLQ concentrations were set to 0. Regression line LOESS (span=1.5). Dose regimen based on the last administered dose prior to Week 52. Change from Part A baseline.

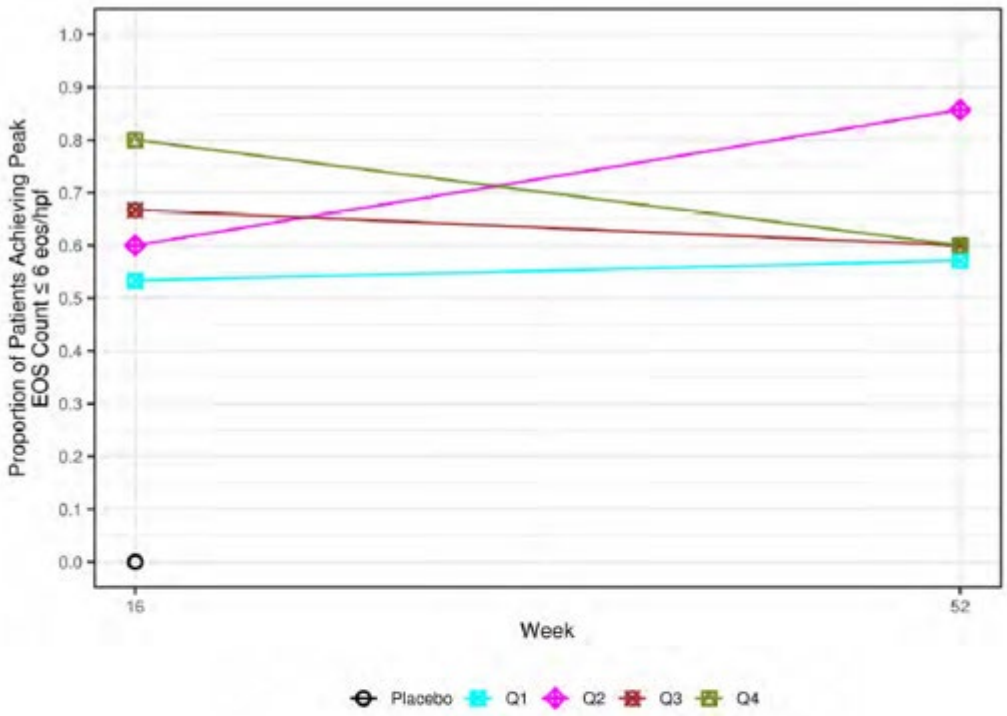
Figure 22. Plot of Change From Baseline in BMI for Age Z-score vs. Trough Concentration of Functional Dupilumab at Week 52 by Treatment Group in Pediatric Patients 1 to <12 Years with Eosinophilic Esophagitis Receiving Dupilumab in Part A and Part B (Study R668-EE-1877, Part B)



N = Number of patients. BLQ concentrations were set to 0. Regression line LOESS (span=1.5). Dose regimen based on the last administered dose prior to Week 52. Change from Part A baseline.

The proportion of participants achieving an esophageal intraepithelial eosinophil count of ≤6 eos/hpf is presented by quartiles of Ctrough of dupilumab in the Figure 23 below.

Figure 23. Proportion of Participants Achieving Esophageal Intraepithelial Eosinophil Count ≤6 eos/hpf by Quartile of Concentrations of Functional Dupilumab in Serum in Pediatric Participants ≥1 to <12 Years with EoE in Part B (Study R668-EE-1877, CRAS)



Quartile	Week 16	Week 52
Placebo	0/31	NA
Q1	8/15 [47.8, 81.4]	12/21 [34.6, 76.2]
Q2	9/15 (81.4, 113.5]	18/21 (76.2, 124.0]
Q3	10/15 (113.5, 167.5]	12/20 (124.0, 163.0]
Q4	12/15 (167.5, 355.0]	12/20 (163.0, 396.0]

Q = Quartile; NA = Not available
Note: BLQ concentrations were set to 0. The table shows the total number of participants in each concentration quartile at each time point, as well as the quartile range in parentheses.

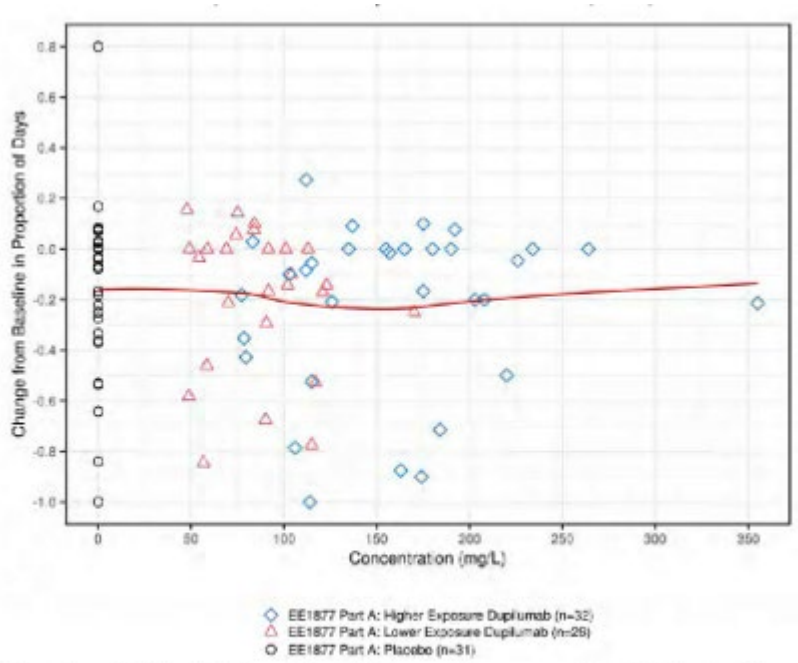
Logistic regression demonstrated a flat relationship in Part B between dupilumab concentrations and the probability of participants achieving a histologic response of peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 52. While response was rank ordered by dupilumab concentration quartile at week 16, at week 52 the highest probability of achieving a histologic response of peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf was observed in the second quartile (18/21 in Q2), with similar response rates among other quartiles (12/21 in Q1 and 12/20 in Q3 and Q4). A flat relationship was also observed between trough concentrations of dupilumab and percent change from baseline in peak esophageal intraepithelial eosinophil count at week 52.

PESQ-C

The continuous endpoints of change from baseline in the proportion of days with 1 or more EoE signs as measured by the PESQ-C were assessed as a secondary endpoint in Study R668-EE-1877 Parts A and B.

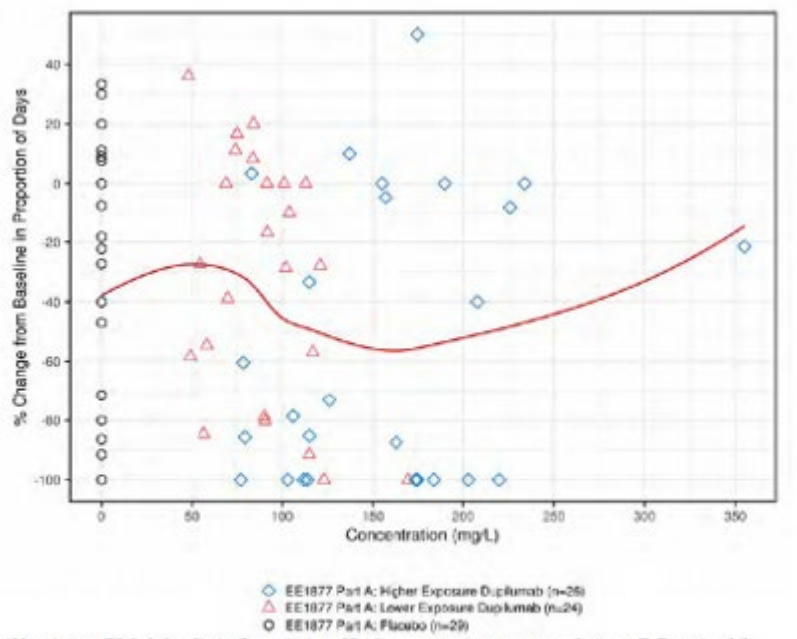
Study R668-EE-1877 Part A (Double-Blind, Placebo-Controlled 16-week Treatment Period)

Figure 24. Plot of Change from Baseline in the Proportion of Days with 1 or More EoE Signs as Measured by the PESQ-C Versus Functional Dupilumab Trough Concentration in Serum at Week 16 by Treatment Group in Children (≥1 to <12 Years) with EoE in Study R668-EE-1877 Part A (CRAS)



Abbreviations: BLQ=below limit of quantitation; CRAS=concentration-response analysis set; EoE=eosinophilic esophagitis; EOS=eosinophils; LOESS=locally weighted scatterplot smoothing; N=number of participants.
Note: BLQ concentrations were set to 0. Regression line LOESS (span 0.8). The primary imputation strategy was applied to clinical response endpoints; missing drug concentrations were not imputed.

Figure 25. Sensitivity Analysis of Percent Change from Baseline in the Proportion of Days with 1 or More EoE Signs as Measured by the PESQ-C Versus Functional Dupilumab Trough Concentration in Serum at Week 16 by Treatment Group in Children ((≥1 to <12 Years) with EoE in Study R668-EE-1877 Part A (CRAS)

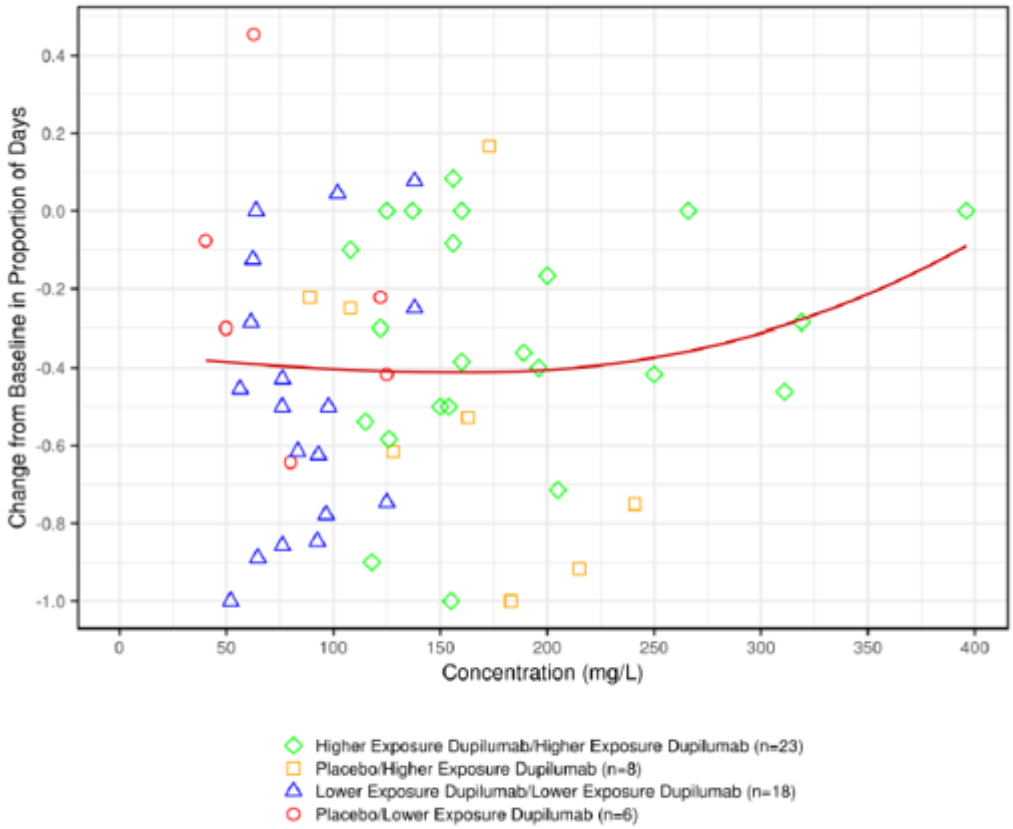


Abbreviations: BLQ=below limit of quantitation; CRAS=concentration-response analysis set; EoE=eosinophilic esophagitis; LOESS=locally weighted scatterplot smoothing; N=number of participants.
Note: BLQ concentrations were set to 0. Regression line LOESS (smooth 0.8). The primary imputation strategy was applied to clinical response endpoints; missing drug concentrations were not imputed. Participants who had zero days with 1 or more EoE signs at baseline were excluded. A single outlier participant in the placebo group with a 400% increase from baseline in the number of days with 1 or more EoE signs was excluded.

No consistent relationship was apparent between exposure to dupilumab and the change from baseline in the proportion of days with 1 or more EoE signs by PESQ-C (Figure 24 and Figure 25 above).

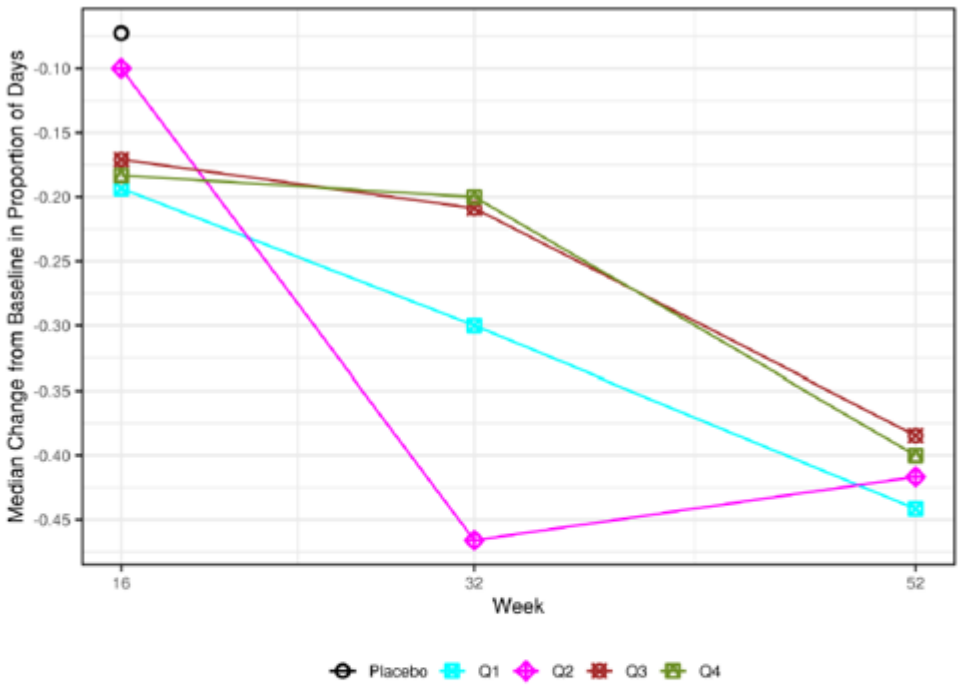
Study R668-EE-1877 Part B (36-week Extended Active Treatment Period)

Figure 26. Plot of Change from Baseline in the Proportion of Days with 1 or More EoE Signs as Measured by the PESQ-C vs. Trough Concentration of Functional Dupilumab at Week 52 by Treatment Group in Pediatric Patients 1 to <12 Years with Eosinophilic Esophagitis (Study R668-EE-1877 Part B, CRAS)



N = Number of patients. BLQ concentrations were set to 0. Regression line LOESS (span=1.5). Change from Part A baseline.

Figure 27. Median Change from Baseline in the Proportion of Days with 1 More EoE Signs as Measured by the PESQ-C by Quartiles of Functional Dupilumab Trough Concentration in Serum in Pediatric Patients 1 to <12 Years with Eosinophilic Esophagitis (Study R668-EE-1877 Part B, CRAS)



Quartile	Week 16	Week 32	Week 52
Placebo	24	NA	NA
Q1	10 [47.8, 81.4]	18 [0.0, 97.0]	14 [40.3, 83.4]
Q2	10 (81.4, 113.5]	18 (97.0, 144.0]	15 (83.4, 125.0]
Q3	11 (113.5, 167.5]	17 (144.0, 192.0]	13 (125.0, 163.0]
Q4	14 (167.5, 355.0]	17 (192.0, 302.0]	13 (163.0, 396.0]

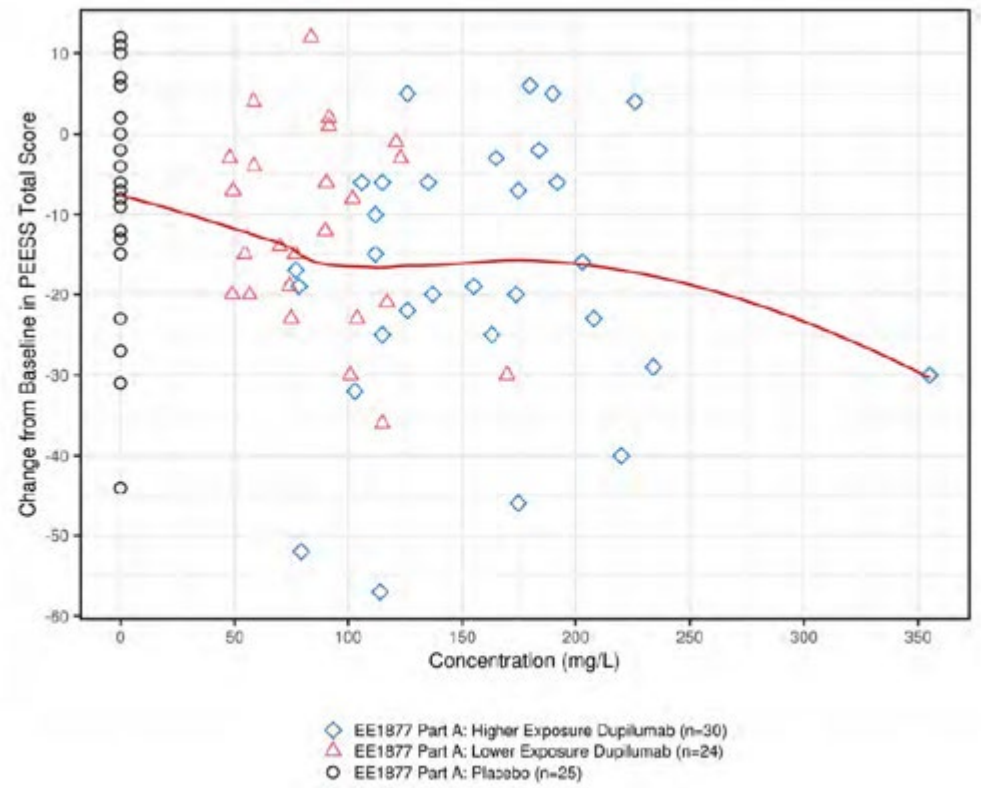
N = Number of patients. BLQ concentrations were set to 0. The table shows the total number of patients in each concentration quartile at each time point,as well as the quartile range in parentheses. Change from Part A baseline.

No clear relationship was observed between individual concentrations of dupilumab and change from baseline or percent change from baseline in the proportion of days with 1 or more EoE signs by PESQ-C as assessed at week 52 or between quartile of dupilumab concentration and median change from baseline in the proportion of days with 1 or more EoE signs by PESQ-C between weeks 16 and 52 in Part B.

Change from Baseline in the PEESSv2.0-Caregiver questionnaire

Symptom burden was also assessed in Study R668-EE-1877 Part A by the PEESSv2.0-Caregiver version (secondary endpoint), which is an ObsRO measure of EoE signs that assessed both the frequency and severity of EoE symptoms among pediatric patients on a scale of 0 to 100.

Figure 28. Plot of Change from Baseline in PEESSv2.0-Caregiver Total Score Versus Functional Dupilumab Trough Concentration in Serum at Week 16 by Treatment Group in Children (≥1 to <12 Years) with EoE in Study R668-EE-1877 Part A (CRAS)



Abbreviations: BLQ=below limit of quantitation; CRAS=concentration-response analysis set; EoE=eosinophilic esophagitis; LOESS=locally weighted scatterplot smoothing; N=number of participants.
Note: BLQ concentrations were set to 0. Regression line LOESS (smooth 0.8). Based on observed data; missing

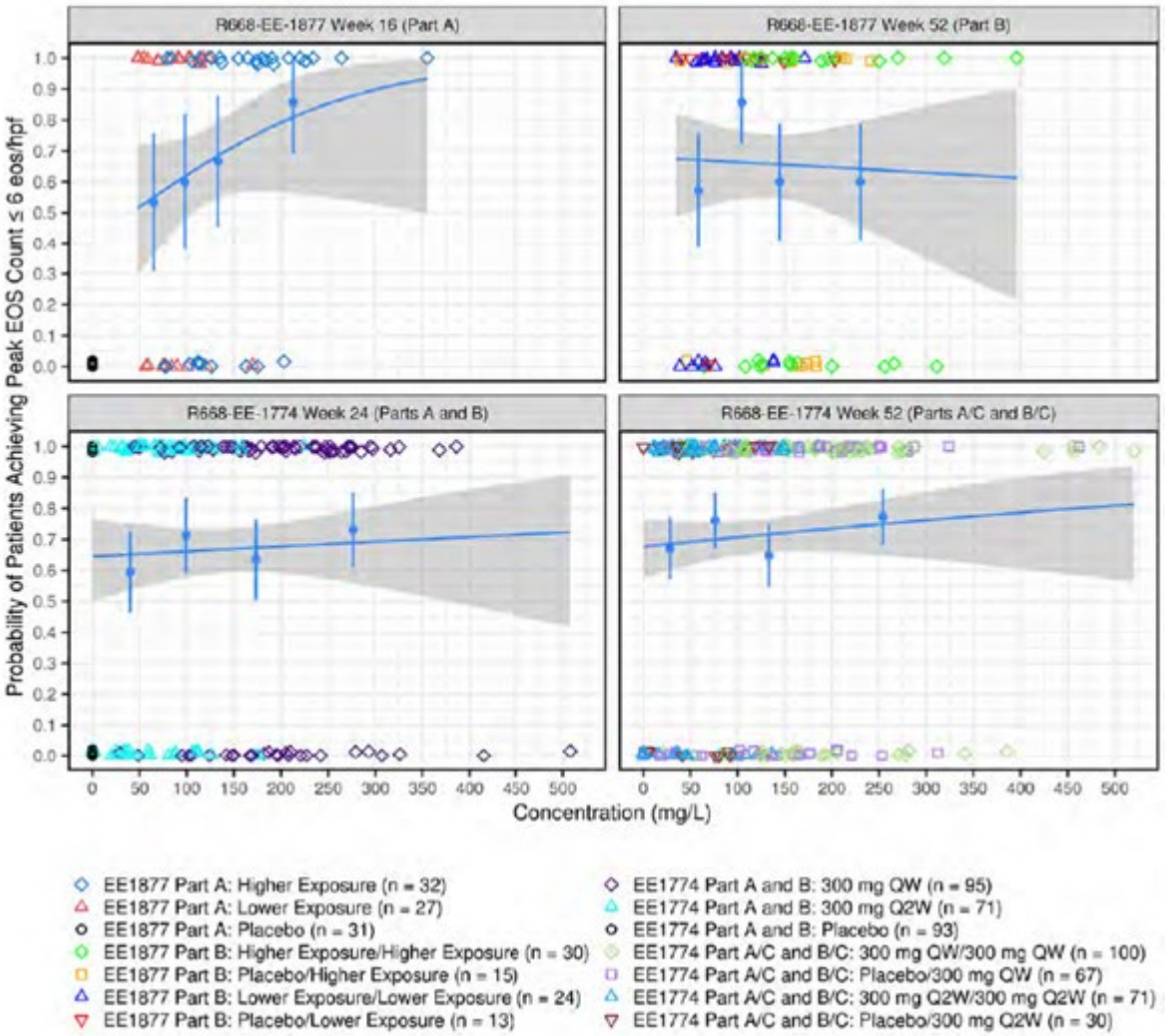
An E-R assessment of the change from baseline in PEESSv2.0-Caregiver total score during the double-blind treatment period (Part A) showed a slight positive trend between increasing trough concentrations of dupilumab and greater improvements in PEESSv2.0-Caregiver.

Exposure-Response Analysis for Safety

E-R for safety was evaluated for AESIs (probability of experiencing at least 1 AESI) in Study R668-EE-1877 (Part A) and utilized the PKAS. Logistic regression of the proportion of participants from Part A experiencing at least 1 AESI (0 if no events, 1 if ≥1 event) versus trough concentration of functional dupilumab at week 16 did not indicate a clinically meaningful E-R relationship between the probability of experiencing an AESI.

Comparability and exposure-response between populations

Figure 29. Logistic Regression Relating Probability of Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count <6 eos/hpf Versus Trough Concentration of Functional Dupilumab in Children (≥1 to <12 Years) in Study R668-EE-1877 (Weeks 16 and 52) or in Adults and Adolescents in Study R668-EE-1774 (Weeks 24 and 52) with EoE (CRAS)



2.3.5. Discussion on clinical pharmacology

This application is supported by data from the completed phase 3 study R668-EE-1877 Parts A and B in children ⩾1 to <12 years of age with EoE. In addition, the PK, PD, and E-R data from children (⩾1 to <12 years) in study R668-EE-1877 are compared to data from adults and adolescents with EoE in Study R668-EE-1774.

Part A and B (Study R668-EE-1877)

PK data collected from Part A and B followed a high and low dose regimen each applying weight tiered approach resulting in three (Part A) and four (Part B) different dosing regimen for the paediatric population. It was initially intended to select a posology that would match the observed Ctrough at steady state following 300 mg QW as being the approved posology for adults and adolescent weighing at least 40 kg and investigate PK comparability. Observed PK and exploratory PK analysis indicate that those paediatric subjects following the high dose regimen in Part A and B are closer to the targeted

exposure range, compared to the low dose subpopulation. Thus, the high dose program is more in line with the concept of extrapolation based on exposure bridging than the low dose program (see following Sections of discussion on extrapolation and posology). Nevertheless, an even more intense posology was proposed and applied in the ongoing Part C (N=61), with partial PK collected (N=21 subjects). PK data collected from the first weight group (5 to 15 kg) are considered not balanced (Part A and B), especially in the high dose cohorts (N=3). There were hardly any PK observations from paediatric subjects below 15 kg and none below 10 kg. As weight was observed to be predictive on CL, it is not surprising, that – following a fix dosing regimen - the mean observed concentration values are at the lower end of the expected distribution. Exploratory data analysis indicates that overall an apparent weight effect on exposure as well as the apparent sparseness in data from paediatric patients below 15 kg. As data from C did not compensate for this lack of information, and pop PK modelling was deemed not qualified for credible exposure predictions below 15 kg, the indication was restricted to subjects weighing 15 kg or above.

Part C (Study R668-EE-1877)

No patients with drug concentration data are available at Week 100 or later weighed <15 kg or later from Part C. PK data following 300 mg QW was only observed in one subject at Week 100. Most of the data (Part C) resulted following 200 mg Q2W (subjects weighing >=15kg to <30kg comparable to Part B). Thus, PK data from the ongoing part C are considered too sparse to be used for a meaningful update in pop PK or provide confirmative information to justify the more intense posology for subjects below 15 kg and above 40 kg.

Pop PK Model

A population PK model was developed and used to justify the proposed posology (i.e. ≥40 kg (300 mg QW); ≥30 to <40 kg (300 mg Q2W); ≥15 to <30 kg (200 mg Q2W) and ≥5 to <15 kg (200 mg Q3W) that has not been clinically tested in study Part A and B. This is targeting the very young and lowest weight cohort (5-15 kg of weight), for whom a higher and extensive posology is proposed, similar to the posology currently under investigation in Cohort C of the paediatric study. Given there are no confirmative PK for subjects below 15 kg following the proposed posology (200 mg Q3W), the impact of the pharmacometrics exercise and model-based conclusions is considered high. As a consequence, the predictive performance is considered not adequate given that the pop PK is used to justify a very intensive posology for paediatric patients weighing below 15 kg, while there is hardly any support from clinical and PK observation for this subpopulation from the paediatric study. Especially for the dosing regimen 200 mg Q4W and 100 mg Q2W, the predictive performance is considered not acceptable. The poor performance may be attributed to the sparseness of data to inform the pop PK model on exposure following these treatments in weight cohort 5 to 15 kg.

In addition, no maturation has been implemented and weight was included as a time-varying covariate (estimated) in some PK parameters (CL, Vss) while assumed to be fixed on Q, which is inconsistent. On the basis of reporting the model development progress, predictive pop PK performance and the assumption, that PK is considered comparable over indications, the current methodology for allometric scaling and description of PK and young subjects weighing 5 kg or more could not be agreed. It is understood that there are not enough data available to estimate a specific maturation function for the EoE paediatric population. Nevertheless, there is a detailed discussion missing on why not considering maturation in addition to allometric scaling needed for subjects from 5 kg of weight. As all type 2 inflammatory diseases studied to date show similar PK for dupilumab the inclusion of maturation function as identified for AD paediatric subjects needed to describe PK may be considered. The model development to investigate model qualification for the context of use was therefore questioned by the CHMP. In addition, the MAH was requested to provide a sensitivity analysis investigating effects of weight and age (paediatric subjects) and further model simulations. Model comparison and selection

should include allometric scaling (by base weight and time varying) in combination with and without maturation function as characterized for AD paediatric subjects. Predictive performance and model qualification should be reported. Nevertheless, the requested analyses were not provided. The MAH provided as additional information an external validation of the final pop PK model using paediatric PK data from AD and asthma indication which is acknowledged. Only VPC plots and only few information on the methodological aspects were provided. These plots appear overall acceptable, however, as no sensitivity analysis towards EoE data were provided, and the pop PK model and PK data are not changed or were further challenged, the CHMP maintain their view and conclusions. Concerns about model predictivity remain. The pop PK model (high impact) is still considered not adequate to be used for credible simulations that would justify the posology in the paediatric subpopulation (≥5 kg to <15 kg).

Posology – Concept of exposure bridging

Overall, mean trough concentrations of dupilumab at steady-state for children ≥1 to <12 years of age with EoE in the higher exposure dupilumab treatment groups were within the range observed for adults and adolescents with EoE who received dupilumab 300 mg QW, based on data from Study Parts A and B. Within the higher exposure dupilumab regimen, mean trough concentrations were closest to the dupilumab 300 mg QW reference for participants who received dupilumab 200 mg Q2W (≥15 to <30 kg), while mean values were slightly lower for participants who received dupilumab 100 mg Q2W (≥5 to <15 kg) and, to a lesser extent, dupilumab 300 mg Q2W (≥30 to <60 kg). The MAH was proposing to prevent this discrepancy by suggesting a more intensive posology. The main aim underlying the proposed posology in paediatrics was to match the observed Ctrough at steady state following 300 mg QW as being the approved posology for adults and adolescent weighing at least 40 kg. For this posology histologic and symptomatic benefit (based on differential scores) was observed in study R668-EE-1774. Based on the PK findings in children ≥1 to <12 years of age (Study R668-EE-1877) and in adults and adolescents (Study R668-EE-1774), the MAH proposed alternative dosing regimens to those evaluated in part A and B of Study R668-EE-1877 in children ≥5 to <15 kg and children >40 kg (and below the age of 12). The dupilumab weight-tiered regimens posology applied for within this extension of indication are currently being evaluated in R668-EE-1877 Part C. Partial clinical and pharmacological data from Part C have been provided upon CHMP's request. Dose cohorts for paediatric subjects between 15 and 40 kg are comparable to Part B (R668-EE-1877, high dose program), while for weight cohort <15 kg and >40 kg a more intense posology was requested. While clinical and PK data are available for subjects >40 kg following the more intense regimen 300 mg QW are available from Study R668-EE-1774, the data base is very sparse for subjects below 15 kg. From the N=61 participants continued into Part C, N=21 added to additional PK data at week 100, N=4 at week 160 (no results shown), and N=3 at week 172 (no results shown). None of the 21 participants was weighing below 15 kg, so no additional data was collected and provided so far following 200 mg Q3W. No patients with drug concentration data are available at Week 100 weighed <15 kg or later, that could be considered useful and confirmative information. The initially proposed subgroup of paediatric subjects weighing 5 to less than 15 kg was therefore not supported by CHMP and removed from the indication.

Comparison of Ctrough observed across studies

Observed and predicted exposure based on the current final pop PK model have been presented focussing on the exposure range to be matched and the posology proposed for children below 15 kg. In addition, a comparison of Ctrough values observed across studies was also provided.

In study R668-EE-1774, a decrease in Ctrough mean from Week 24 (time point for primary efficacy endpoint assessment in adults/adolescents) to Week 52 was observed from 196 (86.3) to 159 (99.4) mg/L in the treatment group receiving dupilumab 300 mg QW while the level following 300 Q2W was

observed in the same range (73.6 to 65.7) mg/L as expected at steady state. It has been clarified that this is not attributed to body weight but that the differential time since last dose can account for these differences. Therefore, this does not impact the exposure range for the population PK model.

Simulations based on the final pop PK model indicate that the exposure range for paediatric subjects below 12 years of age weighing at least 40 kg following 300 mg QW would exceed the expected exposure range for adults/adolescents weighing at 40 kg in terms of AUC and Cmax_ss. Nevertheless, as it could be agreed that weight is the most significant covariate for PK in particular for patients of at least 6 years of age, the proposed posology of 300 mg QW for all subjects weighing at least 40 kg is supported.

A more detailed comparison regarding weight cohorts was requested. This was grounded on the fix dosing regimen applied, together with the claimed increase in dosing needed, while having very sparse (10-15 kg) and/or no PK data (5-10 kg) to either built or validate the pop PK model. Results (Table 1, Section 2.3.2) clearly indicate that in terms of Ctrough, values are about 1.5 times higher in the subgroup 5-10 kg compared to those weighing 10-15 kg following the same dosing regimen 200 mg Q3W.
Observed trough concentrations from Part C at Week 100 in each weight-tiered dose group for which data is available collected in N=21 subjects are overall consistent with expectations based on the population PK analysis conducted in paediatric EoE patients. No patients with drug concentration data available at Week 100 or later weighed <15 kg. PK data following 300 mg QW was only observed in one subject. The predicted median (P5, P95) for Ctrough by dose in this population was 194 (96, 366) mg/L for 200 mg Q3W [5 to <15 kg], 152 (76, 322) mg/L for 200 mg Q2W [15 to <30 kg], 147 (77, 269) mg/L for 300 mg Q2W [30 to <40 kg], and 261 (140, 452) mg/L for 300 mg QW [≥40 kg].

Of note, simulations were provided using the former final popPK model considered not adequate for application – in particular regarding the predictiveness of exposure in the paediatric weight group 5-15 kg. Thus model-based results should be interpreted with caution. On the basis of reporting the model development progress, predictive pop PK performance and the assumption, that PK is considered comparable over indications, the current methodology for allometric scaling and description of PK and young subjects weighing below 15 kg or more could not be agreed. Taking the model deficiencies and lack of confirmatory data and related concern with regard to safety (see section 2.5.1) into account, the proposed posology for paediatric subjects below 15 kg is considered still not acceptable. Therefore, the MAH agreed to exclude children weighing less than 15 kg from the indication.

Comparability and exposure-response between populations

An inconsistency in the primary endpoint for efficacy and very flat exposure response was noted. The co-primary endpoints for both Parts A and B (study R688-EE-1774) were the proportion of participants achieving peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 and absolute change in DSQ score from baseline to week 24. The key secondary endpoints for both Parts A and B of the study were the 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, and absolute change in EoE grade and stage scores from the EoEHSS from baseline to week 24. The histological endpoint (proportion of participants achieving peak esophageal intraepithelial eosinophil count ≤6 eos/hpf) is comparable between the relevant studies – although assessed at week 16 (paediatrics) instead of week 24 (Study R688-EE-1774). The co-primary endpoint - DSQ score – however, has not been investigated in Study R668-EE-1877. The DSQ was not developed or validated for use in young children and, therefore, not utilized in Study R668-EE-1877. Symptoms in children (<12 years) are more heterogeneous and non-specific and, unlike in adults and adolescents, dysphagia is not always a prominent symptom although it does occur in paediatric patients. This complicates the direct comparability between populations in terms of exposure needed to achieve comparable efficacy.

No consistent association was observed between baseline total IgE or eotaxin-3 and treatment response (histological response). Treatment with higher exposure or lower exposure dupilumab in Part A and B of this study reduced biomarkers of type 2 inflammation (plasma eotaxin-3 and serum total IgE) relative to placebo treatment. Of note, median percent decreases in plasma eotaxin-3 were consistently greater for children ≥1 to <12 years of age with EoE than in adults and adolescents with EoE, even following the low dose regimen. This questions the need for a posology that would lead to an increase in exposure beyond the high dose regimen tested in R668-EE-1877. Similar effect across low and high dupilumab treatment groups within each population were detected.

E-R analysis for efficacy indicated very flat relationships, with slight trends towards greater improvement in relevant clinical response variables at week 16 in children (≥1 to <12 years) with EoE who had higher levels of exposure. Of note, there was very low sample size between 10 and 15 kg and no information are available for children below 10 kg. The data collected in Part A and B do not allow any conclusive analysis regarding E-R for safety.

It was thus requested to provide a critical discussion on the potential benefit gained from the proposed intensive regimen (200 mg Q3W, patients below 15 kg) over potential risk for these subjects that would exceed exposure for which safety is considered established. The MAH mainly argued with comparability of Ctrough levels. The Exposure-Response results as observed from Parts A and B were hardly considered for discussion on the potential benefit gained from the proposed intensive regimen (200 mg Q3W, patients below 15 kg) over potential risk for these subjects. Of note, in contrast to the adult data, when investigating low and high dose regimen from Part A and B, conclusions drawn from exposure response analyses in the paediatric population are not in support of a further increase in dosing, as discussed above.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology data are sufficient to support the following posology (SmPC section 4.2) of dupilumab in the treatment of eosinophilic esophagitis in adults, adolescents and children aged 1 year and older, weighing at least 15 kg who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy:

The recommended dose of dupilumab is 200 mg every other week for paediatric patients who weighed 15 to less than 30 kg, 300 mg every other week in paediatric patients weighing 30 to less than 40kg, and 300 mg every week in patients weighing 40 kg or more.

2.4. Clinical efficacy

2.4.1. Main study

R668-EE-1877

Study R668-EE-1877 is a randomised, double-blind, placebo-controlled, multi-center, phase 3 study consisting of 3 parts: Part A (a 16-week double-blind treatment period), Part B (a 36-week extended active treatment period), and Part C (an open-label extension period), followed by a 12-week follow-up period.

Methods

Study design

In **Part A**, participants were randomized 2:2:1:1 to receive a higher exposure dupilumab regimen (exposures approximating those in adolescents and adults receiving 300 mg dupilumab QW), a lower exposure dupilumab regimen (exposures approximating those in adolescents and adults receiving 300 mg dupilumab Q2W), placebo to match the higher exposure regimen or the lower exposure regimen.

The higher exposure dupilumab regimen was 100 mg Q2W for participants weighing ≥5 to <15 kg, 200 mg Q2W for participants weighing ≥15 to <30 kg, and 300 mg Q2W for participants weighing ≥30 to <60 kg.

The lower exposure dupilumab regimen was 200 mg once every 4 weeks (Q4W) for participants weighing ≥5 to <15 kg, 300 mg Q4W for participants weighing ≥15 to <30 kg, and 200 mg Q2W for participants weighing ≥30 to <60 kg.

For Part B, a ≥60 kg regimen was added with 300 mg QW in the higher exposure groups and 300 mg Q2W in the lower exposure group, for participants whose bodyweight went over 60 kg. This was not needed in Part A as participants had to be <60 kg according to eligibility criteria.

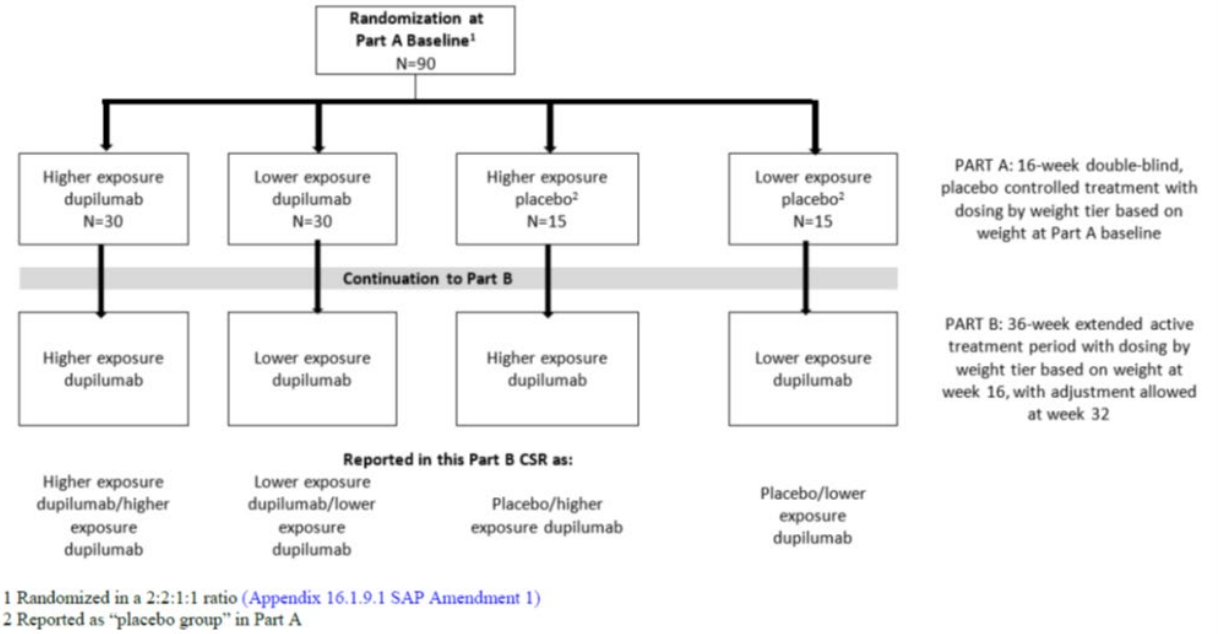
The primary endpoint of histologic remission was assessed at week 16. Following completion of Part A, participants could continue into Part B to receive dupilumab (higher or lower exposure regimen) for an additional 36 weeks in a double-blind manner according to the treatment regimen assigned at randomization. Participants who did not enter Part B were to enter a 12-week posttreatment follow-up period.

In **Part B**, all participants remained on the originally assigned exposure regimen (higher or lower). Participants randomized to one of the placebo regimens in Part A received the same regimen with dupilumab dosing in Part B. Dosing in Part B was double-blinded with respect to the regimen and was initially based on body weight at week 16 (ie, at the end of the double-blind treatment period/start of the extended active treatment period).

If a participant's weight tier changed at week 32, the dose was adjusted to the corresponding weight tier in their originally assigned exposure regimen, as appropriate.

Following completion of Part B (before implementation of Protocol Amendment 4), participants entered the 12-week follow-up period. After implementation of Protocol Amendment 4, participants could directly continue into **Part C** to receive dupilumab as higher exposure regimen only for up to 108 weeks of open-label treatment or until dupilumab becomes commercially available in the country of the participating patients. Participants who were ongoing in or had completed the Part B follow-up at the time of Protocol Amendment 4 implementation could also enter the Part C open-label extension period. After completing Part C, participants will enter a final 12-week follow-up period. Part C is ongoing, but partial data with a cut-off date of 17 January 2024 have been submitted upon CHMP's request. Final Results and follow-up periods will be reported separately and are not included in this submission. Part C has an expected study completion date of July2025.

Study 1. ***Study Design of Part A and Part B***



1 Randomized in a 2:2:1:1 ratio (Appendix 16.1.9.1 SAP Amendment 1)
2 Reported as "placebo group" in Part A

Study participants

The eligibility criteria defined a study population in **Part A** of males and females ≥1 year to <12 years of age at the time of study entry with EoE, with a body weight ≥5 kg and <60 kg. Of note, no patient with less than 10 kg body weight was enrolled. Study participants were required to have a confirmed diagnosis of EoE that was not responsive to proton pump inhibitor (PPI) therapy. Non-responsiveness to PPI may have been established either by a prior historical biopsy showing ≥15 intraepithelial eos/hpf from at least 1 oesophageal region after at least 8 weeks of treatment with an approved PPI regimen or by biopsies performed after approximately 8 weeks of PPI treatment initiated prior to screening or during the screening period, which demonstrated ≥15 intraepithelial eos/hpf in at least 2 out of 3 oesophageal regions (proximal, mid, and distal).

All participants were required to have a history (by participant or caregiver report) of EoE symptoms (e.g., abdominal pain, chest pain, acid reflux, food regurgitation, dysphagia, vomiting, or refusal to eat) in the month prior to screening. Participants or their caregivers had to be able to understand the study requirements and complete the study-related questionnaires. At least 8 out of 14 days of eDiary completion for the PESQ-C was required prior to visit 3 (baseline) to confirm compliance with the eDiary. However, no minimum level of EoE signs per PESQ-C was required for inclusion.

Participants who were receiving PPIs during the screening period and eligible to enrol in the study were either to remain on the PPI regimen during the entire study or stop the PPI regimen prior to baseline; they then had to remain off of PPIs during the entire study.

Participants with other causes of esophageal eosinophilia or conditions like eosinophilic gastroenteritis, hypereosinophilic syndrome, or eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) were excluded.

Participants entering **Part B** were required to have completed the week 16 assessments of Part A. Participants who met any of the following criteria were not permitted to enter Part B:

- developed an SAE and/or AE related to the study intervention during Part A which led to discontinuation of the investigational product
- prematurely withdrawn during Part A due to a protocol violation, poor compliance, or inability to complete required study assessments
- did not undergo endoscopy with biopsies at week 16 or prior to receiving rescue treatment
- female participants who experienced menarche and who were unwilling to follow the precautions for women of childbearing potential.

Treatments

Study R668-EE-1877 evaluated weight-tiered higher exposure and lower exposure dupilumab regimens in children ≥1 to <12 years of age with EoE. These weight-tiered higher exposure and lower exposure dupilumab regimens were designed to produce trough concentrations at steady-state in children that approximated those in adults who received 300 mg QW (higher exposure dupilumab) or 300 mg Q2W (lower exposure dupilumab), which were evaluated in the adolescent and adult study R668-EE-1774 (also see supportive study section).

The higher exposure dupilumab regimen was:

- 100 mg Q2W for participants weighing ≥5 to <15 kg
- 200 mg Q2W for participants weighing ≥15 to <30 kg
- 300 mg Q2W for participants weighing ≥30 to <60 kg
- 300 mg QW in participants weighing ≥60 kg (Part B only) *

The lower exposure dupilumab regimen was:

- 200 mg Q4W for participants weighing ≥5 to <15 kg
- 300 mg Q4W for participants weighing ≥15 to <30 kg
- 200 mg Q2W for participants weighing ≥30 to <60 kg
- 300 mg Q2W in participants weighing ≥60 kg (Part B only) *

* For Part B, a ≥60 kg regimen was added with 300 mg QW in the higher exposure groups and 300 mg Q2W in the lower exposure group, for participants whose bodyweight went over 60 kg.

Part C (ongoing): up to 108-week open-label extension period followed up by a

12-week follow-up period. Following participant completion of Part B, participants could continue into Part C to receive dupilumab. All participants receive a higher exposure regimen in Part C, irrespective of prior randomization, as follows:

– 200 mg Q3W for participants weighing ≥5 to <15 kg

– 200 mg Q2W for participants weighing ≥15 to <30 kg

– 300 mg Q2W for participants weighing ≥30 to <40 kg

– 300 mg QW for participants weighing ⩾40 kg

Rescue Concomitant Medications/Procedures

If medically necessary (eg, for treatment of intolerable EoE symptoms), rescue medications (systemic and/or swallowed topical corticosteroids) or emergency oesophageal dilation were allowed during the study. No participant in any treatment group used rescue medication or underwent a rescue procedure for EoE during the Part A 16-week treatment period.

Objectives

Part A

Primary Objective:

- To demonstrate the efficacy of dupilumab treatment compared with placebo in pediatric patients with active EoE based on histologic improvement meeting validated histologic criteria

Main Secondary objectives:

- To demonstrate the efficacy of dupilumab compared to placebo in pediatric patients with active EoE after 16 weeks of treatment as assessed by endoscopic visual measurements of disease activity using the EoE-EREFS and histologic abnormalities as measured by the EoE-HSS
- To evaluate the safety, tolerability, and immunogenicity of dupilumab treatment for up to 16 weeks in pediatric patients with active EoE
- To evaluate the effects of dupilumab on transcriptomic signatures associated with EoE and type 2 inflammation
- To study the effects of dupilumab on the type 2 inflammation gene expression signature
- To evaluate the impact of dupilumab treatment on EoE signs and symptoms

Part B

Primary:

- To demonstrate the efficacy of dupilumab treatment compared with placebo in pediatric patients with active EoE based on histologic improvement meeting validated histologic criteria

Secondary:

- To assess efficacy of long-term (up to 160 weeks) dupilumab treatment
- To assess safety, tolerability, and immunogenicity of long-term (up to 60 weeks) dupilumab treatment
- To evaluate the effects of dupilumab on transcriptomic signatures associated with EoE and type 2 inflammation
- To study the effects of dupilumab on the type 2 inflammation gene expression signature
- To evaluate the impact of dupilumab treatment on EoE signs and symptoms
- To assess the impact of dupilumab treatment on changes in weight and growth during the extended active period of the study

Outcomes/endpoints

Part A

Primary:

- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf (400×) at week 16

Secondary:

- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 16
- Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 16
- Absolute change in mean EoE grade score from the EoE-HSS from baseline to week 16
- Absolute change in mean EoE stage score from the EoE-HSS from baseline to week 16
- Absolute change in EoE-EREFS from baseline to week 16
- Change from baseline in the type 2 inflammation transcriptional signature score at week 16
- Change from baseline to week 16 in the proportion of days with 1 or more EoE signs as measured by the PESQ-C (for patients aged ≥1 to <12 years)
- Number of sign-free days during the 14-day period preceding week 16 as measured by the PESQ-C (for patients aged ≥1 to <12 years)

Part B

Primary:

There were no primary efficacy endpoints for Part B.

Secondary:

- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf (400×) at week 52
- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 52
- Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 52
- Absolute change in mean EoE grade score from the EoE-HSS from baseline to week 52
- Absolute change in mean EoE stage score from the EoE-HSS from baseline to week 52
- Absolute change in EoE EREFS from baseline to week 52
- Change from baseline in the type 2 inflammation transcriptional signature score at week 52
- Change from baseline to week 52 in the proportion of days with 1 or more EoE signs as measured by the PESQ-C (for patients aged ≥1 to <12 years)

Sample size

Parts A and B:

The planned sample size was a total of approximately 90 patients (2:2:1:1 ratio, 30 patients in the higher exposure dupilumab group, 30 patients in the lower exposure dupilumab group, 15 patients in the higher exposure-matched placebo group, and 15 patients in the lower exposure-matched placebo group).
The assumptions used in the sample size calculation were based on Part A of the R668-EE-1774 study in adults and adolescents with EoE. Based upon the similarity of pathophysiology and expected similarity of histologic response between adults and pediatric patients, a similar proportion of responders at week 16 was assumed for sample size calculation. The lower exposure dupilumab group was assumed to have a similar treatment effect to the higher exposure dupilumab group.
The treatment group difference observed in the R668-EE-1774 Part A adolescents was assumed for the sample size calculation for this study in children aged ≥1 year to <12 years. In Part A of R668-EE-1774, the proportions of patients achieving a peak oesophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 were 59.5% and 5.1% for dupilumab and placebo, respectively. In Part A of R668-EE-1774, the proportions of adolescent patients achieving peak oesophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 were 36.4% and 0% for dupilumab and placebo, respectively. The treatment group difference observed in adolescents was approximately 36.5%. It was estimated that with a total number of 90 patients (30 patients in the higher exposure dupilumab group, 30 patients in the lower exposure dupilumab group, and 30 patients in the combined placebo group), at the 2-sided 5% significance level using Fisher's exact test, the study can provide 95% power to detect a treatment difference of 35.6% in the proportion of histologic responders (i.e., patients achieving peak oesophageal intraepithelial eosinophil count ≤6 eos/hpf) at week 16 between placebo (5.1%) and each dupilumab treatment group (40.7%).

Randomisation

Part A: Approximately 90 patients aged ≥ 1 year to <12 years were planned to be randomized in a 2:2:1:1 ratio to receive a higher exposure dosing regimen, a lower exposure dosing regimen of dupilumab, a higher exposure-matched placebo or a lower exposure-matched placebo for a 16-week treatment period according to a central randomization scheme provided by an IWRS to the designated study pharmacist (or qualified designee). Randomization was planned to be stratified according to weight at baseline (≥5 kg to <15 kg, ≥15 kg to <30 kg, or ≥30 kg to <60 kg).

Part B: There was no additional randomization step for Part B. At the end of Part A, eligible patients had an option to enter into Part B, which was a 36-week extended active treatment period with dupilumab. All patients (Part A active and placebo) received dupilumab based on body weight at visit 8/week 16 per the higher- and lower-exposure dosing group to which they were assigned at randomization.

Blinding (masking)

Part A and B:

Study patients, the principal investigators, and study site personnel remained blinded to all randomization assignments. For Parts A and B, study drug administration at the study sites was performed only by injection personnel who did not perform any clinical assessment/procedures. During the conduct of Parts A and B, the blinded Regeneron medical/study director, study monitor, and any

other Regeneron and contract research organization (CRO) personnel who were in regular contact with the study site remained blinded to all patient randomization assignments.

For the primary analysis of Part A selected sponsor study personnel was unblinded while Part B was ongoing. The team performing the primary analysis was separate from the ongoing study team. No study personnel involved in the day-today conduct of the study had access to any unblinded data before the database was locked for Part B of this study. Blinded study drug kits coded with a medication numbering system was used for the double-blind (Part A) and extended active (Part B) treatment periods. In order to maintain the blind (until the database was locked for Part B), lists linking these codes with product lot numbers were not accessible to individuals involved in study conduct. Part C study drug was labeled with dupilumab.

During the double-blind (Part A) and extended active (Part B) treatment periods, anti-drug antibody, drug concentration results, any post-treatment tissue eosinophil counts and histologic results, and biomarker results (eotaxin-3 and total IgE) were not communicated to the sites, and the sponsor's blinded study team had no access to results associated with patient identification until after the database was locked for the respective study part.

Study drug was discontinued for patients whose treatment has been unblinded.

If unblinding was required:

- Only the investigator made the decision to unblind the treatment assignment.
- Only the affected patients were unblinded.
- The designated study pharmacist(s)/designee at the study site provided the treatment assignment to the investigator. If there was no study pharmacist, the investigator for the site unblinded the patient. Unblinding was performed using the IVRS/IWRS which notified Regeneron.
- The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient.

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the patient's treatment assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

Statistical methods

Analysis Populations/Sets

Part A:

Full Analysis Set (FAS): The FAS includes all randomized patients in Part A; it is based on the treatment allocated (as randomized). Efficacy endpoints in Part A (double-blind treatment period) were analyzed using the FAS.

Safety analysis set (SAF): The SAF includes all randomized patients who received any Part A study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables were analyzed using the SAF.

Part B:

For efficacy and safety analyses of Parts B and C, only a subset of SAF for Part A was included, which is defined as those patients who received at least 1 dose of Part B or/and Part C study drug.

Primary Endpoint / Primary Estimand

Summary of Primary Estimand for Primary Endpoint and Secondary Endpoints in Part A

Endpoint Category	Estimands			
	Endpoint(s)	Population	Intercurrent event(s) strategy and missing data handling	Population-level summary/Analysis
Primary Endpoint	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf (400×) at week 16	FAS	The intercurrent events will be handled as follows: • Treatment discontinuation: data collected after the patient discontinued treatment will be included in the analysis (treatment policy strategy) • Initiation of treatment with systemic and/or swallowed topical corticosteroids drugs and dilation: patients will be considered as non-responders after such event (composite variable strategy) Note: the composite strategy will be considered if a patient receives rescue treatment [a] any time during the study. Missing data handling: patients with a missing value for the primary endpoint at week 16 due to study discontinuation or other reasons will be considered non-responders. Missing data due to COVID-19 will be imputed by multiple imputation (MI).	Cochran-Mantel-Haenszel (CMH) test adjusting for the randomization stratification factor (baseline weight group) will be utilized. The Mantel-Haenszel estimate of odds ratios between each of dupilumab groups and placebo, and its 2-sided 95% confidence intervals will be provided.

Supplementary Analysis for Primary Endpoint

Sensitivity analyses were planned to assess alternative methods of missing data imputation.

1. Tipping point analysis approach: To assess the robustness of analysis results under MNAR (missing not at random) assumption, a delta-adjusting pattern-mixture approach for tipping point analysis (Ratitch, 2013) was conducted for the primary endpoint. The impact from missing data due to study discontinuation or other reasons on the comparisons in proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16 between each dupilumab group and placebo control group was examined, by adjusting for stratification factor:

    - A series of analyses was performed by applying a specified sequence of different values of shift parameter to the 3 treatment groups for the data imputation: in the placebo group, different values (>0) of shift parameter was subtracted from the imputed peak eosinophil count; in each of dupilumab group, different values (<0) of shift parameter were added to the imputed peak eosinophil count. The imputed peak eosinophil count which was negative was replaced by 0. Patients who achieve peak eosinophil count of ≤6 eos/hpf were derived based on the imputed peak eosinophil count after shifting.

    - For each combination of different values of shift parameter applied to the 3 treatment groups, 10 multiple imputed datasets were generated using a seed number of 6681877. Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf were analyzed using CMH test. The results obtained from 10 multiple imputed datasets were combined using Rubin's formula (Ratitch, 2013) for statistical inference, i.e., p-value and treatment difference between active treatment groups and placebo group.

- A "tipping point" was identified when the result is no longer statistically significant (i.e., p-value >0.05).

2. Worst observation carried forward - multiple imputation (WOCF-MI) approach: Data after rescue treatment or the missing peak esophageal intraepithelial eosinophil count at week 16 due to AE/lack of efficacy was imputed with patient's baseline value or the available post-baseline value up to week 16, whichever is worse, i.e., WOCF. The missing data due to other reasons was imputed by MI using a seed number of 6681877 for 10 times based on patients who have non-missing eosinophil counts at week 16. The imputed week 16 eosinophil counts were determined whether that patient was classified as a responder or non-responder. The 10 complete datasets after the imputations were analyzed using CMH test. The results from the 10 analyses were combined using the SAS MIANALYZE procedure (Ratitch, 2013).

Secondary Endpoints / Secondary Estimands

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary/Analysis**
Secondary Endpoints	Binary endpoints (e.g., proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 16)	FAS	The intercurrent events strategy and missing data handling methods will be the same with the primary endpoint.	The primary analysis method will be the same as for the primary endpoint.
	Continuous endpoints that are scheduled to be measured repeatedly post-baseline up to week 16 (e.g., change in the proportion of days with 1 or more EoE signs from baseline to week 16 as measured by the PESQ-C)	FAS	The intercurrent events will be handled as follows: • Treatment discontinuation: data collected after the patient discontinued treatment will be included in the analysis (treatment policy strategy) • Initiation of treatment with systemic and/or swallowed topical corticosteroids drugs and dilation: data after such events will be assigned by the worst observed value (composite variable strategy) Missing data handling: after discontinuation of the study due to AE/lack of efficacy [b] prior to week 16, patients with a missing value at week 16 will be imputed using WOCF method, and MI approach will be used for the missing data due to other reasons.	Continuous secondary efficacy endpoints at week 16 will be analyzed using an analysis of covariance (ANCOVA) model with treatment groups, randomization stratification factor, and relevant baseline measurement as a covariate included in the model. The least square (LS) means and difference in LS means between dupilumab groups and placebo will be presented.

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary/Analysis**
	Continuous endpoints that are scheduled to be measured only once post-baseline up to week 16 (e.g., absolute change in EoE-EREFS from baseline to week 16)	FAS	The intercurrent events will be handled as follows: • Treatment discontinuation: data collected after the patient discontinued treatment will be included in the analysis (treatment policy strategy) • Initiation of treatment with systemic and/or swallowed topical corticosteroids drugs and dilation: data after such events will be assigned by the worst observed value (composite variable strategy) Missing data handling: patients with a missing value due to COVID-19 will be imputed using MI approach, and WOCF method will be used for missing not due to COVID-19. WOCF method refers to missing values at week 16 will be imputed with patient's baseline value or the available post-baseline value, whichever is worse.	

[a]: The rescue treatment(s) include systemic and/or swallowed topical corticosteroid drugs and esophageal dilation. Blinded adjudication (blinded to the treatment assignment) of rescue treatment(s) will be performed by medical director (or medical monitor) prior to the Part A database lock.

[b]: Patients who are discontinued from the study due to AE or lack of efficacy are captured in the case report form "Study Completion".

Part B:

Secondary endpoints at week 52 (Part B) were analyzed descriptively at given visits for treatment received in Part B as well as by treatment group as in Part A (double-blind treatment period). No missing values will be imputed.

All observed values, regardless of whether rescue treatment is used, or data are collected after withdrawal from study treatment, will be used for analysis. No missing values will be imputed. For categorical efficacy variables, the proportion of patients meeting response criteria at each visit will be calculated using the number of patients with non-missing value at the visit as the denominator.

For efficacy variables whose calculations involve baseline values, e.g., absolute (or percent) change from baseline, separate summaries will be provided for analyses using the study baseline and Part B baseline values. The study baseline is the latest available valid measurement taken prior to or on the date of the first dose of study drug administration (scheduled to be administered at the baseline visit 3). Part B baseline is the last available valid measurement taken prior to or on the date of the first dose of extended active treatment period (scheduled to be administered at week 16 visit).

Multiplicity

Part A:

The following multiplicity adjustment approach, a hierarchical procedure, was used to control the overall Type-1 error rate at 0.05 for the primary endpoint and the secondary endpoints across the 2 dupilumab dose regimens versus placebo in Part A only. Each hypothesis was formally tested only if the preceding one was significant at the 2-sided 0.05 significance level. The hierarchical testing order is shown in the below table (all comparisons are with the placebo).

	Endpoints	Dupilumab	
		Higher Exposure Dupilumab	Lower Exposure Dupilumab
Primary endpoint	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16	1	2
Secondary endpoints	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 16	3	11
	Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 16	4	12
	Absolute change in mean EoEHSS grade score from the EoE-HSS from baseline to week 16	5	13
	Absolute change in mean EoEHSS stage score from the EoE-HSS from baseline to week 16	6	14
	NES for the relative change from baseline to week 16 in the type 2 inflammation transcriptome signature	7	15
	NES for the relative change from baseline to week 16 in the EoE diagnostic panel (EDP) transcriptome signature	8	16
	Absolute change in EoE EREFS from baseline to week 16	9	17
	Change from baseline to week 16 in the proportion of days with 1 or more EoE signs as measured by the PESQ-C (for patients aged ≥1 to <12 years)	10	18

Subgroup Analyses

PART A:

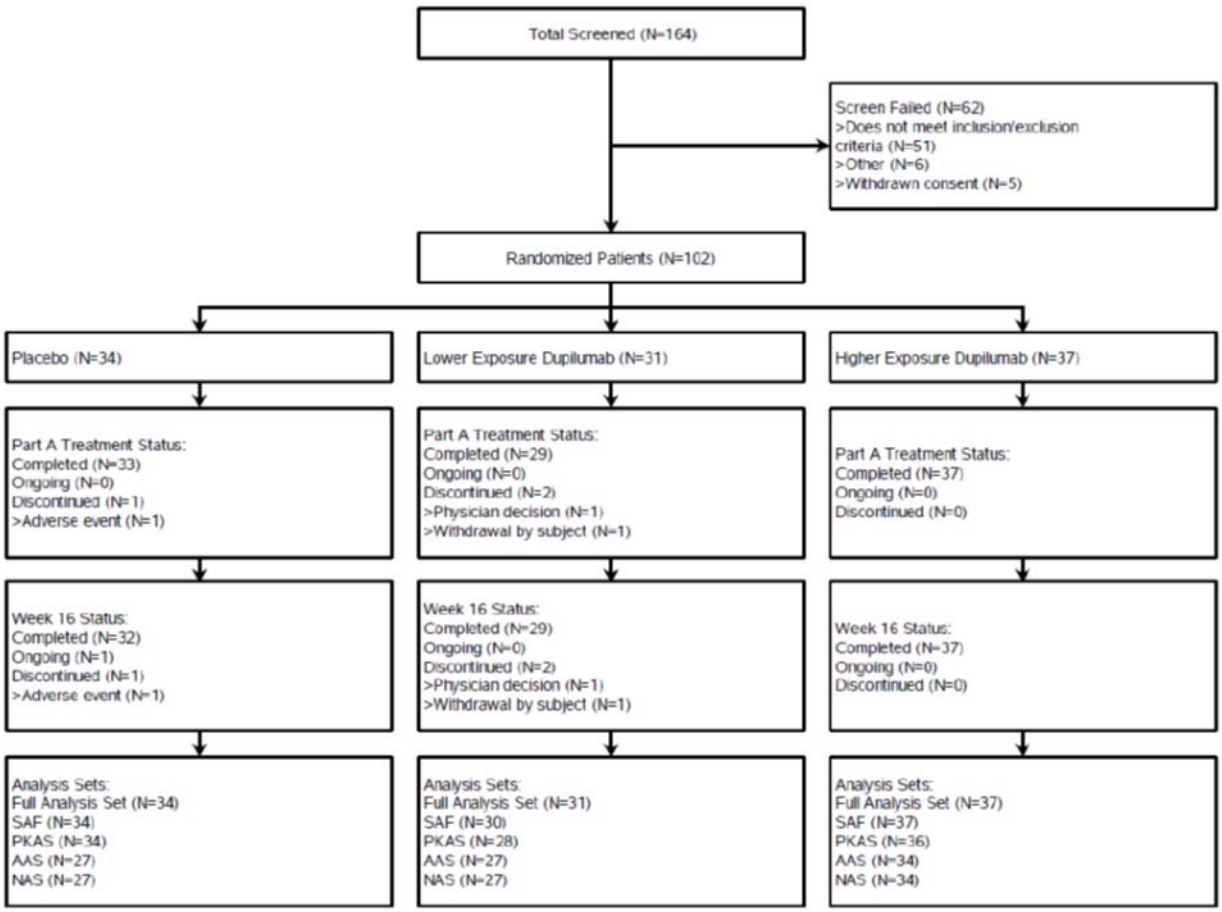
Subgroups were considered for both primary efficacy and safety analyses:

- Age group (years; ≥1- <6, ≥6 -<12; ≥1- <8, ≥8 -<12)
- Sex (Male, Female)
- Duration of EoE (years from start date of EoE to randomization date; <5, ≥5)
- Baseline weight group (≥5 - <15 kg, ≥15- <30 kg, ≥30- <60 kg)
- Prior use of swallowed topical steroids (STC) for the treatment of EoE (Yes, No)
- Inadequate response, intolerant and/or contraindicated to swallowed topical corticosteroids (STC) (Yes, No)
- History of atopic dermatitis (Yes, No)
- History of asthma (Yes, No)
- History of allergic rhinitis (Yes, No)
- History of food allergy (Yes, No)
- Baseline BMI group (kg/m2; overweight: ≥85 percentile of BMI for ≥2 years based on age and gender, ≥95 percentile of weight based on length (height), age and gender for <2 years, not overweight: not meeting the criteria of overweight) [based on CDC (Center for Disease Control and Prevention) chart]
- Use of PPI at randomization (Yes, No)
- Prior esophageal dilations (Yes, No)
- Subject on a food elimination diet at the time of screening (Yes, No)
- Subject on a food elimination diet in the past (Yes, No)

The subgroup analysis was not performed if the number of patients within the subgroup was <10% of overall sample size. The stratification factor was not included in the subgroup analysis of primary efficacy endpoint.

Results

Participant flow



Of the 98 participants (96.1%) who completed the double-blind treatment period (Part A), 97 entered **Part B** of the study. One participant (1.0%) did not enter Part B. This participant in the placebo group discontinued by study day 113 due to an AE of Anxiety.

All participants who entered Part B received at least 1 dose of study intervention in Part B and were included in the Part B SAF. Nearly all treated participants (95.9%) completed 52 weeks of study treatment (i.e., 16 weeks of study intervention in Part A plus 36 weeks of study intervention in Part B) and received the final dose of Part B study intervention per protocol. Overall, 3 participants (3.1%) discontinued study intervention during Part B and 1 participant was still receiving study intervention in Part B at the time of data cut-off. This was the same patient, who had a delayed week 16 visit in Part A of the study due to health issues, as described above.

However, this instance pushed out the Part B dosing such that, at the time of data Cut-off, the participant's last recorded study intervention in Part B was at week 46.

Of the 3 participants who discontinued study intervention:

- 1 participant in the higher exposure dupilumab/higher exposure dupilumab group discontinued by study day 192 (last dose on study day 148 at week 18 due to an AE (PT: Drug hypersensitivity)
- 1 participant in the lower exposure dupilumab/lower exposure dupilumab group discontinued

by study day 373 (last dose on study day 341) due to family challenges disrupting the study participation (this participant also had important protocol deviations relating to treatment compliance and the data are also included in the data errata)

- 1 participant in the placebo/lower exposure dupilumab group inadvertently missed the final (week 50) dose (last dose week 48 dose), which was recorded by the site as premature discontinuation of study intervention

Overall, 95 of the 98 participants (96.9%) completed the week 52 visit (i.e., at the end of the extended active treatment period) of Part B, with no participants unable to complete the week 52 visit due to the COVID-19 pandemic. 2 participants (2.0%) were ongoing in Part B at the time of data cut-off and the 1 participant (1.0%) in the higher exposure dupilumab/higher exposure dupilumab group who discontinued study intervention due to an AE of Drug hypersensitivity also did not complete the week 52 visit. Of the 2 participants who were ongoing, 1 was still receiving study intervention and the other participant had completed study intervention but not the week 52 visit at the time of data cut-off due to health issues (non-COVID infection).

Recruitment

Part A:

Study Initiation Date: 01 Sep 2020 (date of first consent for first screened participant in Part A)

Final Analysis Date: 28 Apr 2022 (date of last week 16 visit completed in Part A)

The analyses presented in the CSR are based on a database lock date of 06 Jun 2022.

Part B:

First participant's first visit in Part B: was on 02 Mar 2021.

Part B Analysis Date: 17 Jan 2023 (date of last week 52 visit completed in Part B for this analysis). The analyses presented in the submission are based on a data cut-off date of 17 Jan 2023 and a database lock date of 07 Feb 2023.

Conduct of the study

Protocol Deviations

Summary of Important Protocol Deviations in Part A (Part A FAS)

		Dupilumab			
	Placebo (N=34)	Lower Exposure Dupilumab (N=31)	Higher Exposure Dupilumab (N=37)	Combined (N=68)	Total (N=102)
Number of Protocol Deviations	127	155	147	302	429
Number of Important Protocol Deviations	5	13	18	31	36
Number of Minor Protocol Deviations	122	142	129	271	393
Patients with Any Protocol Deviations, n (%)	29 (85.3%)	29 (93.5%)	32 (86.5%)	61 (89.7%)	90 (88.2%)
Patients with Any Important Protocol Deviation, n (%)	5 (14.7%)	9 (29.0%)	13 (35.1%)	22 (32.4%)	27 (26.5%)
Patients with Any Minor Protocol Deviation, n (%)	29 (85.3%)	29 (93.5%)	31 (83.8%)	60 (88.2%)	89 (87.3%)
Patients with Any Important Protocol Deviations by Categories, n (%)					
Procedure Not Performed	2 (5.9%)	9 (29.0%)	7 (18.9%)	16 (23.5%)	18 (17.6%)
Missed Pediatric EoE Symptom Questionnaire assessment (PESQ-C) more than 6 times in 14 day block (Day -14 through Day -1 and/or Day 99 to Day 113 and/or Day 351 to Day 365)	2 (5.9%)	7 (22.6%)	6 (16.2%)	13 (19.1%)	15 (14.7%)
Hematology not collected at Screening Visit 1	0	1 (3.2%)	0	1 (1.5%)	1 (1.0%)
Imaging of endoscopy not performed at Screening Visit 2, Visit 8, Visit 17, UV before rescue, or Early Termination	0	0	1 (2.7%)	1 (1.5%)	1 (1.0%)
Insufficient (eg, fewer than 3 areas collected) Esophageal biopsy samples collected at Visit 2, Visit 8, Visit 17, UV before rescue, or Early Termination	0	1 (3.2%)	0	1 (1.5%)	1 (1.0%)
Entered Study Even Though Entry Criteria Was Not Satisfied	0	2 (6.5%)	2 (5.4%)	4 (5.9%)	4 (3.9%)
Received Wrong Treatment Or Incorrect Dose	1 (2.9%)	0	4 (10.8%)	4 (5.9%)	5 (4.9%)
Inadequate Informed Consent Administration	0	1 (3.2%)	0	1 (1.5%)	1 (1.0%)
Other Treatment Compliance	2 (5.9%)	0	1 (2.7%)	1 (1.5%)	3 (2.9%)
Received An Excluded Concomitant Treatment	0	0	1 (2.7%)	1 (1.5%)	1 (1.0%)
Patients with Any Protocol Deviations due to COVID-19, n (%)	2 (5.9%)	9 (29.0%)	7 (18.9%)	16 (23.5%)	18 (17.6%)
Number of Important Protocol Deviations due to COVID-19	0	0	0	0	0
Patients with Any Important Protocol Deviation due to COVID-19, n (%)	0	0	0	0	0

The percentage is based on the number of randomized patients in each treatment group as denominator.
Abbreviations: COVID-19=Coronavirus Disease-2019; EoE=eosinophilic esophagitis; FAS=full analysis set; PESQ-C=Pediatric EoE Symptom Questionnaire-Caregiver version; UV=unscheduled visit.

Update via Addendum

There were 5 protocol deviation records included in the EDC system at the time of the Part A database lock (06 Jun 2022) that were no longer considered protocol deviations at the time of the Part B database lock (07 Feb 2023) and were removed. 4 of these were minor deviations related to procedures not performed. Three records were no longer considered protocol deviations because these

records were identified to be duplicates (missed visits and missed procedures associated with these visits were initially identified as protocol deviations, however the programming algorithm was later updated to avoid this duplication) and 1 record was no longer considered a protocol deviation due to the fact that the procedure was performed after Part A database lock.

One important protocol deviation related to received prohibited concomitant medication of a live (attenuated) vaccine was removed due to a change in adjudication after Part A database lock due to the confirmation that the vaccine was an inactivated vaccine and not a live vaccine.

New Protocol Deviation Records via Addendum

There were 19 new protocol deviations added between the Part A database lock (06 Jun 2022) and the Part B database lock (07 Feb 2023)]. Four of these were considered important deviations.

One participant had an early termination visit not performed. This protocol deviation for this participant was originally incorrectly assigned to the Part B treatment period. For one Participant EoE-EREFS imaging not performed. This participant had the investigator assessment of EoE-EREFS minor features completed, however the central portion of EoE-EREFS was not done. In the Part A CSR, this was originally captured under a protocol deviation (imaging of endoscopy for central reading not done). One participant had an initiation or change of food elimination diet, which was reported after Part A database lock. One participant received an excluded concomitant treatment, which was reported after Part A database lock.

Part B

During Part B, a total of 691 protocol deviations were reported from 92,9% of the participants. Of these 691 deviations, 9.3% were reported as important protocol deviations from 38 participants.

The most frequently reported important protocol deviation overall was in the category of procedure not performed (25.5% of participants), which was reported for 17.2% to 42.9% of participants across treatment groups. The most frequently reported procedure not performed was eDiary completion of the PESQ-C assessment, which was not completed >6 times in the 14-day period prior to week 52 in 22.4% of participants, varying between 10.8% in the higher exposure dupilumab/higher exposure dupilumab group, 17.2% in the lower exposure dupilumab/lower exposure dupilumab group, 38.9% in the placebo/higher exposure dupilumab group, and 42.9% in the placebo/lower exposure dupilumab group.

Although the protocol deviations are reflected in the number of participants with missing data at week 52, the data trends prior to week 52 were consistent with what was observed at week 52 across the treatment groups. This indicates that the protocol deviations do not unduly impact the interpretation of the data. In contrast to Part A, missing data were not imputed for the Part B analysis.

Other important protocol deviations categorized as procedure not performed were Weight not collected (4.1% of participants), EoE-EREFS imaging and imaging of endoscopy not performed (3.1% of participants) and Insufficient oesophageal biopsy samples collected (1.0%).

Overall, 8.2% had an important protocol deviation of "received wrong treatment or incorrect dose". Two participants (14.3%) in the placebo/lower exposure dupilumab group, 2 participants (6.9%) in the lower exposure dupilumab/lower exposure dupilumab group and 4 participants (10.8%) in the higher exposure dupilumab/higher exposure dupilumab group.

Overall, 2 participants (2.0%) had important protocol deviations due to the COVID-19 pandemic. One in the placebo/lower exposure dupilumab group and 1 in the lower exposure dupilumab/lower exposure dupilumab group. In both cases the deviation was procedure not performed.

Protocol Amendments

Part A

Three protocol amendments to the original protocol (dated 18 Nov 2019) were published prior to the database lock of Part A. Amendment 4 was implemented after the database lock of Part A and added the open-label extension Part C to the study design.

Protocol Amendment 1 (dated 07 Apr 2020) added the Pediatric Eosinophilic Esophagitis Symptom Score (PEESSv2.0-Caregiver version) questionnaire as a secondary endpoint and to change the Pediatric EoE Sign/Symptom Questionnaire (PESQ-Caregiver [PESQ-C] and PESQ-Patient [PESQ-P]) questionnaires from exploratory to secondary endpoints. Additionally, the Eosinophilic Esophagitis-Endoscopic Reference Score (EoE-EREFS) procedure was revised to allow for centralized reading and scoring. Other minor changes were made to align with health authority feedback and for general clarification.

Protocol Amendment 2 (dated 18 Nov 2020) added an additional treatment arm to evaluate a lower exposure of dupilumab, per health authority request. Additional updates were made for clarification of study conduct.

Protocol Amendment 3 (dated 13 Jun 2021) addressed health authority requests to include an exit interview with caregivers at week 16 (participants aged ≥8 to <12 years old could also join a portion of the exit interview), to support interpretation of clinically meaningful change in signs/symptoms during the study. Additional updates were the addition of symptom/sign-free days based on the PESQ-P or PESQ-C as a secondary endpoint and an update to the definition of the primary estimand for participants treated with corticosteroids.

Part B

Four protocol amendments to the original protocol (dated 18 Nov 2019) were published prior to the database lock of Part B:

Protocol Amendment 1 (dated 07 Apr 2020) added the PEESSv2.0-Caregiver version questionnaire as a secondary endpoint and changed the PESQ-C and PESQ-P questionnaires from exploratory to secondary endpoints. Additionally, the EoE-EREFS procedure was revised to allow for centralized reading and scoring. Other minor changes were made to align with health authority feedback and for general clarification.

Protocol Amendment 2 (dated 18 Nov 2020) added an additional treatment arm to evaluate a lower exposure of dupilumab, per health authority request. Additional updates were made for clarification of study conduct.

Of note, Protocol Amendment 2 allowed for certain study procedures to occur at delayed time points and/or outside of the clinic environment as a result of the COVID-19 pandemic:

- If necessary, the visit schedule could be adjusted, in-person visits could be converted to telephone contacts and study procedures could be postponed until the next available in clinic study visit. The randomization visit (visit 3) and the first visit of Part B had to occur in the clinic.
- Endoscopies with biopsies were required at approximately week 16 (Part A) and week 52 (Part B). If it was not possible to complete the endoscopies with biopsies due to COVID-19 restrictions and provided there were no specific safety concerns for the participant, participants may have continued their current study medication regimen until the endoscopies with biopsies could be performed.

Protocol Amendment 3 (dated 13 Jun 2021) was implemented to address health authority requests to include an exit interview with caregivers at week 16 (participants aged ≥8 to <12 years old could also join a portion of the exit interview), to support interpretation of clinically meaningful change in signs and symptoms during the study. Additional updates were the addition of symptom/sign-free days based on the PESQ-P or PESQ-C as a secondary endpoint and an update to the definition of the primary estimand for participants treated with corticosteroids.

Protocol Amendment 4 (dated 03 Aug 2022) added the open-label extension Part C to the study design and updated the exploratory objective and endpoints relating to changes in weight and growth to a secondary objective and endpoints.

Change to Study Conduct Related to the COVID-19 Pandemic

Study R668-EE-1877 was conducted during the COVID-19 pandemic.

The continuity of clinical study conduct and oversight required implementation of temporary or alternative mechanisms. Alternate mechanisms employed included, but were not limited to phone contact, virtual visits, online meetings, and remote monitoring. Of note, Protocol Amendment 2 allowed for certain study procedures to occur at delayed time points and/or outside of the clinic environment as a result of the COVID-19 pandemic. If it was not possible to complete the endoscopies with biopsies due to COVID-19 restrictions and provided there were no specific safety concerns for the participant, participants may have continued their current study medication regimen until the endoscopies with biopsies could be performed. Additionally, no waivers to deviate from protocol enrolment criteria due to COVID-19 were granted. All temporary mechanisms utilized, and deviations from planned study procedures were documented as being related to COVID-19 and remained in effect only for the duration of the public health emergency.

Baseline data

Table 16. Summary of Demographics (Part A FAS)

		Dupilumab			
	Placebo (N=34)	Lower Exposure Dupilumab (N=31)	Higher Exposure Dupilumab (N=37)	Combined (N=68)	Total (N=102)
Age (years)					
n	34	31	37	68	102
Mean (SD)	7.2 (3.03)	7.2 (3.07)	6.8 (3.11)	7.0 (3.07)	7.1 (3.05)
Median	7.5	8.0	7.0	8.0	8.0
Q1 : Q3	6.0 : 10.0	5.0 : 10.0	4.0 : 10.0	4.0 : 10.0	5.0 : 10.0
Min : Max	1 : 11	1 : 11	1 : 11	1 : 11	1 : 11
Age Group, n (%)					
≥1 - <6 years	8 (23.5%)	11 (35.5%)	14 (37.8%)	25 (36.8%)	33 (32.4%)
≥6 - <12 years	26 (76.5%)	20 (64.5%)	23 (62.2%)	43 (63.2%)	69 (67.6%)
≥1 - <8 years	17 (50.0%)	12 (38.7%)	20 (54.1%)	32 (47.1%)	49 (48.0%)
≥8 - <12 years	17 (50.0%)	19 (61.3%)	17 (45.9%)	36 (52.9%)	53 (52.0%)
Ethnicity, n (%)					
Not Hispanic or Latino	30 (88.2%)	29 (93.5%)	33 (89.2%)	62 (91.2%)	92 (90.2%)
Hispanic or Latino	3 (8.8%)	2 (6.5%)	2 (5.4%)	4 (5.9%)	7 (6.9%)
Unknown	1 (2.9%)	0	0	0	1 (1.0%)
Not Reported	0	0	2 (5.4%)	2 (2.9%)	2 (2.0%)
Race, n (%)					
White	30 (88.2%)	22 (71.0%)	32 (86.5%)	54 (79.4%)	84 (82.4%)
Black or African American	3 (8.8%)	4 (12.9%)	4 (10.8%)	8 (11.8%)	11 (10.8%)
Asian	0	1 (3.2%)	1 (2.7%)	2 (2.9%)	2 (2.0%)
Other	1 (2.9%)	4 (12.9%)	0	4 (5.9%)	5 (4.9%)
Sex, n (%)					
Male	25 (73.5%)	25 (80.6%)	28 (75.7%)	53 (77.9%)	78 (76.5%)
Female	9 (26.5%)	6 (19.4%)	9 (24.3%)	15 (22.1%)	24 (23.5%)
Height (cm)					
n	34	31	37	68	102

Mean (SD)	124.8 (19.83)	122.8 (18.80)	120.2 (19.50)	121.4 (19.09)	122.5 (19.31)
Median	127.8	129.8	122.0	126.5	126.5
Q1 : Q3	116.0 : 138.5	104.7 : 136.3	101.5 : 140.0	101.8 : 138.5	102.5 : 138.5
Min : Max	81 : 170	83 : 148	82 : 148	82 : 148	81 : 170
Weight (kg)					
n	34	31	37	68	102
Mean (SD)	28.3 (11.99)	26.1 (10.06)	26.0 (10.60)	26.1 (10.28)	26.8 (10.87)
Median	24.8	25.4	24.8	25.4	25.1
Q1 : Q3	21.0 : 35.2	17.5 : 31.9	15.7 : 32.2	17.2 : 32.1	17.3 : 33.6
Min : Max	11 : 60	10 : 48	12 : 47	10 : 48	10 : 60
Weight group, n (%)					
≥5-<15 kg	5 (14.7%)	5 (16.1%)	5 (13.5%)	10 (14.7%)	15 (14.7%)
≥15-<30 kg	18 (52.9%)	18 (58.1%)	19 (51.4%)	37 (54.4%)	55 (53.9%)
≥30-<60 kg	11 (32.4%)	8 (25.8%)	13 (35.1%)	21 (30.9%)	32 (31.4%)
Weight for Age Percentile at Baseline					
n	34	31	37	68	102
Mean (SD)	47.68 (32.843)	40.09 (33.423)	47.21 (28.662)	43.96 (30.893)	45.20 (31.443)
Median	38.19	35.37	46.47	41.35	39.71
Q1 : Q3	19.26 : 80.93	9.59 : 74.24	19.30 : 68.93	14.76 : 69.31	15.55 : 72.57
Min : Max	1.1 : 99.8	0.1 : 98.9	1.8 : 96.8	0.1 : 98.9	0.1 : 99.8
Weight for Age Percentile at Baseline Categories, n (%)					
0 to <25%	11 (32.4%)	13 (41.9%)	10 (27.0%)	23 (33.8%)	34 (33.3%)
25% to <50%	7 (20.6%)	8 (25.8%)	12 (32.4%)	20 (29.4%)	27 (26.5%)
50% to <75%	7 (20.6%)	3 (9.7%)	8 (21.6%)	11 (16.2%)	18 (17.6%)
≥75%	9 (26.5%)	7 (22.6%)	7 (18.9%)	14 (20.6%)	23 (22.5%)
Weight for Age Z-score at Baseline					
n	34	31	37	68	102
Mean (SD)	0.0 (1.27)	-0.4 (1.29)	-0.1 (0.94)	-0.2 (1.12)	-0.1 (1.17)
Median	-0.3	-0.4	-0.1	-0.2	-0.3
Q1 : Q3	-0.9 : 0.9	-1.3 : 0.7	-0.9 : 0.5	-1.0 : 0.5	-1.0 : 0.6
Min : Max	-2 : 3	-3 : 2	-2 : 2	-3 : 2	-3 : 3
BMI (kg/m^2)					
n	34	31	37	68	102
Mean (SD)	17.3 (2.88)	16.6 (2.79)	17.3 (2.89)	17.0 (2.84)	17.1 (2.84)
Median	16.3	15.9	16.4	16.1	16.1
Q1 : Q3	15.0 : 19.1	14.9 : 17.2	15.3 : 18.1	15.1 : 17.4	15.0 : 18.4
Min : Max	14 : 25	14 : 26	14 : 26	14 : 26	14 : 26
BMI group, n (%)					
Overweight: Yes	9 (26.5%)	5 (16.1%)	8 (21.6%)	13 (19.1%)	22 (21.6%)
Overweight: No	25 (73.5%)	26 (83.9%)	29 (78.4%)	55 (80.9%)	80 (78.4%)
BMI for Age Z-score at Baseline					
n	34	31	37	68	102
Mean (SD)	0.2 (1.09)	-0.1 (1.19)	0.2 (1.02)	0.1 (1.11)	0.1 (1.10)
Median	0.3	-0.1	0.1	-0.1	0.1
Q1 : Q3	-0.5 : 1.1	-0.9 : 0.8	-0.4 : 1.0	-0.6 : 0.9	-0.6 : 1.0
Min : Max	-2 : 3	-2 : 2	-2 : 2	-2 : 2	-2 : 3
Country, n (%)					
Canada	0	1 (3.2%)	0	1 (1.5%)	1 (1.0%)
United States	34 (100%)	30 (96.8%)	37 (100%)	67 (98.5%)	101 (99.0%)

BMI group: overweight was defined as ≥85 percentile of BMI for ≥2 years based on age and gender, ≥95 percentile of weight based on length (height), age, and gender for <2 years; not overweight was defined as not meeting the criteria of overweight [based on CDC chart].
Abbreviations: BMI=body mass index; CDC=Centers for Disease Control and Prevention; FAS=full analysis set; Max=maximum; Min=minimum; Q1=quartile 1; Q3=quartile 3; SD=standard deviation.

Demographic characteristics for participants from Part A who enrolled in Part B were consistent with those for participants from the Part A FAS. The mean weight of participants when entering Part B was 28.1 kg with 12.2% of participants ≥5 to <15 kg, 50.0% of participants ≥15 to <30 kg, and 37.8% of participants ≥30 to <60 kg; there were no participants ≥60 kg.

Baseline Disease Characteristics

The mean peak eosinophil count of 3 oesophageal regions (proximal, mid, and distal) at baseline was 83.3 eos/hpf. The mean (SD) EoE-EREFS total score at baseline was 6.9 points. The mean proportion of days with 1 or more EoE signs (assessed by PESQC) at baseline was 0.54 days (calculated from the 14-day period prior to the baseline visit).

The mean EoE-EREFS inflammation and remodelling subscores at baseline ranged from 5.6 to 6.3 and 0.8 to 1.0, respectively, across treatment groups.

Most participants (85.3%) had a baseline blood peripheral eosinophil count ≥0.30 giga/L. A number of participants in the FAS had other type 2 co-morbidities, including AD (60.8%), asthma (58.8%), allergic rhinitis (76.5%), and food allergies (82.4%).

Participants were required to have a confirmed diagnosis of EoE that was not responsive to at least 8 weeks of treatment with a PPI regimen. Participants were to continue the same or similar approved dosage regimen for the duration of the treatment period, or stop the PPI regimen prior to baseline and remain off of PPIs during the entire study. Approximately one-half of participants (48.0%) were receiving PPIs at the time of randomization.

Almost all participants (98.0%) in the FAS had a current history of at least 1 atopic/allergic condition other than EoE. The most frequently reported current allergic conditions were food allergy (81.4%) and allergic rhinitis (76.5%). Over one-half of participants (54.9%) reported a current history of asthma and over one-half (53.9%) reported a current history of AD.

The baseline disease characteristics indicated a symptomatic population, with the majority of participants having previously used STCs for the treatment of EoE (80.4%). Only 30/102 participants (29.4%) reported STCs as being previously effective for EoE. Over one-half of participants (57.8%) had a history of an inadequate response, intolerance, and/or contraindication to STCs. The majority of participants (62.7%) reported that EoE symptoms recurred within 3 months after stopping STCs. Only few pediatric participants (2.0%) had a prior oesophageal dilation.

Almost all participants (96.1%) in the Part A FAS used at least 1 prior medication (other than PPIs and corticosteroids used to treat EoE): 96.8% in the lower exposure dupilumab group, 97.3% in the higher exposure group and 94.1% in the placebo group. The most frequently reported Anatomical Therapeutic Classification (ATC) Therapeutic Classes of prior medications were Anesthetics (70.6%), Blood Substitutes and Perfusion Solutions (62.7%), Antihistamines for Systemic Use (61.8%), Antiemetics and Antinauseants (57.8%), Cardiac Therapy (57.8%), and Drugs for Obstructive Airway Diseases (54.9%). Of note, some of the prior medications (Anesthetics and Perfusion Solutions, most commonly propofol and electrolyte solutions) were administered in the course of performing the study-required screening endoscopy.

Participants on a food-elimination diet were to remain on the same diet throughout the study. Most participants (88.2%) had been on a food elimination diet in the past, including 84/102 participants (82.4%) who were on a food elimination diet at screening.

Numbers analysed

Summary of Study Analysis Sets by Treatment Group

		Dupilumab			
	Placebo (N=34)	Lower Exposure Dupilumab (N=31)	Higher Exposure Dupilumab (N=37)	Combined (N=68)	Total (N=102)
All Randomized Patients, n	34	31	37	68	102
Patients Included in the Safety Analysis Set (SAF), n (%)	34 (100%)	30 (96.8%)	37 (100%)	67 (98.5%)	101 (99.0%)
Patients Excluded from SAF, n (%)	0	1 (3.2%)	0	1 (1.5%)	1 (1.0%)
Patients included in the Full Analysis Set (FAS), n (%)	34 (100%)	31 (100%)	37 (100%)	68 (100%)	102 (100%)
Patients in PK analysis set, n (%)	34 (100%)	28 (90.3%)	36 (97.3%)	64 (94.1%)	98 (96.1%)
Patients in ADA analysis set, n (%)	27 (79.4%)	27 (87.1%)	34 (91.9%)	61 (89.7%)	88 (86.3%)
Patients in NAb analysis set, n (%)	27 (79.4%)	27 (87.1%)	34 (91.9%)	61 (89.7%)	88 (86.3%)

The percentage is based on the number of randomized patients in each treatment group as denominator.
Abbreviations: ADA=anti-drug antibody; FAS=full analysis set; NAb=neutralizing antibody; PK=pharmacokinetic; SAF=safety analysis set.

All 98 participants who entered Part B were included in the SAF, PK, ADA, and NAb analysis sets: 14 in the placebo/lower exposure dupilumab group, 18 in the placebo/higher exposure dupilumab group, 29 in the lower exposure dupilumab/lower exposure dupilumab group, and 37 in the higher exposure dupilumab/higher exposure dupilumab group. The Part B SAF is the basis for the Part B efficacy and safety analyses.

Outcomes and estimation

Primary Efficacy Endpoint

Part A

- Proportion of Participants Achieving Peak Oesophageal Intraepithelial Eosinophil Count ≤6 eos/hpf at Week 16

Table 17. Primary Analysis for the Proportion of Participants Achieving Peak Oesophageal Intraepithelial Eosinophil Count of ≤6 eos/hpf in All Three Regions at Week 16 (Participants Considered Non-responder after Rescue Treatment Use and MI Method for Missing due to COVID-19) (Part A FAS)

Treatment	Patients with Peak Esophageal Intraepithelial Eosinophil Count of ≤6 eos/hpf at Week 16, n (%)	95 % CI [1]	Difference (95% CI) [2]	Odds Ratio (95% CI) [3]	P-value [3]
Higher Exposure Dupilumab (N=37)	25 (67.6)	(50.21, 81.99)	64.5 (48.19, 80.85)	53.8 (7.37, 392.82)	<0.0001
Lower Exposure Dupilumab (N=31)	18 (58.1)	(39.08, 75.45)	55.1 (36.85, 73.42)	46.7 (5.47, 399.54)	<0.0001
Placebo (N=34)	1 (2.9)	(0.07, 15.33)			

Participants were considered as non-responders after rescue treatment. Participants with missing peak esophageal intraepithelial eosinophil count at Week 16 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] The CI for proportion of responders in each treatment was calculated using exact binomial method.
[2] Differences between dupilumab groups and placebo and corresponding CI are based on Mantel-Haenszel method and are stratified by baseline weight group (≥5 - <15 kg, ≥15 - <30 kg, ≥30 - <60 kg).
[3] Odds ratios, CIs and p-values were derived by CMH test stratified by baseline weight group (≥5 - <15 kg, ≥15 - <30 kg, ≥30 - <60 kg).
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.

Sensitivity analyses, using Tipping point analysis and a WOCF-MI approach, yielded similar results as the primary analysis and confirmed that, regardless of the assumptions used for missing data, treatment with the higher exposure dupilumab regimen produced a greater clinical effect size in comparison with placebo. The positive effect was also observed for the lower exposure dupilumab regimen when compared with placebo but was of numerical lesser magnitude than in the higher dupilumab dose regimen.

The tipping point analyses which assessed treatment effect using MIs under various MNAR assumptions, showed that the treatment effect remained significant (nominal $p<0.05$) even when using extremely implausible conditions, confirming the robustness of the study results. The results of the sensitivity analysis by WOCF-MI approach also support the findings of the primary analysis and thus, the robustness of the results.

Secondary Efficacy Endpoints (selected)

Part A

In the higher exposure dupilumab regimen, secondary endpoints for histology, endoscopy, and transcriptomic outcomes showed statistically significant p-values until the endpoint assessing the

proportion of days with 1 or more EoE signs by PESQ-C in the higher exposure dupilumab regimen. After this endpoint (hierarchy break), the p-values are nominal.

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

Table 18. Proportion of Participants Achieving Peak Oesophageal Intraepithelial Eosinophil Count of <15 eos/hpf in All Three Regions at Week 16, Participants Considered Non-responder after Rescue Treatment Use and MI Method for Missing due to COVID-19 (Part A FAS)

Treatment	Patients with Peak Esophageal Intraepithelial Eosinophil Count of <15 eos/hpf at Week 16, n (%)	95 % CI [1]	Difference (95% CI) [2]	Odds Ratio (95% CI) [3]	P-value [3]
Higher Exposure Dupilumab (N=37)	31 (83.8)	(67.99, 93.81)	81.1 (68.07, 94.10)	178.0 (18.84,1682.4)	<0.0001
Lower Exposure Dupilumab (N=31)	21 (67.7)	(48.63, 83.32)	65.4 (48.02, 82.81)	55.3 (7.45,410.23)	<0.0001*
Placebo (N=34)	1 (2.9)	(0.07, 15.33)			

Participants were considered as non-responders after rescue treatment. Participants with missing peak esophageal intraepithelial eosinophil count at Week 16 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.
*P-value for lower exposure dupilumab is nominal (see Table 16).
[1] The CI for proportion of responders in each treatment was calculated using exact binomial method.
[2] Differences between dupilumab groups and placebo and corresponding CI are based on Mantel-Haenszel method and are stratified by baseline weight group (≥5 - <15 kg, ≥15 - <30 kg, ≥30 - <60 kg).
[3] Odds ratios, CIs and p-values were derived by CMH test stratified by baseline weight group (≥5 - <15 kg, ≥15 - <30 kg, ≥30 - <60 kg).
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.

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

Table 19. Percent Change from Baseline in Peak Oesophageal Intraepithelial Eosinophil Count (eos/hpf) at Week 16, WOCF-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]
Higher Exposure Dupilumab (N=37)	-86.09 (11.841)	(-109.595, -62.586)	-87.43 (19.887)	92.0 (48.04)	37/0	Higher Exposure Dupilumab vs Placebo	-107.07 (-139.249,-74.900)	<0.0001
Lower Exposure Dupilumab (N=31)	-77.93 (12.893)	(-103.525, -52.339)	-73.03 (39.463)	74.7 (30.56)	28/3	Lower Exposure Dupilumab vs Placebo	-98.92 (-132.463, -65.370)	<0.0001*
Placebo (N=34)	20.98 (12.232)	(-3.296, 45.265)	23.20 (110.167)	81.8 (36.14)	31/3			

Values after first rescue treatment use were set to missing (censoring). Missing values were imputed by WOCF method if not due to COVID-19 and by MI method if due to COVID-19
* P-value for lower exposure dupilumab is nominal (see Table 16).
[1] The CI with p-value is based on treatment difference (Dupilumab groups vs. placebo) of the LS mean change using ANCOVA model with baseline measurement as covariate and the treatment, baseline weight group (≥5 - <15 kg, ≥15 - <30 kg, ≥30 - <60 kg) strata as fixed factors.
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; COVID-19=Coronavirus Disease-2019; FAS=full analysis set; LS=least squares; MI=multiple imputations; SD=standard deviation; SE=standard error; WOCF=worst observation carried forward.

- Absolute Change from Baseline in EoE-HSS Mean Grade Score

The EoE-HSS evaluates more detailed histologic changes than are captured by the 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 8 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.

Table 20. Absolute Change from Baseline in EoE-HSS Mean Grade Score at Week 16, WOCF-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]
Higher Exposure Dupilumab (N=37)	-0.879 (0.0481)	(-0.9742, -0.7833)	-0.919 (0.4146)	1.321 (0.4128)	37/0	Higher Exposure Dupilumab vs Placebo	-0.902 (-1.0325, -0.7714)	<0.0001
Lower Exposure Dupilumab (N=31)	-0.757 (0.0524)	(-0.8612, -0.6534)	-0.701 (0.4035)	1.195 (0.3326)	28/3	Lower Exposure Dupilumab vs Placebo	-0.780 (-0.9170, -0.6440)	<0.0001*
Placebo (N=34)	0.023 (0.0498)	(-0.0756, 0.1219)	0.029 (0.3443)	1.260 (0.3621)	31/3			

Values after first rescue treatment use were assigned using WOCF (worst observation carried forward) method. Missing values were imputed by WOCF method if not due to COVID-19 and by MI method if due to COVID-19.
*P-value for lower exposure dupilumab is nominal (see Table 16).
[1] The CI with p-value is based on treatment difference (Dupilumab groups vs. Placebo) of the LS mean change using ANCOVA model with baseline measurement as covariate and the treatment, baseline weight group (≥5 - <15 kg, ≥15 - <30 kg, ≥30 - <60 kg) strata as fixed factors.
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; COVID-19=Coronavirus Disease-2019; EoE-HSS=Eosinophilic Esophagitis Histology Scoring System; FAS=full analysis set; LS=least squares; MI=multiple imputations; SD=standard deviation; SE=standard error.

- Absolute Change from Baseline in EoE-HSS Mean Stage Score

Treatment with the higher exposure dupilumab regimen resulted in a significant improvement (ie, decrease) in EoE-HSS mean stage score compared with placebo at week 16, with a greater LS mean (SE) change from baseline (-0.835 [0.0466]) compared with placebo (0.048 [0.0482]; p<0.0001). In the lower exposure dupilumab regimen, LS mean (SE) change also showed an improvement compared with placebo (-0.721 [0.0507] versus 0.048 [0.0482], respectively; nominal p<0.0001). The LS Mean Difference (95% CI) for the higher exposure dupilumab regimen vs placebo was -0.883 (-1.0095, -0.7568; p<0.0001) and -0.769 (-0.9013, -0.6362; nominal p<0.0001) for the lower dupilumab regimen vs placebo.

- Absolute Change from Baseline in EoE-EREFS (Central Reading) Total Score

The EoE-EREFS is a validated endoscopic scoring system for inflammatory and remodelling features of EoE including edema, rings, exudates, furrows, and stricture; the score was assessed in the proximal and distal oesophageal regions with each region scored from 0 to 9 with total scores possibly ranging from 0 to 18. Higher scores indicate worse endoscopic inflammatory and remodelling findings.
Treatment with higher exposure dupilumab regimen resulted in significant improvement (ie, decrease) in EoE-EREFS total score compared to placebo at week 16, with a greater LS mean change from baseline (-3.5) compared with placebo (0.3 ; p<0.0001).
In the lower exposure dupilumab regimen, LS mean change also showed an improvement compared with placebo (-3.0 versus 0.3 respectively; nominal p<0.0001).
The LS Mean Difference (95% CI) for the higher exposure dupilumab regimen vs placebo was -3.8 (-4.94, -2.63; p<0.0001) and -3.3 (-4.59, -2.10; nominal p<0.0001) for the lower dupilumab regimen vs placebo.
Exploratory endpoints assessing changes in EoE-EREFS excluding strictures and EoE-ERFES inflammation subscores at week 16, also showed greater improvements in both dupilumab treatment regimens compared with placebo. The EoE-EREFS remodelling subscore did not show any differences between either dupilumab regimens compared with placebo. This is expected as the fibrostenotic changes, such as rings and strictures are uncommon in children (Singla, 2016), and evidenced by the

low EoE-EREFS remodelling subscore mean values at baseline in the study participants (0.9 and 0.8 for the higher and lower exposure dupilumab regimens, respectively, and 1.0 for placebo).

- Change from Baseline to Week 16 in Proportion of Days with 1 or More EoE Signs as Measured by the PESQ-C

PESQ-C is a novel, observer-reported outcome measure intended to be completed independently by caregivers of all pediatric EoE participants in the study. The PESQ-C measures the signs of EoE observed by the caregiver, including stomach pain, heartburn, acid reflux, regurgitation, vomiting, food refusal, and trouble swallowing food.

The PESQ-C score was calculated based on the daily responses over a 14-day period (ie, the 14 days prior to the baseline visit and the week 16 visit). The score ranges from 0 to 1. There was no requirement to have a minimum PESQ-C score for inclusion in the study. The mean baseline scores for PESQ-C were 0.46, 0.64, and 0.53 for the higher exposure dupilumab, lower exposure dupilumab, and placebo groups respectively, corresponding to an average of 6.44, 8.96, and 7.42 days of symptoms (out of the prior 14 days) for the 3 respective treatment groups. The highest score is found in the lower exposure dupilumab group. This could indicate that these patients were more symptomatic.

Table 21. Change from Baseline to Week 16 in the Proportion of Days with 1 or More EoE Signs as Measured by the PESQ-C, WOCF-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]
Higher Exposure Dupilumab (N=37)	-0.28 (0.052)	(-0.378, -0.173)	-0.23 (0.299)	0.46 (0.378)	31/5	Higher Exposure Dupilumab vs Placebo	-0.10 (-0.244, 0.038)	0.1526
Lower Exposure Dupilumab (N=31)	-0.18 (0.060)	(-0.295, -0.059)	-0.20 (0.291)	0.64 (0.368)	23/6	Lower Exposure Dupilumab vs Placebo	-0.00 (-0.155, 0.146)	0.9533
Placebo (N=34)	-0.17 (0.054)	(-0.279, -0.067)	-0.16 (0.366)	0.53 (0.361)	30/4			

Values after first rescue treatment use were set to missing (censoring). WOCF approach was used for imputing the missing data due to rescue treatment/AE/lack of efficacy, and the MI approach was used for the missing data due to other reasons.
[1] The CI with p-value is based on treatment difference (Dupilumab groups vs. Placebo) of the LS mean change using ANCOVA model with baseline measurement as covariate and the treatment, baseline weight group (≥5 - <15 kg, ≥15 - <30 kg, ≥30 - <60 kg) strata as fixed factors.
Abbreviations: AE=adverse event; ANCOVA=analysis of covariance; CI=confidence interval; FAS=full analysis set; LS=least squares; MI=multiple imputations; PESQ-C=Pediatric EoE Sign/Symptom Questionnaire-Caregiver version; SD=standard deviation; SE=standard error; WOCF=worst observation carried forward.

- Changes in Other PESQ-C Secondary Endpoints
    - Number of Sign-free Days During the 14-Day Period prior to Week 16

The LS mean number of sign-free days during the 14-day period prior to week 16 as assessed by PESQ-C showed a non-significant trend in improvement for the higher exposure dupilumab regimen (10.38 sign-free days) compared to placebo (8.93 sign-free days; p=0.1507), but no difference between lower exposure dupilumab regimen (8.93 sign-free days) and placebo (p=0.9965).

    - Change from Baseline to Week 16 in the Proportion of Total Segments Within a Day with 1 or More EoE Signs

The proportion of total segments (night, morning, afternoon, evening) with 1 or more EoE signs measured by the PESQ-C during a 14-day period is calculated as the total number of segments in which a patient has 1 or more EoE signs divided by the total number of segments with non-missing eDiary entries.

The LS mean change from baseline to week 16 in the proportion of total segments within a day with 1 or more EoE signs as assessed by PESQ-C showed a trend towards improvement in the higher exposure dupilumab regimen but not for the lower exposure dupilumab regimen (−0.16 and −0.09, respectively) compared to the placebo group (−0.11).

- Changes in PESQ-P Secondary Endpoints

PESQ-P is a novel, patient-reported outcomes measure which assesses symptoms of EoE, including stomach pain, heartburn, acid reflux, regurgitation, vomiting, food refusal and trouble swallowing food. The PESQ-P is intended to be completed independently by patients with EoE aged ≥8 to <12 years. This can result in smaller sample sizes (ie, N=53) and there can be a high placebo effect in children.

The mean change from Baseline to Week 16 in Proportion of Days with 1 or More EoE Symptoms as measured by the PESQ-P was -0.13 in the higher exposure group, -0.18 in the lower exposure group and -0.27 in the placebo group. According to these results the placebo showed the greater improvement. Of note, the baseline means in the higher exposure group were lower compared to lower treatment and placebo group.

- Change in Total Score from Baseline to Week 16 as Measured by the PEESSv2.0-Caregiver Version Questionnaire

The PEESSv2.0-Caregiver version score is a validated, observer-reported outcomes measure through which caregivers assess the frequency and severity of EoE signs in pediatric patients (Franciosi, 2011). The PEESSv2.0-Caregiver version consists of 20 items and has a 1-month recall period. The total PEESSv2.0 score ranges from 0 to 100 with higher scores indicating greater symptom burden.

The LS mean change from baseline to week 16 in the PEESSv2.0-Caregiver version questionnaire total score showed a greater decrease improvement in the higher exposure dupilumab group (-19.86) compared to the placebo group (-11.83), but not for the lower exposure dupilumab regimen (-10.10). The mean difference between the higher exposure dupilumab group and placebo was -8.03 points, which was nominally significant with a nominal p=0.0328. The lower exposure dupilumab group did not improve symptoms relative to placebo, with a LS mean difference from baseline compared with placebo of 1.73 points, p=0.6573.

- Percent Change in Total Score from Baseline to Week 16 as Measured by the Pediatric EoE Impact Scale-Caregiver Version

The PEIS-C is intended to be completed independently by caregivers of pediatric EoE patients aged ≥1 to <12 years and assesses the impact of the pediatric patient's EoE on caregiver QoL (anxiety, social and professional activities, activities of daily living, and relationships) during the past 1 week. The average PEIS-C score ranges from 0 to 4, where a higher score is indicative of greater negative impact of EoE on caregiver QoL.

Differences in baseline scores were observed across treatment arms, with the lower exposure dupilumab group presenting the highest mean value. The mean percent change from baseline to week 16 in the PEIS-C total score showed a greater improvement (decrease) in the higher exposure dupilumab regimen (-53.98%) compared with placebo (-7.53%). A lesser degree of reduction was observed for the lower exposure dupilumab group (-30.68%).

- Percent Change in Total Score from Baseline to Week 16 as Measured by the Pediatric EoE Impact Scale-Patient Version

The PEIS-P is a patient-reported outcomes measure intended to be completed independently by pediatric EoE patients aged ≥8 to <12 years which assesses the impact of EoE on patients QoL during

the past 1 week. The average PEIS-P score ranges from 0 to 4 with a higher score indicating greater negative impact of EoE on patient QoL.

In contrast to the PESQ-P assessment which did not demonstrate any improvement in the participant's EoE symptoms, an improvement (decrease) was shown in the PEIS-P total score with a mean percent change from baseline to week 16 of -35.76% in the higher exposure dupilumab regimen, -12.96 in the lower exposure group and -13.44 in the placebo group.

However, for PEIS-C and PEIS-P it has to be noted that differences in baseline score values were observed across treatment arms with the highest values in the lower exposure group, which could indicate that these patients were more symptomatic than the patients in higher exposure groups and the placebo group, which had the lowest values.

Part B

There were no primary efficacy endpoints for Part B of the study. Primary and secondary efficacy endpoints assessed at the end of double-blind, 16-week treatment period (ie, Part A) were assessed at week 52 as secondary endpoints for Part B of the study (ie, 36-week extended active treatment period for participants who completed Part A).

Table 22. Results for Secondary Efficacy Endpoints at Part B Baseline (End of Part A [ie, Week 16]) and Week 52 (End of Part B), All Observed Values Regardless of Rescue Treatment Use (Part B SAF) (Abbrev.)

Efficacy Endpoints	Part A/ Part B Treatment							
	Week 16 (End of Part A/Part B Baseline)				Week 52 (End of Part B)			
	Placebo/ Lower Exposure Dupi (N=14)	Placebo/ Higher Exposure Dupi (N=18)	Lower Exposure Dupi/ Lower Exposure Dupi (N=29)	Higher Exposure Dupi/ Higher Exposure Dupi (N=37)	Placebo/ Lower Exposure Dupi (N=14)	Placebo/ Higher Exposure Dupi (N=18)	Lower Exposure Dupi/Lower Exposure Dupi (N=29)	Higher Exposure Dupi/ Higher Exposure Dupi (N=35)
Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf	1/13 (7.7%)	0/18	18/28 (64.3%)	25/37 (67.6%)	13/14 (92.9%)	9/17 (52.9%)	19/29 (65.5%)	22/35 (62.9%)
Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf	1/13 (7.7%)	0/18	21/28 (75.0%)	31/37 (83.8%)	13/14 (92.9%)	11/17 (64.7%)	20/29 (69.0%)	30/35 (85.7%)
Part A baseline peak esophageal intraepithelial count, mean (SD)	*67.07 (28.723) (N1=14)*	*90.56 (38.764) (N1=18)*	*72.07 (27.262) (N1=29)*	*92.00 (48.039) (N1=37)*	*67.07 (28.723) (N1=14)*	*90.56 (38.764) (N1=18)*	*72.07 (27.262) (N1=29)*	*92.00 (48.039) (N1=37)*
Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline, mean (SD)[a]	11.06 (70.354) (N1=13)	36.98 (140.144) (N1=18)	-80.85 (32.778) (N1=28)	-87.43 (19.887) (N1=37)	-92.72 (19.229) (N1=14)	-76.83 (41.228) (N1=17)	-85.41 (22.851) (N1=29)	-90.97 (14.482) (N1=35)
Part A baseline EoE-HSS mean grade score, mean (SD)	*1.148 (0.3403) (N1=14)*	*1.345 (0.3671) (N1=18)*	*1.190 (0.3181) (N1=29)*	*1.321 (0.4128) (N1=37)*	*1.148 (0.3403) (N1=14)*	*1.345 (0.3671) (N1=18)*	*1.190 (0.3181) (N1=29)*	*1.321 (0.4128) (N1=37)*
Absolute change in mean EoE grade score from the EoE-HSS from baseline to week 52[a]	-0.055 (0.3939) (N1=13)	0.085 (0.3228) (N1=18)	-0.776 (0.3471) (N1=28)	-0.919 (0.4146) (N1=37)	-0.804 (0.3099) (N1=14)	-0.885 (0.2962) (N1=17)	-0.773 (0.3374) (N1=29)	-0.967 (0.3920) (N1=35)
Part A baseline EoE-HSS mean stage score, mean (SD)	*1.184 (0.3428) (N1=14)*	*1.382 (0.3589) (N1=18)*	*1.231 (0.2955) (N1=29)*	*1.287 (0.3227) (N1=37)*	*1.184 (0.3428) (N1=14)*	*1.382 (0.3589) (N1=18)*	*1.231 (0.2955) (N1=29)*	*1.287 (0.3227) (N1=37)*

Absolute change in mean EoE stage score from the EoE-HSS from baseline [a]	0.005 (0.3568) (N1=13)	0.048 (0.3561) (N1=18)	-0.766 (0.3310) (N1=28)	-0.852 (0.3427) (N1=37)	-0.767 (0.3114) (N1=14)	-0.855 (0.3485) (N1=17)	-0.784 (0.3183) (N1=29)	-0.892 (0.3181) (N1=35)
Part A baseline EoE-EREFS total score, mean (SD)	*7.58 (2.151) (N1=12)*	*7.27 (2.939) (N1=15)*	*6.63 (2.464) (N1=24)*	*6.79 (2.660) (N1=34)*	*7.58 (2.151) (N1=12)*	*7.27 (2.939) (N1=15)*	*6.63 (2.464) (N1=24)*	*6.79 (2.660) (N1=34)*
Absolute change in EoE-EREFS from baseline[a]	-1.00 (2.629) (N1=12)	0.93 (2.492) (N1=15)	-3.62 (3.106) (N=21)	-3.78 (2.697) (N1=32)	-5.82 (1.722) (N1=11)	-3.64 (3.342) (N1=14)	-4.50 (3.203) (N=22)	-4.77 (3.081) (N=30)
Part A baseline proportion of days with 1 or more EoE signs as measured by the PESQ-C, mean (SD)	*0.50 (0.339) (N1=14)*	*0.61 (0.365) (N1=18)*	*0.66 (0.353) (N1=28)*	*0.46 (0.378) (N1=36)*	*0.50 (0.339) (N1=14)*	*0.61 (0.365) (N1=18)*	*0.66 (0.353) (N1=28)*	*0.46 (0.378) (N1=36)*
Change from baseline in the proportion of days with 1 or more EoE signs as measured by the PESQ-C (for patients aged ≥1 to <12 years)[a]	-0.12 (0.382) (N1=14)	-0.21 (0.388) (N1=18)	-0.22 (0.305) (N1=28)	-0.22 (0.302) (N1=36)	-0.20 (0.373) (N1=6)	-0.47 (0.395) (N1=9)	-0.49 (0.339) (N1=18)	-0.30 (0.299) (N1=27)
Part A baseline number of sign-free days as measured by the PESQ-C, mean (SD)	*7.06 (4.741) (N1=14)*	*5.43 (5.107) (N1=18)*	*4.79 (4.944) (N1=28)*	*7.61 (5.296) (N1=36)*	*7.06 (4.741) (N1=14)*	*5.43 (5.107) (N1=18)*	*4.79 (4.944) (N1=28)*	*7.61 (5.296) (N1=36)*
Number of sign-free days during the 14-day period preceding week 16/week 52 as measured by the PESQ-C (for patients aged ≥1 to <12 years)	8.81 (5.837) (N1=14)	8.33 (5.936) (N1=18)	8.01 (5.261) (N1=29)	10.67 (4.703) (N1=37)	11.58 (3.968) (N1=6)	12.10 (4.652) (N1=9)	11.35 (3.947) (N1=18)	12.13 (4.053) (N1=27)

Part C (cut-off date of 17 January 2024)

The preliminiary efficacy results from Part C up to a cut-off date of 17 January 2024 demonstrate the long-term efficacy of the dupilumab weight-tiered regimens in pediatric participants with EoE who continued to receive treatment from the end from Part B (36-week extended active treatment period) to Week 100 during Part C open-label extension period. No patients had efficacy data available at Week 100 in the dupilumab weighed-tier regimen for <15 kg. Data presented represent the total number of participants across all the dupilumab weight-tiered regimens.

Table 23. Summary of Proportion of Patients Achieving Peak Esophageal Intraepithelial Eosinophil Count of <=6 eos/hpf in All Three Regions During Part C. All Observed Values Regardless of Rescue Treatment Use (Part C – Safety Analysis Set)

Visit	>=5kg to <15kg (N=2)	>=15kg to <30kg (N=38)	>=30kg to <40kg (N=17)	>=40kg (N=4)	Total (N=61)
Baseline of Part C	1/2 (50.0%)	28/38 (73.7%)	13/17 (76.5%)	1/4 (25.0%)	43/61 (70.5%)
Week 100	0/0	8/14 (57.1%)	6/7 (85.7%)	1/2 (50.0%)	15/23 (65.2%)
Week 160	0/0	0/0	0/0	0/0	0/0
Early EOT Visit	0/0	0/0	2/3 (66.7%)	0/1	2/4 (50.0%)

Percentage is based on the number of participants with non-missing values at each visit.
Cutoff date: 01/17/2024

Table 24. Summary of Summary of Proportion of Patients Achieving Peak Esophageal Intraepithelial Eosinophil Count of <=15 eos/hpf in All Three Regions During Part C. All Observed Values Regardless of Rescue Treatment Use (Part C – Safety Analysis Set)

Visit	>=5kg to <15kg (N=2)	>=15kg to <30kg (N=38)	>=30kg to <40kg (N=17)	>=40kg (N=4)	Total (N=61)
Baseline of Part C	1/2 (50.0%)	30/38 (78.9%)	14/17 (82.4%)	2/4 (50.0%)	47/61 (77.0%)
Week 100	0/0	14/14 (100%)	7/7 (100%)	1/2 (50.0%)	22/23 (95.7%)
Week 160	0/0	0/0	0/0	0/0	0/0
Early EOT Visit	0/0	0/0	2/3 (66.7%)	1/1 (100%)	3/4 (75.0%)

Percentage is based on the number of participants with non-missing values at each visit.
Cutoff date: 01/17/2024

Further histologic examination was carried out through the evaluation of EoE-HSS Grade and Stage Scores. Severity (grade) and extent (stage) of abnormalities were scored by blinded, central pathologists using a 4-point scale (0=normal; 3=maximum change) for 8 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.

During Part C, participants receiving dupilumab weight-tiered regimens maintained their improvement in EoE-HSS mean grade score from the double-blind treatment period (Part A). Across weight-tiered regimens, the mean change from the Part A baseline was −0.806 points at the Part C baseline (ie, Week 52; n=61) and −0.899 points at Week 100 (n=23). During Part C, participants receiving dupilumab weight-tiered regimens maintained their improvement in EoE-HSS mean stage score from the double-blind treatment period (Part A). Across all weight-tiered regimens, the mean change from the Part A baseline was −0.781 points at the Part C baseline (ie, Week 52; n=61) and −0.892 points at Week 100 (n=23).

The EoE-EREFS is a validated endoscopic scoring system for inflammatory and remodelling features of EoE including edema, 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 remodeling findings. During Part C, participants receiving dupilumab weight-tiered regimens showed sustained improvement in EoE-EREFS total score with continued treatment. Across all weight-tiered regimens, the mean change from the Part A baseline total score was −4.74 points at the Part C baseline (ie, Week 56; n=47) and −4.75 at Week 100 (n=16).

The aforementioned improvements in histologic and endoscopic outcomes in pediatric participants were further supported by improvements in other symptomatic reported outcome measures such as Pediatric Eosinophilic Esophagitis Symptom Score (PEESS), Pediatric EoE Impact Scale- Caregiver version (PEIS-C) and the Pediatric EoE Impact Scale-Patient version (PEIS-P) which assessed quality of life (QoL), and Global Impression of Severity (GIS)-Patient, Caregiver and Clinician Version Scores which measured the change in overall EoE status.

Overall, efficacy data collected to date in Part C show durable efficacy as participants continued treatment. At the Week 100 endoscopy, the majority of participants who reached this timepoint maintained the histologic response of both <=15 eosinophils per high powered field and the more stringent criterion of <=6 eosinophils per high power fields. Maintained responses in the EoE HSS grade and stage scores as well as EREFS and clinical parameters were also observed up to Week 100.

Ancillary analyses

Descriptive analyses were performed on the primary endpoint to summarize the treatment effects across the subgroups of age (≥1 to <6 years, ≥6 to <12 years, ≥1 to <8 years, and ≥8 to <12 years), baseline body weight (≥5 to <15 kg, ≥15 to <30 kg, or ≥30 to <60 kg), sex, BMI (overweight yes or no), race, ethnicity (these last 2 were included as post-hoc analyses), and baseline disease characteristics (including duration of EoE [<5 years or ≥5 years], history of prior STC use for treatment of EoE [yes or no], use of PPI at randomization per electronic data capture [yes or no], history of prior oesophageal dilations [yes or no], food elimination diet at screening [yes or no], food elimination ever in the past [yes or no], history of AD [yes or no], history of asthma [yes or no], history of allergic rhinitis [yes or no], history of food allergy [yes or no], and inadequate response, intolerant and/or contraindicated to STCs [yes or no]).

A generally consistent effect on the proportion of participants who achieved peak oesophageal intraepithelial eosinophil count ≤6 eos/hpf at week 16 was demonstrated for dupilumab treatment compared with placebo, with observed effects of greater numerical magnitude in the higher exposure dupilumab regimen compared with the lower exposure dupilumab regimen in most of the subgroups analyzed. Regardless of history of prior STC treatment, a larger proportion of participants treated with higher and lower exposure dupilumab regimens achieved peak oesophageal intraepithelial eosinophil

count ≤6 eos/hpf at week 16 than participants treated with placebo, with responses of greater numerical magnitude in the higher exposure dupilumab regimen in participants with prior use of STCs.

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 25. Summary of Efficacy for trial R668-EE-1877

Title: A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab in paediatric patients with active eosinophilic esophagitis			
Study identifier	R668-EE-1877 (Part A)		
Design	Randomized, double-blind, placebo-controlled, parallel-group design		
	Duration of main phase: Duration of Run-in phase:		16 weeks N/A
Hypothesis	Superiority		
Treatments groups	Higher Exposure Dupilumab Regimen (N= 37)		• 100 mg Q2W for 16 weeks in patients who weigh ≥5 kg to <15 kg • 200 mg Q2W for 16 weeks in patients who weigh ≥15 kg to <30 kg • 300 mg Q2W for 16 weeks in patients who weigh ≥30 kg to <60 kg
	Lower Exposure Dupilumab Regimen (N= 31)		• 200 mg Q4W for 16 weeks in patients who weigh ≥5 kg to <15 kg • 300 mg Q4W for 16 weeks in patients who weigh ≥15 kg to <30 kg • 200 mg Q2W for 16 weeks in patients who weigh ≥30 kg to <60 kg
	Matching placebo (N= 34)		Matching placebo Q2W[1] for 16 weeks
Endpoints and definitions	Primary endpoint	Peak eos count of ≤6 eos/hpf at week 16	Proportion of participants achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16
	Secondary endpoints (as pre-specified in statistical hierarchy)	Peak eos count of <15 eos/hpf at week 16	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 16
		Percent change in peak eos count (eos/hpf) to week 16	Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 16
		Change in EoEHSS grade score to week 16	Absolute change in mean EoE Grade Score from the EoEHSS from baseline to week 16

Title: A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab in paediatric patients with active eosinophilic esophagitis			
Study identifier	R668-EE-1877 (Part A)		
		Change in EoEHSS stage score to week 16	Absolute change in mean EoE Stage Score from the EoEHSS from baseline to week 16
		NES change to wk 16 in T2 inflammation signature	NES for the relative change from baseline to week 16 in the type 2 inflammation transcriptome signature
		NES change to wk 16 in EDP	NES for the relative change from baseline to week 16 in the EoE Diagnostic Panel transcriptome signature
		Change in EoE-EREFS to week 16	Absolute change in EoE-EREFS from baseline to week 16
		Change in PESQ-C score to week 16	Change from baseline in the proportion of days with 1 or more EoE signs by PESQ-C (for patients aged ≥1 to <12 years)
Database lock	06 June 2022		

Results and Analysis

Analysis description	**Primary endpoint analysis**			
Analysis population and time point description	Full Analysis Set Week 16			
Descriptive statistics and estimate variability	**Treatment group**	**Dupilumab Higher Exposure**	**Dupilumab Lower Exposure**	**Placebo**
	Number of subjects	**37**	**31**	**34**
	Peak eos count of ≤6 eos/hpf at week 16 (n (%))	25 (67.6)	18 (58.1)	1 (2.9)
	95% CI (%)	(50.21, 81.99)	(39.08, 75.45)	(0.07, 15.33)
Effect estimate per comparison	**Primary endpoint:** Peak eos count of ≤6 eos/hpf at week 16	**Comparison groups**	**Dupilumab Higher Exposure vs. Placebo**	**Dupilumab Lower Exposure vs. Placebo**
		Difference vs Placebo (95% CI)	64.5 (48.19, 80.85)	55.1 (36.85, 73.42)
		P-value	<0.0001	<0.0001
Analysis description	**Secondary endpoint analysis**			
Analysis population and time point description	Full Analysis Set Week 16			
Descriptive statistics and estimate variability	**Treatment group**	**Dupiluma b Higher Exposure**	**Dupilumab Lower Exposure**	**Placebo**
	Number of subjects	**37**	**31**	**34**

Title: A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab in paediatric patients with active eosinophilic esophagitis				
Study identifier	R668-EE-1877 (Part A)			
	Secondary Endpoint: Peak eos count of <15 eos/hpf at week 16, n (%)	31 (83.8)	21 (67.7)	1 (2.9)
	95% CI (%)	(67.99, 93.81)	(48.63, 83.32)	(0.07, 15.33)
	Secondary Endpoint: Percent change in peak eos count (eos/hpf) to week 16, LS Mean % Change	-86.09	-77.93	20.98
	LS Mean % Change 95% CI	(-109.595, -62.586)	(-103.525, -52.339)	(-3.296, 45.265)
	Secondary Endpoint: Change in EoEHSS grade score to week 16 (LS mean change)	-0.879	-0.757	0.023
	LS Mean Change 95% CI	(-0.9742, -0.7833)	(-0.8612, -0.6534)	(-0.0756, 0.1219)
	Secondary Endpoint: Change in EoEHSS stage score to week 16 (LS mean change)	-0.835	-0.721	0.048
	LS Mean Change 95% CI	(-0.9276 , -0.7426)	(-0.8214 , -0.6201)	(-0.0477 , 0.1437)
	Secondary Endpoint: NES change to wk 16 in T2 inflammation signature (median change (n^2))	-1.895 (24)	-1.930 (15)	0.340 (21)
	Secondary Endpoint: NES change to wk 16 in EDP (median change (n^2))	-2.630 (24)	-2.710 (15)	0.180 (21)
	Secondary Endpoint: Change in EoE-EREFS to week 16 (LS mean change)	-3.5	-3.0	0.3
	LS Mean Change 95% CI	(-4.30, -2.62)	(-3.96, -2.07)	(-0.57, 1.22)
	Secondary Endpoint: Change in PESQ-C score to week 16 (LS mean change)	-0.28	-0.18	-0.17
	LS Mean Change 95% CI	(-0.378, -0.173)	(-0.295, -0.059)	(-0.279, -0.067)
Effect estimate per comparison	**Secondary Endpoint**	**Comparison groups**	**Dupilumab Higher Exposure vs. Placebo**	**Dupilumab Lower Exposure vs. Placebo**

Title: A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab in paediatric patients with active eosinophilic esophagitis				
Study identifier	R668-EE-1877 (Part A)			
	Peak eos count of <15 eos/hpf at week 16	Difference vs Placebo (95% CI)	81.1 (68.07, 94.10)	65.4 (48.02, 82.81)
		P-value	<0.0001	<0.0001*
	Secondary Endpoint Percent change in peak eos count (eos/hpf) to week 16	**Comparison groups**	**Dupilumab Higher Exposure vs. Placebo**	**Dupilumab Lower Exposure vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-107.07 (-139.249, -74.900)	-98.92 (-132.463, -65.370)
		P-Value	<0.0001	<0.0001*
	Secondary Endpoint Change in EoEHSS grade score to week 16	**Comparison groups**	**Dupilumab Higher Exposure vs. Placebo**	**Dupilumab Lower Exposure vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-0.902 (-1.0325, -0.7714)	-0.780 (-0.9170, -0.6440)
		P-value	<0.0001	<0.0001*
	Secondary Endpoint Change in EoEHSS stage score to week 16	**Comparison groups**	**Dupilumab Higher Exposure vs. Placebo**	**Dupilumab Lower Exposure vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-0.883 (-1.0095 , -0.7568)	-0.769 (-0.9013 , -0.6362)
		P-value	<0.0001	<0.0001*
	Secondary Endpoint NES change to wk 16 in T2 inflammation signature	**Comparison groups**	**Dupilumab Higher Exposure vs. Placebo**	**Dupilumab Lower Exposure vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-2.220 (-2.4400, -1.9500)	-2.190 (-2.4500, -1.8200)
		P-value	<0.0001	<0.0001*
	Secondary Endpoint NES change to wk 16 in EDP	**Comparison groups**	**Dupilumab Higher Exposure vs. Placebo**	**Dupilumab Lower Exposure vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-2.840 (-3.3500, -1.9600)	-2.700 (-3.3100, -1.6200)
		P-value	<0.0001	<0.0001*
	Secondary Endpoint Change in EoE-EREFS to week 16	**Comparison groups**	**Dupilumab Higher Exposure vs. Placebo**	**Dupilumab Lower Exposure vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-3.8 (-4.94, -2.63)	-3.3 (-4.59, -2.10)

Title: A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab in paediatric patients with active eosinophilic esophagitis				
Study identifier	R668-EE-1877 (Part A)			
		P-value	<0.0001	<0.0001*
	Secondary Endpoint Change in PESQ-C score to week 16	**Comparison groups**	**Dupilumab Higher Exposure vs. Placebo**	**Dupilumab Lower Exposure vs. Placebo**
		Difference vs Placebo LS Mean (95% CI)	-0.10 (-0.244, 0.038)	-0.00 (-0.155, 0.146)
		P-value	0.1526	0.9533

*Nominal P-value

1.Participants randomized to a Q4W dupilumab regimen received alternating placebo doses to maintain an injection frequency of Q2W for blinding purposes.

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

Abbreviations: CI=confidence interval; 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; PESQ-C: Paediatric EoE Sign/Symptom Questionnaire-Caregiver Q2W=every 2 weeks; Q4W=every 4 weeks; T2=Type 2

Supportive study

Data from Study R668-EE-1774, which have been submitted for extension of indication in adolescents and adults with EoE are considered supportive.

This 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 received dupilumab during Part B receive 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 for 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 oesophageal dilation was allowed.

Paediatric data summary

In Part A study 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

oesophageal 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).

Of the 240 participants randomized in Part B, 79 (32.9%) were adolescents (≥12 to <18 years of age): 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 oesophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 was greater in both the dupilumab 300 mg QW (57.7%) and 300 mg Q2W (48.1%) groups than in the placebo group (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 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 oesophageal intraepithelial eosinophil count ≤6 eos/hpf at week 24 was 51.4% in the dupilumab 300 mg QW group versus 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 and -17.23 points in the placebo group.

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 of was smaller. The MAH claims that this is likely due to higher placebo effect, which is acknowledged. However, 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.

In Part C, 33.3% adolescent participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group and 75.0% in the placebo/dupilumab 300 mg QW group achieved a peak oesophageal 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 oesophageal 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 their improvement in DSQ total score with continued treatment during Part C. The mean change from the Part A baseline was -24.80 points at the Part C baseline (week 24) and −25.57 points at week 52. 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 was -25.45 points at week 52.

The results of Part C show that adolescent participants in the dupilumab/dupilumab group had a decrease in Proportion of Participants Achieving Peak Oesophageal 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.

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. In Part B 58.8% of participants had achieved peak oesophageal 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. 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 52. This is indicating that dupilumab 300 mg QW is the appropriate regimen to achieve continuous improvement.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study R668-EE-1877 is the pivotal phase 3 study that has been conducted. It consists of 3 parts: Part A (a 16-week randomized, double-blind, placebo-controlled treatment period) and Part B (a 36-week extended active treatment period), which have been completed while Part C (an open-label extension period) is ongoing and a 12-week follow-up period.

Weight-tiered higher exposure and lower exposure dupilumab regimens were evaluated that resulted in trough concentrations at steady-state in children that approximated those in adults who received 300 mg QW (higher exposure dupilumab) or 300 mg Q2W (lower exposure dupilumab). Of note, the results in study R668-EE-1774 for the 300 mg QW dose showed clinically meaningful efficacy in improving histologic, endoscopic and symptomatic measures of EoE in adult and adolescent patients and supported the authorisation of dupilumab 300 mg QW for the treatment of EoE in adult and adolescent patients weighing at least 40 kg. However, the proposed dosing regimens differ from the evaluated regimens in Part A and B of this study. These dosing regimens were introduced in Part C, but no data has been submitted with the initial submission. Part C has an expected study completion data of July 2025.

In **Part A** of Study R668-EE-1877, participants receiving higher exposure dupilumab were assigned based on baseline body weight to 100 mg Q2W (≥5 to <15 kg), 200 mg Q2W (≥15 to 30 kg) and 300 mg Q2W (≥30 to <60 kg). Participants receiving lower exposure dupilumab were assigned based on baseline body weight to 200 mg Q4W (≥5 to <15 kg), 300 mg Q4W (≥15 to <30 kg) and 200 mg Q2W (≥30 to <60 kg).

After completion of Part A, participants continued in a 36-week extended treatment period (**Part B**). Participants in the dupilumab groups received the same treatment as in Part A, while participants who received placebo in Part A were switched to higher exposure or lower exposure dupilumab according to the exposure regimen assigned at randomization. Individual weight-tiered doses within each treatment group were adjusted, if needed, based on body weight measured at week 16 and also at week 32. For Part B, a ≥60 kg regimen was added with 300 mg QW in the higher exposure groups and 300 mg Q2W in the lower exposure group, for participants whose bodyweight went over 60 kg.

Rescue medications or emergency oesophageal dilation were allowed during the study. No participant in any treatment group used rescue medication or procedure for EoE during the Part A and B.

Following completion of Part B, participants entered the 12-week follow-up period. After implementation of Protocol Amendment 4, participants could directly enrol into Part C to receive open-label dupilumab higher exposure regimen for up to 108 weeks or until commercially available.

Part C is ongoing. However, partial data with a cut-off date of 17 January 2024 have been submitted upon CHMP's request. Final results and follow-up periods will be reported separately and are not included in this submission. Overall, the study design is considered adequate.

Eligible for enrolment in Study R668-EE-1877 were males and females ≥1 to <12 years of age at the time of study entry with EoE, with a body weight ≥5 kg and <60 kg. Participants were required to have

a confirmed diagnosis of EoE that was not responsive to PPI therapy. Diagnostic criteria in both adults and pediatric patients is ≥15 eos/hpf (400x) in mucosal oesophageal biopsies, regardless of age. Non-responsiveness to PPI may have been established either by a prior historical biopsy showing ≥15 intraepithelial eos/hpf from at least 1 oesophageal region after at least 8 weeks of treatment or by biopsies performed after approximately 8 weeks of PPI treatment initiated prior to screening or during the screening period, which demonstrated ≥15 intraepithelial eos/hpf in at least 2 out of 3 oesophageal regions (proximal, mid, and distal).

Participants were also required to have a history of EoE symptoms in the month prior to screening with at least 8 out of 14 days of eDiary completion for the PESQ-C prior to baseline. However, no minimum level of EoE signs per PESQ-C was required for inclusion. Furthermore, participants were required to maintain diets without removal or introduction of foods that could affect the participant's EoE. Additionally, specific medications were excluded if they could either treat or worsen the disease. The patient population as defined by the eligibility criteria is considered adequate.

Of 164 participants screened, 62 participants were considered screen failures. The 102 participants who met eligibility criteria, were randomized to 1 of the 3 treatment groups in Part A: 34 participants in the placebo group, 31 participants in the lower exposure dupilumab group, and 37 participants in the higher exposure dupilumab group. Of note, data presented in section 5.1 of the SmPC only relate to the participants in the higher exposure group (e.g. approved posology) and placebo group.

Overall, 98 of 102 randomized participants (96.1%) completed the week 16 visit of Part A and therefore the double-blind treatment period, with no participants unable to complete the week 16 visit due to the COVID-19 pandemic. Of the 98 participants who completed Part A, 97 entered Part B of the study.

Demographic characteristics for participants in study R668-EE-1877 were generally balanced across the 3 treatment groups and consistent with published literature for an EoE population with a significant disease burden. The majority of participants were male (76.5%) and most participants were White (82.4%). The mean age of participants was 7.1 years with 32.4% of participants ≥1 to <6 years of age and 67.6% of participants ≥6 to <12 years of age. Additionally, 48.0% of participants were ≥1 to <8 years of age and 52.0% of participants were ≥8 to <12 years of age. The mean weight of participants was 26.8 kg with 14.7% of participants ≥5 to <15 kg, 53.9% of participants ≥15 to <30 kg and 31.4% ≥30 to <60 kg. It has to be noted that the numbers of participants in the ≥5 to <15 kg weight group were very low. Furthermore, no participant with less than 10 kg of bodyweight has been enrolled.

Active disease was evidenced by high peak oesophageal intraepithelial eosinophil count and enrolled participants were non-responsive to PPIs. The mean peak eosinophil count of 3 oesophageal regions at baseline of 83.3 eos/hpf was similar to the population of study R668-EE-1774.

However, differences are seen in the mean baseline scores in Part A for PESQ-C. Lower values were reported in the higher exposure dupilumab/higher exposure dupilumab group (0.46) compared to the lower exposure dupilumab/lower exposure dupilumab group (0.66) and the placebo/dupilumab groups (placebo/higher exposure dupilumab group: 0.61 and placebo/lower exposure dupilumab group: 0.50). These baseline values corresponded to an average of 6.44, 9.24, 8.54, and 7.00 days with signs of EoE (out of the prior 14 days) for the 4 respective treatment groups. Furthermore, for PEIS-C and PEIS-P differences in baseline score values were observed across treatment arms with the highest values in the lower exposure group.

Major oesophageal features such as rings and strictures (ie, fibrostenotic changes) were uncommon in children, which was expected. These endoscopic findings in EoE appear to vary by age with more inflammatory features such as edema and exudates in children and more fibrotic findings seen at older

ages. Despite these differences in symptom presentation between age groups, the clinical/pathological findings of the disease across all ages is eosinophil-predominant inflammation of the mucosa.

The study was powered on the primary histology endpoint as assessed by the proportion of participants achieving peak intraepithelial eosinophil count ≤6 per hpf. This primary endpoint used in study R668-EE-1877 was also used as one of the co-primary endpoints in the adult and adolescents in study R668-EE-1774. The EoE-HSS grade and stage scores were used as secondary assessments to provide further detail of other histologic abnormalities.

Novel Sponsor-developed ObsRO measures were utilized for daily collection of signs and symptoms (Kamat, 2022). The PESQ-C was completed by caregivers of participants aged ≥1 to <12 years and PESQ-P was completed by participants aged ≥8 to <12 years. Study R668-EE-1877 was neither designed nor powered to demonstrate statistically significant differences in symptoms. The PEESSv2.0-Caregiver version was included to measure observer-reported signs of EoE at the request of a health authority and was assessed as a secondary endpoint. HRQoL was assessed through the novel, Sponsor-developed PEIS-C and PEIS-P questionnaires.

Efficacy data and additional analyses

In study R668-EE-1877 Part A, a clinically relevant effect in the primary endpoint was statistically significantly demonstrated (with p values <0.0001) with a 2-sided significance level of 0.05 and Part A of the study was considered positive for treatment with dupilumab with both higher or lower exposure regimens compared with placebo at week 16.

Sensitivity analyses for the primary endpoint using different imputation methods to account for missing data support the robustness of the results.

The higher exposure dupilumab regimen met all the pre-specified secondary efficacy endpoints for histology (EoE-HSS), endoscopy (EoE-EREFS) and transcriptome (all with p-values <0.0001). The statistical hierarchy broke at the 10th ranked endpoint, with the higher exposure dupilumab regimen showing trends for improvement but not achieving statistical significance for the endpoint assessing "changes in the proportion of days with 1 or more EoE signs measured by PESQ-C." After this endpoint, all p-values were considered nominal.

Overall, 67.6% of participants in the higher exposure dupilumab group in Part A achieved peak oesophageal intraepithelial eosinophil count ≤6 eos/hpf at week 16 (primary endpoint; placebo group 2,9%), which is considered clinically meaningful. These results were maintained with 62.9% after 52 weeks with continued treatment in Part B. Furthermore, 83.8% of participants in higher exposure dupilumab group achieved <15 eos/hpf after 16 weeks of treatment (placebo group 2,9%), which was maintained at 85.7% after 52 weeks.

Participants who received placebo in Part A and then were switched to 36 weeks of treatment with higher exposure dupilumab during Part B of the study also achieved improvements in histology (≤6 eos/hpf at week 52: 52.9% and ≤15 eos/hpf at week 52: 64.7%). For the EoE-HSS grade and stage scores, the higher exposure dupilumab group had improvements observed at week 16 (EoE-HSS grade: −0.919 and EoE-HSS stage: −0.852), which were maintained at week 52 (EoE-HSS grade: −0.967; EoE-HSS stage: −0.892). In addition, participants who received placebo in Part A and then were switched to 36 weeks of treatment with higher exposure dupilumab during Part B of the study also achieved improvements in other histological abnormalities (from Part A baselines at week 52: EoE-HSS grade: −0.886 and EoE-HSS stage: −0.855).

Similar to the histologic improvements, effects on efficacy were observed for endoscopic improvements in the oesophagus, where participants in the higher exposure dupilumab group showed endoscopic

improvements at week 16 (−3.78), which were further improved at week 52 (−4.77). Participants who received placebo in Part A and were switched to 36 weeks of treatment with higher exposure dupilumab during Part B of the study also achieved endoscopic improvements (from Part A baselines at week 52: −3.64).

For the primary endpoint, 58.1% of the participants in the lower exposure group achieved peak oesophageal intraepithelial eosinophil count ≤6 eos/hpf at week 16 which was lower than the results for the higher treatment group (67.6%) but significantly greater compared with placebo (2.9%; p<0.0001). Similar were the results for the lower exposure dupilumab regimen compared with placebo and the higher exposure dupilumab regimen on the prespecified secondary efficacy endpoints (histology, endoscopy, transcriptome and the proportion of days with 1 or more EoE signs as assessed by PESQ-C). All had nominal p-values <0.0001, except for the PESQ-C endpoint included in the prespecified statistical hierarchy which did not separate from placebo.

The higher exposure dupilumab regimen also showed a trend towards symptomatic improvements over placebo in the proportion of days with 1 or more EoE signs, as measured by PESQ-C, although not statistically significant. Absolute change from baseline to week 16 in the proportion of days with 1 or more EoE signs (-0.28 vs -0.17), the number of sign-free days during the 14-day period up to week 16 (10.38 vs 8.93 days) and change from baseline to week 16 in the proportion of total segments within a day (night, morning, afternoon, evening) with 1 or more EoE signs (-0.16 vs -0.11). No improvements were observed for the lower exposure dupilumab regimen compared with placebo for these endpoints.

In contrast were the improvement (decrease) reported for the mean change from Baseline to Week 16 in Proportion of Days with 1 or More EoE Symptoms as measured by the PESQ-P with -0.13 in the higher exposure group, -0.18 in the lower exposure group and -0.27 in the placebo group. It has to be noted that the baseline means in the higher exposure group were lower compared to lower treatment and placebo group.

Overall, the validity of the novel, observer-reported outcome measure implemented remains difficult to assess. It is acknowledged, that the study was not powered to show symptomatic improvement measured by the PESQ-C. However, the baseline PESQ-C values showed a large variation in the treatment groups and clinically relevant differences (defined as change from baseline of -0.14) were observed in all treatment groups (including the placebo group). The validity of the novel, observer-reported outcome measures implemented in this study is unclear and the study was not powered to show symptomatic improvement. Therefore, it is unclear whether the higher histologic and endoscopic improvement seen in the higher exposure dupilumab group will translate into symptomatic benefit for the patients over time. However, due to the fact that clinical, histological and molecular evidence suggests that EoE has the same underlying pathogenesis in different age groups and histologic, biomarker and genetic studies have demonstrated a generally similar pattern of inflammation and genetic abnormalities across age groups, a similar benefit of the treatment with a higher dupilumab dosing regimen as seen in the adolescent and adult study R668-EE-1774 can be assumed for all age groups.

The higher exposure dupilumab regimen again showed greater improvements compared with the lower exposure dupilumab regimen in secondary and exploratory efficacy endpoints assessing EoE signs reported by caregivers (PEESSv2.0-Caregiver version) and QoL impacts on both caregivers and patients (PEIS-C and PEIS-P). The LS mean difference in the PEESSv2.0-Caregiver version between the higher exposure dupilumab group and placebo was -8.03 points, which was nominally significant with a nominal p=0.0328. The mean percent change from baseline to week 16 in the PEIS-C total score showed a greater improvement in the higher exposure dupilumab regimen (-53.98%) compared with placebo (-7.53%). A lesser degree of reduction was observed for the lower exposure dupilumab group (-30.68%).

An improvement was shown in the PEIS-P total score in the higher exposure dupilumab regimen, with a mean percent change from baseline to week 16 with -35.76%, in the lower exposure dupilumab group with -12.96% and in the placebo group with -13.44%.

However, for PEIS-C and PEIS-P, differences in baseline score values were observed across treatment arms with the highest values in the lower exposure group, which could indicate that these patients were more symptomatic than the patients in higher exposure groups and the placebo group, which had the lowest values.

In Part B, the efficacy was mainly maintained and the results were similar as already summarized above. However, it should be noted that in the lower exposure dupilumab group 65.5% Achieving Peak Oesophageal Intraepithelial Eosinophil Count ≤6 eos/hpf in All 3 Regions at Week 52 compared to 62.9% in the higher dupilumab group. Furthermore, 52.9% [9/17] and 92.9% [13/14] of participants in the placebo/higher exposure dupilumab and placebo/lower exposure dupilumab regimens, respectively, achieved a peak oesophageal intraepithelial eosinophil count ≤6 eos/hpf in all 3 regions at week 52. However, the sample size in these groups was very small. For the other secondary endpoints, the higher exposure dupilumab group showed greater improvements compared to placebo than the lower exposure group.

It is acknowledged that the efficacy results from Part C of Study R668-EE-1877 up to a cut-off date of 17 January 2024 show the long-term efficacy of the dupilumab weight-tiered regimens (ie, its ability to improve and/or maintain both the histologic, endoscopic, symptom, quality of life and growth endpoints related to EoE) in pediatric participants with EoE who continued to receive treatment from Part B (36-week extended active treatment period) to Week 100 during Part C open-label extension period. However, the number of patients with a body weight below 15 kg was very small. In Part C, only 2 patients have been treated. For none of the patients, efficacy data were available at Week 100 in the dupilumab group with the adapted higher dosing regimen for <15 kg.

Besides, the MAH claims that the primary endpoint peak intraepithelial esophageal eosinophil counts ≤6 eos/hpf is not adequate to describe the benefit for patients with EoE. Furthermore, the MAH states that it is challenging to evaluate the signs and symptoms of EoE in young children and that they believe that a higher dosing regimen is most likely to show symptomatic benefit. This response is questioned as an adapted dosing is not implemented for all weight-groups. No clear answer is given, why the lowest weight group needs a dosing regimen that produces the highest exposure values to achieve benefit.

In conclusion, the discussion on the additional benefit and the data presented are considered not sufficient to justify the planned higher dosing regimen in children with less than 15 kg of body weight. Especially, due to the higher exposure and the not proven additional benefit in this weight group, the indication is restricted to patients with a body weight of ≥15 kg.

2.4.3. Conclusions on the clinical efficacy

Efficacy has been demonstrated for paediatric patients 1 years and above and weighing at least 15 kg with eosinophilic esophagitis at 16 weeks and up to 52 weeks. The primary endpoint was statistically significant and showed that overall the participants in the dupilumab higher exposure regimen achieved clinically relevant greater histologic improvement compared to placebo and the lower exposure regimen. Similar results were obtained for the secondary endpoints.

The CHMP concluded that the clinical efficacy has been demonstrated for use in Dupixent in the following indication:

Dupixent is indicated for the treatment of eosinophilic esophagitis in adults, adolescents and children

aged 1 year and older, weighing at least 15 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.

2.5. Clinical safety

Introduction

Dupilumab is approved for treatment of children ≥6 months with atopic dermatitis and children ≥6 years with asthma. In these 2 paediatric indications dupilumab showed an overall similar safety profile as compared the profile established for adult patients.

Dupilumab is also currently approved for adults and adolescents (≥12 years, ≥40kg) with EoE.

The safety profile in adult participants was considered consistent with that seen in other indications for which dupilumab was approved at the time of the variation (ie. atopic dermatitis, asthma and CRSwNP).

The incidence of Injection Side Reaction was high in the EoE population in dupilumab but also placebo-treated participants. There was a higher incidence of adverse events in the SOC *Infections and infestations* that was mainly driven by a higher number of COVID-19 infections in the dupilumab groups (Part B was conducted by the time of the COVID-19 pandemic: Aug. 2019 – Sep. 2021). The majority of COVID-19 infections were in adults (7 of the 9 cases). The safety profile in adolescents ≥12 years with EoE appeared generally similar to that of adults.

Safety Data for children ≥1 to <12 years of age with EoE
Safety data of dupilumab in children ≥1 to <12 years of age with EoE are derived from Study **R668 EE-1877**, which assessed the safety and efficacy of dupilumab over a 16-week randomized, double-blind, placebo-controlled treatment period (**Part A**) and a 36-week extended active treatment period (**Part B**) in children ≥1 to <12 years of age with EoE. Please see Section 2.4.1 for study details. Additional safety data from the ongoing **Part C** (open-label extension period up to 108 weeks) were provided during the procedure with a data cut-off date of 17 January 2024.

Study analysis sets

No integrated analyses of safety data were performed and separated safety data for Part A and Part B are presented. Descriptive statistics were used in the analyses of safety parameters. The safety analyses was performed on the safety analysis set (SAF) for each study part, which included all participants who received at least 1 dose of any study drug. The SAF, was used for all safety analyses of TEAEs, laboratory, and other safety data, and ADA and NAb sets were defined to assess immunogenicity.

Table 26. Overview of the Phase 3 EoE Study Evaluated in the Summary of Clinical Safety (SAF)

Study R668-EE-1877 Parts A and B in Children Aged ≥1 to <12 Years

Study Period	Screening →	Part A Double-blind Treatment Period →	Part B Extended Active Treatment Period
Study treatment groups[a]	(N=164)	Placebo (N=34)	Placebo/lower exposure dupilumab (N=14) Placebo/higher exposure dupilumab (N=18)
		Lower exposure dupilumab (N=30)	Lower exposure dupilumab/lower exposure dupilumab (N=29)
		Higher exposure dupilumab (N=37)	Higher exposure dupilumab/higher exposure dupilumab (N=37)
Duration	Up to 12 weeks	16 weeks	36 weeks
Data cutoff date		28 Apr 2022 for Part A CSR	17 Jan 2023
Database lock date		06 Jun 2022 for Part A CSR 07 Feb 2023 for Part A CSR Addendum Report	07 Feb 2023
Study status		Completed	Completed
Reporting status		Part A CSR Part A CSR Addendum Report	Part B CSR

a Dosing regimens in the higher and lower exposure groups in Study R668-EE-1877 were based on weight tiers and are described in Section 5.5.1.
Abbreviations: CSR=clinical study report; EoE=eosinophilic esophagitis; N=number of participants screened or in the SAF (as applicable); SAF=safety analysis set of respective study.

Table 27. Number of Participants with EoE Included in the Summary of Clinical Safety by Study Part (SAF)

Study Number Treatment Duration	Treatment Group	Number of Participants	Total
Study R668-EE-1877 Parts A and B in Children Aged ≥1 to <12 Years			
R668-EE-1877 Part A 16 weeks	Placebo	34	
	Lower Exposure Dupilumab	30	
	Higher Exposure Dupilumab	37	
			101
R668-EE-1877 Part B 36 weeks[a]	Placebo/Lower Exposure Dupilumab	14	
	Placebo/Higher Exposure Dupilumab	18	
	Lower Exposure Dupilumab/Lower Exposure Dupilumab	29	
	Higher Exposure Dupilumab/Higher Exposure Dupilumab	37	
			98

[a] Participants who completed Part A could proceed to the extended active treatment period in Part B. Treatment groups are shown as "Treatment received during Part A/Treatment received during Part B"
Abbreviations: EoE=eosinophilic esophagitis; SAF=safety analysis set of respective study.

Patient exposure

Participants in Part A and Part B received weight-tiered dosing regimens. The exposure is summarized by the total number of injections of study intervention (dupilumab and placebo). For participants who received dupilumab injections Q4W, there was a matching placebo injection alternating with dupilumab injections, so the IMP injection frequency was Q2W for regimen-blinding purposes. Similarly, in one participant randomized to a lower exposure regimen and weighing ≥60 kg (ie, receiving Q2W dosing with dupilumab) received alternating placebo doses to maintain a weekly injection frequency. In both Parts A and B, participants could continue treatment with study intervention beyond the planned treatment period if the visits at week 16 or week 52, where endoscopy with biopsies were performed, were delayed due to the COVID-19 pandemic.

Exposure in Part A

During Part A, 101 participants received study intervention (lower exposure: 30; higher exposure: 37; placebo 34). The mean (SD) number of study intervention administrations (injections) during Part A was comparable across treatment groups: 8.0 (1.31) injections in the lower exposure dupilumab group, 8.2 (0.83) injections in the higher exposure dupilumab group, and 7.9 (0.98) injections in the placebo group. A total of 9 participants (lower exposure: 4; higher exposure: 3; placebo: 2) received >8 injections of study intervention (treatment duration could be extended if visits were delayed due to the COVID-19 pandemic).

The mean (SD) treatment duration during Part A was comparable across treatment groups: 114.0 (19.39) days in the lower exposure dupilumab group, 115.6 (11.31) days in the higher exposure dupilumab group, and 111.3 (14.15) days in the placebo group. More than 96% of participants in each treatment group had a cumulative treatment duration during Part A of ≥98 days (14 weeks) and more than 76% of participants in each treatment group had a cumulative treatment duration during Part A of ≥112 days (16 weeks).

Exposure in Part B

There were no participants on a QW regimen at the beginning of Part B (all participants were <60 kg). However, during Part B, 1 participant in the placebo/lower exposure was switched at week 32 to a QW regimen due to weight increase as per study protocol.

Of the 102 participants who were randomized into Part A of the study, 98 participants (lower exposure: 29; higher exposure: 37; placebo: 32) entered Part B and received a weight-tiered dupilumab dosing regimen (see Table 28 below). The mean (SD) number of study intervention administrations (injections) during Part B was 17.9 (2.17), with a median of 18 across all treatment groups. Most participants had at least 18 cumulative injections of study intervention during Part B. A total of 9 participants received >18 Injections of study intervention, 7 of whom received 19 or 20 injections. 2 participants received >20 injections: 1 in the higher exposure dupilumab/higher exposure dupilumab group received 23 injections (the participant had a delayed week 52 visit due to several non-serious TEAEs) and 1 in the placebo/lower exposure dupilumab group received 28 injections after switching to a QW regimen at week 32.

The mean (SD) treatment duration during Part B was 251.7 (26.24) days. Overall, 94.9% of participants had a cumulative treatment duration during Part B of ≥238 days (34 weeks, i.e., time point of last study intervention injection per protocol with a Q2W regimen).

Overall Duration of Treatment with Dupilumab During Parts A and B

Mean (SD) dupilumab treatment duration during both Part A and Part B was 329.3 (68.65) days; 253.2 (13.47) days in the placebo/lower exposure dupilumab group, 251.3 (12.82) days in the

placebo/higher exposure dupilumab group, 361.3 (64.07) days in the lower exposure dupilumab/lower exposure dupilumab group, and 370.1 (39.11) days in the higher exposure dupilumab/higher exposure dupilumab group.

94.0% of participants treated with dupilumab throughout study Part A and Part B (combined dupilumab group) had a cumulative treatment duration during Part A and Part B of ≥357 days (≥51 weeks) and 85.1% of these participants had a cumulative treatment duration ≥364 days (≥52 weeks).

82.4% of participants treated with dupilumab only in Part B (placebo/combined dupilumab group) had a cumulative treatment duration of ≥245 days (≥35 weeks) and 50.0% of these participants had a cumulative treatment duration ≥252 days (≥36 weeks).

Part C

As of the data cut-off 17 January 2024, 61 participants in Part C had a cumulative treatment exposure of at least 1 year exposure during the study (excluding the placebo arm in Part A), with 49/61 (80.3%) participants having at least 1.5 years exposure and 19/61 (31.1%) participants having at least 2 years exposure. 2 participants in the ≥5 to <15 kg weight group enrolled into Part C and received the 200 mg Q3W dose regimen.

Demographics, baseline characteristics, medical history

Part A

Table 28. Summary of Demographics in R668-EE-1877 Part A (Part A FAS)

		Dupilumab			
	Placebo (N=34)	Lower Exposure Dupilumab (N=31)	Higher Exposure Dupilumab (N=37)	Combined (N=68)	Total (N=102)
Age (years)					
n	34	31	37	68	102
Mean (SD)	7.2 (3.03)	7.2 (3.07)	6.8 (3.11)	7.0 (3.07)	7.1 (3.05)
Median	7.5	8.0	7.0	8.0	8.0
Q1 : Q3	6.0 : 10.0	5.0 : 10.0	4.0 : 10.0	4.0 : 10.0	5.0 : 10.0
Min : Max	1 : 11	1 : 11	1 : 11	1 : 11	1 : 11
Age Group, n (%)					
≥1 - <6 years	8 (23.5%)	11 (35.5%)	14 (37.8%)	25 (36.8%)	33 (32.4%)
≥6 - <12 years	26 (76.5%)	20 (64.5%)	23 (62.2%)	43 (63.2%)	69 (67.6%)
≥1 - <8 years	17 (50.0%)	12 (38.7%)	20 (54.1%)	32 (47.1%)	49 (48.0%)
≥8 - <12 years	17 (50.0%)	19 (61.3%)	17 (45.9%)	36 (52.9%)	53 (52.0%)
Ethnicity, n (%)					
Not Hispanic or Latino	30 (88.2%)	29 (93.5%)	33 (89.2%)	62 (91.2%)	92 (90.2%)
Hispanic or Latino	3 (8.8%)	2 (6.5%)	2 (5.4%)	4 (5.9%)	7 (6.9%)
Unknown	1 (2.9%)	0	0	0	1 (1.0%)
Not Reported	0	0	2 (5.4%)	2 (2.9%)	2 (2.0%)
Race, n (%)					
White	30 (88.2%)	22 (71.0%)	32 (86.5%)	54 (79.4%)	84 (82.4%)
Black or African American	3 (8.8%)	4 (12.9%)	4 (10.8%)	8 (11.8%)	11 (10.8%)
Asian	0	1 (3.2%)	1 (2.7%)	2 (2.9%)	2 (2.0%)
Other	1 (2.9%)	4 (12.9%)	0	4 (5.9%)	5 (4.9%)
Sex, n (%)					
Male	25 (73.5%)	25 (80.6%)	28 (75.7%)	53 (77.9%)	78 (76.5%)
Female	9 (26.5%)	6 (19.4%)	9 (24.3%)	15 (22.1%)	24 (23.5%)
Height (cm)					

		Dupilumab			
	Placebo (N=34)	Lower Exposure Dupilumab (N=31)	Higher Exposure Dupilumab (N=37)	Combined (N=68)	Total (N=102)
n	34	31	37	68	102
Mean (SD)	124.8 (19.83)	122.8 (18.80)	120.2 (19.50)	121.4 (19.09)	122.5 (19.31)
Median	127.8	129.8	122.0	126.5	126.5
Q1 : Q3	116.0 : 138.5	104.7 : 136.3	101.5 : 140.0	101.8 : 138.5	102.5 : 138.5
Min : Max	81 : 170	83 : 148	82 : 148	82 : 148	81 : 170
Weight (kg)					
n	34	31	37	68	102
Mean (SD)	28.3 (11.99)	26.1 (10.06)	26.0 (10.60)	26.1 (10.28)	26.8 (10.87)
Median	24.8	25.4	24.8	25.4	25.1
Q1 : Q3	21.0 : 35.2	17.5 : 31.9	15.7 : 32.2	17.2 : 32.1	17.3 : 33.6
Min : Max	11 : 60	10 : 48	12 : 47	10 : 48	10 : 60
Weight group, n (%)					
≥5-<15 kg	5 (14.7%)	5 (16.1%)	5 (13.5%)	10 (14.7%)	15 (14.7%)
≥15-<30 kg	18 (52.9%)	18 (58.1%)	19 (51.4%)	37 (54.4%)	55 (53.9%)
≥30-<60 kg	11 (32.4%)	8 (25.8%)	13 (35.1%)	21 (30.9%)	32 (31.4%)
Weight for Age Percentile at Baseline					
n	34	31	37	68	102
Mean (SD)	47.68 (32.843)	40.09 (33.423)	47.21 (28.662)	43.96 (30.893)	45.20 (31.443)
Median	38.19	35.37	46.47	41.35	39.71
Q1 : Q3	19.26 : 80.93	9.59 : 74.24	19.30 : 68.93	14.76 : 69.31	15.55 : 72.57
Min : Max	1.1 : 99.8	0.1 : 98.9	1.8 : 96.8	0.1 : 98.9	0.1 : 99.8
Weight for Age Percentile at Baseline Categories, n (%)					
0 to <25%	11 (32.4%)	13 (41.9%)	10 (27.0%)	23 (33.8%)	34 (33.3%)
25% to <50%	7 (20.6%)	8 (25.8%)	12 (32.4%)	20 (29.4%)	27 (26.5%)
50% to <75%	7 (20.6%)	3 (9.7%)	8 (21.6%)	11 (16.2%)	18 (17.6%)
≥75%	9 (26.5%)	7 (22.6%)	7 (18.9%)	14 (20.6%)	23 (22.5%)
Weight for Age Z-score at Baseline					
n	34	31	37	68	102
Mean (SD)	0.0 (1.27)	-0.4 (1.29)	-0.1 (0.94)	-0.2 (1.12)	-0.1 (1.17)
Median	-0.3	-0.4	-0.1	-0.2	-0.3
Q1 : Q3	-0.9 : 0.9	-1.3 : 0.7	-0.9 : 0.5	-1.0 : 0.5	-1.0 : 0.6
Min : Max	-2 : 3	-3 : 2	-2 : 2	-3 : 2	-3 : 3
BMI (kg/m^2)					
n	34	31	37	68	102
Mean (SD)	17.3 (2.88)	16.6 (2.79)	17.3 (2.89)	17.0 (2.84)	17.1 (2.84)
Median	16.3	15.9	16.4	16.1	16.1
Q1 : Q3	15.0 : 19.1	14.9 : 17.2	15.3 : 18.1	15.1 : 17.4	15.0 : 18.4
Min : Max	14 : 25	14 : 26	14 : 26	14 : 26	14 : 26
BMI group, n (%)					
Overweight: Yes	9 (26.5%)	5 (16.1%)	8 (21.6%)	13 (19.1%)	22 (21.6%)
Overweight: No	25 (73.5%)	26 (83.9%)	29 (78.4%)	55 (80.9%)	80 (78.4%)
BMI for Age Z-score at Baseline					
n	34	31	37	68	102
Mean (SD)	0.2 (1.09)	-0.1 (1.19)	0.2 (1.02)	0.1 (1.11)	0.1 (1.10)
Median	0.3	-0.1	0.1	-0.1	0.1
Q1 : Q3	-0.5 : 1.1	-0.9 : 0.8	-0.4 : 1.0	-0.6 : 0.9	-0.6 : 1.0
Min : Max	-2 : 3	-2 : 2	-2 : 2	-2 : 2	-2 : 3
Country, n (%)					
Canada	0	1 (3.2%)	0	1 (1.5%)	1 (1.0%)
United States	34 (100%)	30 (96.8%)	37 (100%)	67 (98.5%)	101 (99.0%)

BMI group: overweight was defined as ≥85 percentile of BMI for ≥2 years based on age and gender, ≥95 percentile of weight based on length (height), age, and gender for <2 years; not overweight was defined as not meeting the criteria of overweight [based on CDC chart].

Abbreviations: BMI=body mass index; CDC=Centers for Disease Control and Prevention; FAS=full analysis set; Max=maximum; Min=minimum; Q1=quartile 1; Q3=quartile 3; SD=standard deviation.

The baseline disease characteristics indicated a population with a significant disease burden, with the majority of participants having previously used STCs for the treatment of EoE (82/102; 80.4%). Over one-half of participants (59/102; 57.8%) had a history of an inadequate response, intolerance, and/or contraindication to STCs. The majority of patients were utilizing a food elimination diet for the treatment of their EoE (see 5.4.2 for details).

Table 29. Summary of Atopic/Allergic Disease History in R668-EE-1877 Part A (Part A FAS)

		Dupilumab			
	Placebo (N=34)	Lower Exposure Dupilumab (N=31)	Higher Exposure Dupilumab (N=37)	Combined (N=68)	Total (N=102)
Number (%) of Patients with current history of Atopic/Allergic Conditions	32 (94.1%)	31 (100%)	37 (100%)	68 (100%)	100 (98.0%)
Allergic Rhinitis	22 (64.7%)	27 (87.1%)	29 (78.4%)	56 (82.4%)	78 (76.5%)
Food Allergy	27 (79.4%)	25 (80.6%)	31 (83.8%)	56 (82.4%)	83 (81.4%)
Asthma	14 (41.2%)	18 (58.1%)	24 (64.9%)	42 (61.8%)	56 (54.9%)
Atopic Dermatitis	19 (55.9%)	15 (48.4%)	21 (56.8%)	36 (52.9%)	55 (53.9%)
Other Allergies (Medications, Animals, Plants, Mold, Dust Mites, etc)	9 (26.5%)	10 (32.3%)	14 (37.8%)	24 (35.3%)	33 (32.4%)
Hives	4 (11.8%)	6 (19.4%)	6 (16.2%)	12 (17.6%)	16 (15.7%)
Allergic Conjunctivitis	4 (11.8%)	5 (16.1%)	4 (10.8%)	9 (13.2%)	13 (12.7%)
Contact Dermatitis	2 (5.9%)	5 (16.1%)	4 (10.8%)	9 (13.2%)	11 (10.8%)
Chronic Rhinosinusitis	1 (2.9%)	3 (9.7%)	1 (2.7%)	4 (5.9%)	5 (4.9%)
Nasal Polyps	0	1 (3.2%)	0	1 (1.5%)	1 (1.0%)
Number (%) of Patients with currently resolved Atopic/Allergic Conditions	5 (14.7%)	7 (22.6%)	0	7 (10.3%)	12 (11.8%)
Atopic Dermatitis	3 (8.8%)	4 (12.9%)	0	4 (5.9%)	7 (6.9%)
Asthma	1 (2.9%)	3 (9.7%)	0	3 (4.4%)	4 (3.9%)
Hives	2 (5.9%)	2 (6.5%)	0	2 (2.9%)	4 (3.9%)
Contact Dermatitis	1 (2.9%)	1 (3.2%)	0	1 (1.5%)	2 (2.0%)
Allergic Conjunctivitis	1 (2.9%)	0	0	0	1 (1.0%)
Food Allergy	1 (2.9%)	0	0	0	1 (1.0%)
Other Allergies (Medications, Animals, Plants, Mold, Dust Mites, etc)	1 (2.9%)	0	0	0	1 (1.0%)
Patients with Numbers of Atopic/Allergic Conditions excluding EoE, n(%)					
At Least 1 Atopic/Allergic Condition excluding EoE	32 (94.1%)	31 (100%)	37 (100%)	68 (100%)	100 (98.0%)
>1	29 (85.3%)	30 (96.8%)	32 (86.5%)	62 (91.2%)	91 (89.2%)
>2	24 (70.6%)	27 (87.1%)	28 (75.7%)	55 (80.9%)	79 (77.5%)
>3	16 (47.1%)	17 (54.8%)	19 (51.4%)	36 (52.9%)	52 (51.0%)
>4	6 (17.6%)	8 (25.8%)	9 (24.3%)	17 (25.0%)	23 (22.5%)
>5	4 (11.8%)	7 (22.6%)	3 (8.1%)	10 (14.7%)	14 (13.7%)
>6	1 (2.9%)	4 (12.9%)	3 (8.1%)	7 (10.3%)	8 (7.8%)
>7	0	1 (3.2%)	2 (5.4%)	3 (4.4%)	3 (2.9%)
>8	0	0	1 (2.7%)	1 (1.5%)	1 (1.0%)
>9	0	0	0	0	0

Sorted by decreasing frequency at all levels in the combined dupilumab group.
Abbreviations: EoE=eosinophilic esophagitis; FAS=full analysis set.

Part B

As the majority (98/102) of Part A participants entered Part B of the study, the demographic and other baseline characteristics from Part B were consistent with Part A.

Part C

A total of 61 participants transitioned to Part C of the study: 2 participants in the ≥5kg to <15 kg weight category, 38 in the ≥15 kg to <30kg weight category, 17 in the ≥30kg to <40 kg weight category, and 4 in the ≥40kg weight category. The majority of participants were male (77.0%), and most were White (85.2%) and not Hispanic or Latino (88.5%). The mean (standard deviation) age of participants was 6.3 (2.82) years. The mean (SD) weight at Part C baseline was 27.2 (9.61) kg.

Adverse events

The number and proportion of participants experiencing a TEAE are summarized separately for Part A (16-week placebo-controlled treatment period) and for Part B (36-week extended active treatment period) and sorted by decreasing frequency of SOC and PT for the dupilumab combined treatment group in Part A and total group in Part B.

TEAEs are summarized for the Part A or Part B treatment period based on the onset date. TEAEs that started in Part A and continued in Part B are counted in Part A, but also in Part B if that TEAE worsened in Part B (e.g. worsening in intensity or a non-serious AE became serious).

Adverse events in Part A

Overview of Adverse Events for Part A

The incidence of all TEAEs reported during Part A of the study was numerically lower in the higher exposure dupilumab group (73.0%) versus the lower exposure dupilumab group (86.7%) and the placebo group (91.2%). Interim data for Part C up to 17 January 2024 have been presented.

In the majority of participants, TEAEs were mild or moderate in intensity. None of the participants in Part A of the study experienced TEAEs leading to death. Treatment-emergent SAEs were reported in 1/30 (3.3%) participant in the lower exposure dupilumab group and 2/37 (5.4%) participants in the higher exposure dupilumab group. TEAEs leading to permanent study intervention discontinuation were reported in 2/34 (5.9%) participants in the placebo group and none were reported in the dupilumab treated participants.

Table 30. Overall Summary of Number of Participants with TEAEs During the R668-EE-1877 Part A 16-Week Treatment Period (Part A SAF)

		Dupilumab		
	Placebo (N=34)	Lower Exposure Dupilumab (N=30)	Higher Exposure Dupilumab (N=37)	Combined (N=67)
Any TEAE, n (%)	31 (91.2%)	26 (86.7%)	27 (73.0%)	53 (79.1%)
Any drug related TEAE, n (%)	12 (35.3%)	11 (36.7%)	10 (27.0%)	21 (31.3%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	2 (5.9%)	0	0	0
Maximum intensity for any TEAE, n (%)				
Mild	17 (50.0%)	17 (56.7%)	21 (56.8%)	38 (56.7%)
Moderate	12 (35.3%)	8 (26.7%)	3 (8.1%)	11 (16.4%)
Severe	2 (5.9%)	1 (3.3%)	3 (8.1%)	4 (6.0%)
Any TEAE death, n (%)	0	0	0	0
Any TE SAE, n (%)	0	1 (3.3%)	2 (5.4%)	3 (4.5%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0	0	0
Any TEAE of Special Interest	1 (2.9%)	1 (3.3%)	2 (5.4%)	3 (4.5%)

One participant had a TEAE leading to discontinuation of study intervention permanently and this participant completed Part A treatment.
Abbreviations: SAE=serious adverse event; SAF=safety analysis set; TE=treatment-emergent; TEAE=treatment-emergent adverse event.

The common TEAEs by SOC with a PT occurring in ≥5% of participants in any treatment group in Part A were: Infections and infestations, General disorders and administration site conditions, Skin and subcutaneous tissue disorders, Gastrointestinal disorders, Nervous system disorders, Respiratory, thoracic and mediastinal disorders, Eye disorders, Immune system disorders, Psychiatric disorders.

By PT, the most frequent TEAE reported in dupilumab groups was COVID-19 (30.0% in the lower exposure dupilumab group and 13.5% in the higher exposure dupilumab group). In the placebo group, the most frequently reported PT was Injection site reaction (20.6%).

Of the PTs that occurred in ≥5% of participants in any treatment group, the following PTs occurred at a ≥5% higher incidence in the respective dupilumab groups versus the placebo group:

- In the lower exposure dupilumab group the PTs that met this criterion were: COVID 19, Injection site pain, Nausea, Abdominal pain upper, Gastrooesophageal reflux disease, and Headache.
- In the higher exposure dupilumab group the PTs that met this criterion were: COVID 19, Gastroenteritis viral, Injection site erythema, and Fatigue.

Of the PTs that occurred in ≥5% of participants in any treatment group, PTs that occurred at a ≥5% higher incidence in the placebo group than in the dupilumab combined group were: Sinusitis, Upper respiratory tract infection, Ear infection, Molluscum contagiosum, Viral upper respiratory tract infection, Injection site reaction, Vomiting, and Abdominal pain.

Table 31. Summary of TEAEs Reported by ≥5% of Participants in any Treatment Group by Primary SOC and PT During R668-EE-1877 Part A 16-Week Treatment Period (Part A SAF)

Primary SOC PT	Placebo (N=34)	Dupilumab Lower Exposure Dupilumab (N=30)	Dupilumab Higher Exposure Dupilumab (N=37)	Dupilumab Combined (N=67)
Number of such events	133	106	100	206
Number of patients with at least 1 such event, n (%)	31 (91.2%)	26 (86.7%)	27 (73.0%)	53 (79.1%)
Infections and infestations	14 (41.2%)	11 (36.7%)	13 (35.1%)	24 (35.8%)
COVID-19	0	9 (30.0%)	5 (13.5%)	14 (20.9%)
Gastroenteritis viral	1 (2.9%)	0	4 (10.8%)	4 (6.0%)
Nasopharyngitis	2 (5.9%)	1 (3.3%)	2 (5.4%)	3 (4.5%)
Sinusitis	3 (8.8%)	1 (3.3%)	0	1 (1.5%)
Upper respiratory tract infection	3 (8.8%)	1 (3.3%)	0	1 (1.5%)
Ear infection	2 (5.9%)	0	0	0
Molluscum contagiosum	2 (5.9%)	0	0	0
Viral upper respiratory tract infection	2 (5.9%)	0	0	0
General disorders and administration site conditions	12 (35.3%)	11 (36.7%)	12 (32.4%)	23 (34.3%)
Injection site reaction	7 (20.6%)	4 (13.3%)	4 (10.8%)	8 (11.9%)
Injection site erythema	1 (2.9%)	1 (3.3%)	4 (10.8%)	5 (7.5%)
Injection site pain	0	3 (10.0%)	0	3 (4.5%)
Fatigue	0	0	2 (5.4%)	2 (3.0%)
Pyrexia	1 (2.9%)	0	2 (5.4%)	2 (3.0%)
Skin and subcutaneous tissue disorders	8 (23.5%)	11 (36.7%)	6 (16.2%)	17 (25.4%)
Rash	2 (5.9%)	3 (10.0%)	3 (8.1%)	6 (9.0%)
Urticaria	2 (5.9%)	2 (6.7%)	1 (2.7%)	3 (4.5%)
Eczema	1 (2.9%)	2 (6.7%)	0	2 (3.0%)
Gastrointestinal disorders	11 (32.4%)	10 (33.3%)	5 (13.5%)	15 (22.4%)
Diarrhoea	1 (2.9%)	2 (6.7%)	2 (5.4%)	4 (6.0%)
Nausea	0	3 (10.0%)	1 (2.7%)	4 (6.0%)
Vomiting	6 (17.6%)	1 (3.3%)	3 (8.1%)	4 (6.0%)
Abdominal pain upper	0	2 (6.7%)	1 (2.7%)	3 (4.5%)
Abdominal pain	3 (8.8%)	1 (3.3%)	1 (2.7%)	2 (3.0%)
Gastrooesophageal reflux disease	0	2 (6.7%)	0	2 (3.0%)
Constipation	2 (5.9%)	0	1 (2.7%)	1 (1.5%)
Nervous system disorders	2 (5.9%)	7 (23.3%)	3 (8.1%)	10 (14.9%)
Headache	1 (2.9%)	4 (13.3%)	1 (2.7%)	5 (7.5%)
Dizziness	2 (5.9%)	1 (3.3%)	1 (2.7%)	2 (3.0%)
Respiratory, thoracic and mediastinal disorders	7 (20.6%)	6 (20.0%)	3 (8.1%)	9 (13.4%)
Cough	2 (5.9%)	2 (6.7%)	1 (2.7%)	3 (4.5%)
Rhinitis allergic	2 (5.9%)	2 (6.7%)	0	2 (3.0%)
Eye disorders	3 (8.8%)	3 (10.0%)	1 (2.7%)	4 (6.0%)
Eye swelling	1 (2.9%)	2 (6.7%)	0	2 (3.0%)
Immune system disorders	2 (5.9%)	3 (10.0%)	1 (2.7%)	4 (6.0%)
Seasonal allergy	2 (5.9%)	1 (3.3%)	0	1 (1.5%)
Psychiatric disorders	5 (14.7%)	2 (6.7%)	1 (2.7%)	3 (4.5%)
Fear of injection	2 (5.9%)	1 (3.3%)	0	1 (1.5%)
Insomnia	2 (5.9%)	1 (3.3%)	0	1 (1.5%)

At each level of patient summarization, a patient is counted once if the patient reported 1 or more events.

Primary SOC PT	Placebo (N=34)	Dupilumab Lower Exposure Dupilumab (N=30)	Dupilumab Higher Exposure Dupilumab (N=37)	Dupilumab Combined (N=67)

MedDRA (Version 25.1) coding dictionary applied.
Note: 5% cutoff is based on each PT. The rows for number of patients with at least 1 such event and for each SOC are based on the PTs selected by the cutoff.
Sorted by decreasing frequency at all levels in the combined dupilumab group.
Abbreviations: COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAF=safety analysis set; SOC=system organ class; TEAE=treatment-emergent adverse event.

Adverse events in Part B

Overview of Adverse Events for Part B

Table 32. Overall Summary of Number (%) of Participants with TEAEs During the R668-EE-1877 Part B 36-Week Treatment Period (Part B SAF)

	Placebo / Lower Exposure Dupilumab (N=14)	Placebo / Higher Exposure Dupilumab (N=18)	Placebo / Combined Dupilumab (N=32)	Lower Exposure Dupilumab / Lower Exposure Dupilumab (N=29)	Higher Exposure Dupilumab / Higher Exposure Dupilumab (N=37)	Combined Dupilumab (N=66)	Total (N=98)
Any TEAE, n (%)	14 (100%)	15 (83.3%)	29 (90.6%)	28 (96.6%)	34 (91.9%)	62 (93.9%)	91 (92.9%)
Any drug related TEAE, n (%)	8 (57.1%)	6 (33.3%)	14 (43.8%)	8 (27.6%)	11 (29.7%)	19 (28.8%)	33 (33.7%)
Any TEAE leading to discontinuation of study intervention permanently, n (%)	0	0	0	0	1 (2.7%)	1 (1.5%)	1 (1.0%)
Maximum intensity for any TEAE, n (%)							
Mild	7 (50.0%)	6 (33.3%)	13 (40.6%)	13 (44.8%)	19 (51.4%)	32 (48.5%)	45 (45.9%)
Moderate	6 (42.9%)	9 (50.0%)	15 (46.9%)	15 (51.7%)	13 (35.1%)	28 (42.4%)	43 (43.9%)
Severe	1 (7.1%)	0	1 (3.1%)	0	2 (5.4%)	2 (3.0%)	3 (3.1%)
Any TEAE death, n (%)	0	0	0	0	0	0	0
Any TE SAE, n (%)	1 (7.1%)	0	1 (3.1%)	3 (10.3%)	2 (5.4%)	5 (7.6%)	6 (6.1%)
Any TE SAE leading to discontinuation of study intervention permanently, n (%)	0	0	0	0	0	0	0
Any TEAE of Special Interest	0	1 (5.6%)	1 (3.1%)	3 (10.3%)	4 (10.8%)	7 (10.6%)	8 (8.2%)

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

Table 33. Summary of TEAEs Reported by ≥10% of Participants in any Treatment Group by Primary SOC and PT During Part B 36-week Treatment Period (Part B SAF)

Primary System Organ Class Preferred Term	Placebo / Lower Exposure Dupilumab (N=14)	Placebo / Higher Exposure Dupilumab (N=18)	Placebo / Combined Dupilumab (N=32)	Lower Exposure Dupilumab / Lower Exposure Dupilumab (N=29)	Higher Exposure Dupilumab / Higher Exposure Dupilumab (N=37)	Combined Dupilumab (N=66)	Total (N=98)
Number of such events	102	128	230	176	168	344	574
Number of patients with at least one such event, n (%)	14 (100%)	15 (83.3%)	29 (90.6%)	28 (96.6%)	34 (91.9%)	62 (93.9%)	91 (92.9%)
Infections and infestations	12 (85.7%)	11 (61.1%)	23 (71.9%)	18 (62.1%)	26 (70.3%)	44 (66.7%)	67 (68.4%)
COVID-19	2 (14.3%)	5 (27.8%)	7 (21.9%)	7 (24.1%)	11 (29.7%)	18 (27.3%)	25 (25.5%)
Influenza	4 (28.6%)	1 (5.6%)	5 (15.6%)	4 (13.8%)	3 (8.1%)	7 (10.6%)	12 (12.2%)
Upper respiratory tract infection	2 (14.3%)	1 (5.6%)	3 (9.4%)	7 (24.1%)	2 (5.4%)	9 (13.6%)	12 (12.2%)
Conjunctivitis	0	1 (5.6%)	1 (3.1%)	4 (13.8%)	1 (2.7%)	5 (7.6%)	6 (6.1%)
Viral upper respiratory tract infection	0	0	0	3 (10.3%)	1 (2.7%)	4 (6.1%)	4 (4.1%)
Rhinitis	0	2 (11.1%)	2 (6.3%)	0	0	0	2 (2.0%)
General disorders and administration site conditions	8 (57.1%)	9 (50.0%)	17 (53.1%)	9 (31.0%)	18 (48.6%)	27 (40.9%)	44 (44.9%)
Injection site reaction	4 (28.6%)	5 (27.8%)	9 (28.1%)	4 (13.8%)	5 (13.5%)	9 (13.6%)	18 (18.4%)
Pyrexia	4 (28.6%)	2 (11.1%)	6 (18.8%)	2 (6.9%)	6 (16.2%)	8 (12.1%)	14 (14.3%)
Injection site pain	3 (21.4%)	1 (5.6%)	4 (12.5%)	1 (3.4%)	1 (2.7%)	2 (3.0%)	6 (6.1%)
Fatigue	0	3 (16.7%)	3 (9.4%)	1 (3.4%)	0	1 (1.5%)	4 (4.1%)
Injection site erythema	1 (7.1%)	2 (11.1%)	3 (9.4%)	0	0	0	3 (3.1%)
Respiratory, thoracic and mediastinal disorders	7 (50.0%)	6 (33.3%)	13 (40.6%)	14 (48.3%)	12 (32.4%)	26 (39.4%)	39 (39.8%)
Cough	1 (7.1%)	4 (22.2%)	5 (15.6%)	4 (13.8%)	3 (8.1%)	7 (10.6%)	12 (12.2%)
Asthma	1 (7.1%)	0	1 (3.1%)	3 (10.3%)	4 (10.8%)	7 (10.6%)	8 (8.2%)
Oropharyngeal pain	2 (14.3%)	2 (11.1%)	4 (12.5%)	1 (3.4%)	2 (5.4%)	3 (4.5%)	7 (7.1%)
Rhinitis allergic	0	0	0	3 (10.3%)	2 (5.4%)	5 (7.6%)	5 (5.1%)
Rhinorrhoea	2 (14.3%)	2 (11.1%)	4 (12.5%)	0	1 (2.7%)	1 (1.5%)	5 (5.1%)
Gastrointestinal disorders	3 (21.4%)	8 (44.4%)	11 (34.4%)	11 (37.9%)	12 (32.4%)	23 (34.8%)	34 (34.7%)
Diarrhoea	1 (7.1%)	3 (16.7%)	4 (12.5%)	2 (6.9%)	3 (8.1%)	5 (7.6%)	9 (9.2%)
Vomiting	0	2 (11.1%)	2 (6.3%)	2 (6.9%)	5 (13.5%)	7 (10.6%)	9 (9.2%)
Abdominal pain	1 (7.1%)	2 (11.1%)	3 (9.4%)	2 (6.9%)	3 (8.1%)	5 (7.6%)	8 (8.2%)
Nausea	1 (7.1%)	2 (11.1%)	3 (9.4%)	2 (6.9%)	1 (2.7%)	3 (4.5%)	6 (6.1%)
Abdominal pain upper	1 (7.1%)	0	1 (3.1%)	3 (10.3%)	1 (2.7%)	4 (6.1%)	5 (5.1%)
Dyspepsia	0	2 (11.1%)	2 (6.3%)	1 (3.4%)	0	1 (1.5%)	3 (3.1%)
Skin and subcutaneous tissue disorders	5 (35.7%)	7 (38.9%)	12 (37.5%)	5 (17.2%)	10 (27.0%)	15 (22.7%)	27 (27.6%)
Rash	1 (7.1%)	2 (11.1%)	3 (9.4%)	1 (3.4%)	4 (10.8%)	5 (7.6%)	8 (8.2%)
Urticaria	3 (21.4%)	0	3 (9.4%)	0	1 (2.7%)	1 (1.5%)	4 (4.1%)
Eczema	0	2 (11.1%)	2 (6.3%)	1 (3.4%)	0	1 (1.5%)	3 (3.1%)
Immune system disorders	1 (7.1%)	4 (22.2%)	5 (15.6%)	8 (27.6%)	3 (8.1%)	11 (16.7%)	16 (16.3%)
Seasonal allergy	1 (7.1%)	1 (5.6%)	2 (6.3%)	4 (13.8%)	2 (5.4%)	6 (9.1%)	8 (8.2%)
Food allergy	0	2 (11.1%)	2 (6.3%)	0	1 (2.7%)	1 (1.5%)	3 (3.1%)
Musculoskeletal and connective tissue disorders	2 (14.3%)	3 (16.7%)	5 (15.6%)	3 (10.3%)	4 (10.8%)	7 (10.6%)	12 (12.2%)
Pain in extremity	1 (7.1%)	2 (11.1%)	3 (9.4%)	0	2 (5.4%)	2 (3.0%)	5 (5.1%)
Nervous system disorders	0	4 (22.2%)	4 (12.5%)	3 (10.3%)	3 (8.1%)	6 (9.1%)	10 (10.2%)
Headache	0	4 (22.2%)	4 (12.5%)	3 (10.3%)	3 (8.1%)	6 (9.1%)	10 (10.2%)
Eye disorders	2 (14.3%)	1 (5.6%)	3 (9.4%)	6 (20.7%)	0	6 (9.1%)	9 (9.2%)
Eye swelling	0	0	0	3 (10.3%)	0	3 (4.5%)	3 (3.1%)
Ocular hyperaemia	0	0	0	3 (10.3%)	0	3 (4.5%)	3 (3.1%)

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 25.1) coding dictionary applied.
Note: ≥10% cutoff is based on the incidence of PTs. The rows for number of patients with at least 1 such event and for each SOC are based on the PTs selected by the cutoff.
Sorted by decreasing frequency at all levels in the total group.
Abbreviations: COVID-19=Coronavirus Disease-2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAF=safety analysis set; SOC=system organ class; TEAE=treatment-emergent adverse event.

Adverse events in Part C (cut-off date 17 January 2024)

Overview of Adverse Events for Part C

Table 34. Overall Summary of Number (%) of Participants with TEAEs During the R668EE1877 Part C (108-week Treatment Period) (data cut-off 17-Jan-2024)

	>=5kg to <15kg (N=2)	>=15kg to <30kg (N=38)	>=30kg to <40kg (N=17)	>=40kg (N=4)	Total (N=61)
Any TEAE, n (%)	2 (100%)	33 (86.8%)	14 (82.4%)	3 (75.0%)	52 (85.2%)
Any study drug related TEAE, n (%)	1 (50.0%)	6 (15.8%)	2 (11.8%)	0	9 (14.8%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	0	0	0	0	0
Maximum intensity for any TEAE, n (%)					
Mild	2 (100%)	17 (44.7%)	12 (70.6%)	1 (25.0%)	32 (52.5%)
Moderate	0	16 (42.1%)	2 (11.8%)	2 (50.0%)	20 (32.8%)
Severe	0	0	0	0	0
Any TEAE resulting in death, n (%)	0	0	0	0	0
Any TE SAE, n (%)	0	3 (7.9%)	0	0	3 (4.9%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0	0	0	0
Any TEAE of Special Interest (AESI)	0	4 (10.5%)	1 (5.9%)	0	5 (8.2%)

At the time of data cutoff, during Part C of the study, a total of 293 TEAEs had been reported in 85.2% (52/61) participants.

The most frequently reported SOCs (overall incidence of TEAEs >10%) were:

• Infections and infestations (50.8%; 31/61). Overall, the most commonly reported PTs in this SOC were Pharyngitis streptococcal (16.3%; 10/61) and Upper respiratory tract infection (13.1%; 8/61). COVID-19 was reported in 4.9% of participants (3/61 participants).

• Respiratory, thoracic and mediastinal disorders (34.4%; 21/61).

• Gastrointestinal disorders (31.1%; 19/61).

• General disorders and administration site conditions (29.5%; 18/61).

• Skin and subcutaneous tissue disorders (24.6%; 15/61).

• Injury, poisoning and procedural complications: disorders (16.4%; 10/61).

• Nervous system disorders (14.8%; 9/61).

Serious adverse event/deaths/other significant events

Severity of Treatment-Emergent Adverse Events for Part A

A total of 12 severe events were reported by 6 participants (see Table 35 below). Three of severe TEAEs were also serious TEAEs.

Table 35. Summary of TEAEs of Severe Intensity by PT Reported During R668-EE-1877 Part A 16-Week Treatment Period (Part A SAF)

		Dupilumab		
PT	Placebo (N=34)	Lower Exposure Dupilumab (N=30)	Higher Exposure Dupilumab (N=37)	Combined (N=67)
Number of severe events	4	2	6	8
Number of participants with at least 1 severe event	2 (5.9%)	1 (3.3%)	3 (8.1%)	4 (6.0%)
Oesophageal food impaction	0	1 (3.3%)	0	1 (1.5%)
Procedural pain	0	0	1 (2.7%)	1 (1.5%)
Choking	0	1 (3.3%)	0	1 (1.5%)
Obstructive sleep apnoea syndrome	0	0	1 (2.7%)	1 (1.5%)
Anaphylactic reaction	0	0	1 (2.7%)	1 (1.5%)
Fear of injection	2 (5.9%)	0	0	0
Nephrolithiasis	0	0	1 (2.7%)	1 (1.5%)

At each level of patient summarization, a patient is counted once if the patient reported 1 or more events.
MedDRA (Version 25.1) coding dictionary applied.
Sorted by decreasing frequency at all levels in the combined dupilumab group.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAF=safety analysis set; TEAE=treatment-emergent adverse event.

Severity of Treatment-Emergent Adverse Events for Part B

In Part B, a total of 3 events assessed as severe in intensity were reported (see Table 36 below). One participant experienced a severe TEAE of Asthma (verbatim term: asthma exacerbation) that was a SAE due to hospitalization.

Table 36. Summary of TEAEs of Severe Intensity by PT Reported During Part B 36-week Treatment Period (Part B SAF)

Preferred Term	Placebo / Lower Exposure Dupilumab (N=14)	Placebo / Higher Exposure Dupilumab (N=18)	Placebo / Combined Dupilumab (N=32)	Lower Exposure Dupilumab / Lower Exposure Dupilumab (N=29)	Higher Exposure Dupilumab / Higher Exposure Dupilumab (N=37)	Combined Dupilumab (N=66)	Total (N=98)
Number of severe events	1	0	1	0	2	2	3
Number of patients with at least one severe event, n (%)	1 (7.1%)	0	1 (3.1%)	0	2 (5.4%)	2 (3.0%)	3 (3.1%)
Asthma	0	0	0	0	1 (2.7%)	1 (1.5%)	1 (1.0%)
Diarrhoea	1 (7.1%)	0	1 (3.1%)	0	0	0	1 (1.0%)
Drug hypersensitivity	0	0	0	0	1 (2.7%)	1 (1.5%)	1 (1.0%)

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 25.1) coding dictionary applied.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAF=safety analysis set; TEAE=treatment-emergent adverse event.
Source: PTT 7.3.1.1/1B

Severity of Treatment-Emergent Adverse Events for Part C (cut-off date 17 January 2024)

Overall, TEAEs were reported in 85.2% (52/61) of participants. In all of the participants who experienced TEAEs, the reported TEAEs were assessed as mild or moderate in intensity; no TEAEs of severe intensity were reported. The majority of TEAEs were non-serious and none lead to discontinuation of the study intervention. The majority of TEAEs were assessed as not related to study intervention by the investigator. A total of 4 SAEs were reported in 3 participants (4.9%).

Serious adverse events

Treatment-Emergent Serious Adverse Events for Part A

A total of 4 treatment-emergent SAEs were reported in 3 participants in Part A (1 participant in the lower exposure dupilumab group; 2 participants in the higher exposure dupilumab group). All SAE PTs were observed in single participants. None of the SAEs lead to permanent study intervention discontinuation and none were considered to be related to the study intervention by the investigators.

Table 37. Summary of Serious TEAEs by SOC and PT (Part A SAF)

		Dupilumab		
Primary System Organ Class Preferred Term	Placebo (N=34)	Lower Exposure Dupilumab (N=30)	Higher Exposure Dupilumab (N=37)	Combined (N=67)
Number of such events	0	1	3	4
Number of patients with at least one such event, n (%)	0	1 (3.3%)	2 (5.4%)	3 (4.5%)
Immune system disorders	0	1 (3.3%)	0	1 (1.5%)
Anaphylactic reaction	0	1 (3.3%)	0	1 (1.5%)
Injury, poisoning and procedural complications	0	0	1 (2.7%)	1 (1.5%)
Procedural pain	0	0	1 (2.7%)	1 (1.5%)
Renal and urinary disorders	0	0	1 (2.7%)	1 (1.5%)
Nephrolithiasis	0	0	1 (2.7%)	1 (1.5%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (2.7%)	1 (1.5%)
Sleep apnoea syndrome	0	0	1 (2.7%)	1 (1.5%)

Any patients who had serious TEAE displayed in the table.
At each level of patient summarization, a patient is counted once if the patient reported one or more events.
MedDRA (Version 24.1) coding dictionary applied.
Sorted by decreasing frequency at all levels in the combined dupilumab group.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAF=safety analysis set; SOC=system organ class; TEAE=treatment-emergent adverse event.
Source: PTT 7.7.1.1/1A

The one SAE in the lower exposure dupilumab group was:

Anaphylactic reaction of moderate in intensity that occured in a participant on study day 8; event was also categorized as an AESI. The participant had a history of food allergies (milk, peanut, wheat, barley, beef, chicken, egg, and shellfish), developed cough, hives, emesis, and angioedema after accidental exposure to milk. Treatment included epinephrine, methylprednisolone, and famotidine. The event recovered on the same day. Study treatment continued. The event was assessed by the investigator as not-related to the study intervention. The participant experienced another episode of Anaphylactic reaction in Part B of the study (due to accidental exposure to wheat).

The two SAEs in the higher exposure dupilumab group were:

Nephrolithiasis (kidney stone) and Procedural pain, both severe in intensity, that occurred in a participant on study days 71 and 75, respectively. The participant underwent urogram, laser lithotripsy, and ureteral stent insertion on study day 67. Non-serious post-operative pain reported on study day 69; became serious on study day 75. On study day 71, the participant was admitted to the hospital. SAE of Nephrolithiasis was reported. Fentanyl was given as a pain medication. On study day

74, the participant was discharged from hospital, and re-admitted to hospital on study day 75 due to recurrent flank pain and vomiting; received sennosides (8.6 mg, daily, oral). The SAE of Nephrolithiasis resolved on study day 75 and the SAE of Procedural pain resolved on study day 84. The investigator considered the SAEs of Nephrolithiasis and Procedural pain as not related to study drug. The participant continued in the study.

Obstructive sleep apnoea syndrome, severe in intensity, occurred in a participant on study day 117 . Event was diagnosed in a participant with medical history of asthma, who underwent a sleep study due to worsening snoring. A tonsillectomy/adenoidectomy was performed as corrective treatment. The SAE resolved on study day 118. The event was considered as not-related to the study drug. An additional serious event of asthma was reported for this participant in Part B of the study.

Treatment-Emergent Serious Adverse Events for Part B

In Part B, a total of 8 treatment-emergent SAEs were reported. All SAE PTs were observed in single participants. None of the SAEs were considered to be related to the study intervention by the investigators.

Table 38. Summary of Serious TEAEs by SOC and PT During Part B 36-week Treatment Period (Part B SAF)

Primary System Organ Class Preferred Term	Placebo / Lower Exposure Dupilumab (N=14)	Placebo / Higher Exposure Dupilumab (N=18)	Placebo / Combined Dupilumab (N=32)	Lower Exposure Dupilumab / Lower Exposure Dupilumab (N=29)	Higher Exposure Dupilumab / Higher Exposure Dupilumab (N=37)	Combined Dupilumab (N=66)	Total (N=98)
Number of such events	2	0	2	3	3	6	8
Number of patients with at least one such event, n (%)	1 (7.1%)	0	1 (3.1%)	3 (10.3%)	2 (5.4%)	5 (7.6%)	6 (6.1%)
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (3.4%)	2 (5.4%)	3 (4.5%)	3 (3.1%)
Asthma	0	0	0	0	1 (2.7%)	1 (1.5%)	1 (1.0%)
Sleep apnoea syndrome	0	0	0	0	1 (2.7%)	1 (1.5%)	1 (1.0%)
Throat tightness	0	0	0	1 (3.4%)	0	1 (1.5%)	1 (1.0%)
Blood and lymphatic system disorders	1 (7.1%)	0	1 (3.1%)	0	0	0	1 (1.0%)
Leukocytosis	1 (7.1%)	0	1 (3.1%)	0	0	0	1 (1.0%)
General disorders and administration site conditions	1 (7.1%)	0	1 (3.1%)	0	0	0	1 (1.0%)
Pyrexia	1 (7.1%)	0	1 (3.1%)	0	0	0	1 (1.0%)
Immune system disorders	0	0	0	1 (3.4%)	0	1 (1.5%)	1 (1.0%)
Anaphylactic reaction	0	0	0	1 (3.4%)	0	1 (1.5%)	1 (1.0%)
Infections and infestations	0	0	0	1 (3.4%)	0	1 (1.5%)	1 (1.0%)
HCoV-OC43 infection	0	0	0	1 (3.4%)	0	1 (1.5%)	1 (1.0%)
Injury, poisoning and procedural complications	0	0	0	0	1 (2.7%)	1 (1.5%)	1 (1.0%)
Post procedural haemorrhage	0	0	0	0	1 (2.7%)	1 (1.5%)	1 (1.0%)

At each level of participant summarization, a participant is counted once if the participant reported one or more events.
MedDRA (Version 25.1) coding dictionary applied.
Sorted by decreasing frequency at all levels in the Total group.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAF=safety analysis set; SOC=system organ class; TEAE=treatment-emergent adverse event.
Source: PTT 7.7.1.1/1B

The SAE in the placebo/lower exposure dupilumab group was:

Pyrexia and Leukocytosis, both moderate in intensity, occurred in a participant on study day 360. Participant hospitalized 9 days after the final dose of study intervention and shortly after the week 52 EGD procedure, with fever and leukocytosis, for observation to rule out perforation or sepsis. Both SAEs recovered the next day following supportive treatment (ibuprofen, metronidazole, ceftriaxone, sodium chloride, and acetaminophen); discharged on the same day. The SAEs were considered by the investigator to not-related to the study drug but related to the EGD procedure.

No treatment emergent SAEs were reported in the placebo/higher exposure dupilumab group.

The SAEs in the lower exposure/lower exposure dupilumab group were:

HCoV-OC43 infection, moderate in intensity, occurred in a participant on study day 116 . The participant was hospitalized 1 day after the first dose of study intervention in Part B due to fever and inability to tolerate anything orally; discharged the next day following treatment with IV fluids and ibuprofen. The SAE was resolved on study day 117. Study treatment continued. The investigator considered the event not related to study drug.

Anaphylactic reaction, moderate in intensity, occurred in a participant on study day 216 , also categorized as an AESI. Participant had a previous SAE of Anaphylactic reaction in Part A (due to accidental exposure to milk). The participant had a history of food (including wheat) and milk allergies, experienced anaphylaxis after unintentional exposure to wheat, requiring an ER visit. Most recent dose of dupilumab 200 mg was on study day 197. The SAE resolved the next day after treatment (epinephrine, diphenhydramine hydrochloride, dexamethasone, sodium chloride, and famotidine). The investigator considered the SAE/AESI of Anaphylactic reaction as not related to study drug. Study treatment continued.

Throat tightness, moderate in intensity, occurred in a participant on study day 287 . The event was reported in a participant with a history of food allergy, GERD, and asthma with no identified trigger. No other symptoms were present. Most recent dose of dupilumab 200 mg was on study day 275. (The treatment regimen was changed to dupilumab 200 mg Q2W due to the participant moving up a weight tier (weight increased to ≥30 kg). The participant received a total of 26 doses of study drug (18 doses of dupilumab [eight 300 mg and ten 200 mg doses] and 8 doses of placebo) throughout the study). Treatment included epinephrine, diphenhydramine hydrochloride, omeprazole, and salbutamol. The SAE resolved on the same day. Study treatment continued without recurrence of the event.

The SAEs in the higher exposure/higher exposure dupilumab group were:

Sleep apnoea syndrome and **Post procedural haemorrhage**, both moderate in intensity, occurred in a participant on study day 120 and 132 respectively. The participant with history of sleep apnea underwent tonsillectomy due to worsening sleep apnoea and was hospitalized overnight for observation and was discharged the next day with Sleep apnoea syndrome recovered. On study day 132, was re hospitalized due to multiple episodes of hematemesis. Hemostasis of the tonsillectomy site was achieved. The investigator considered the SAEs of Sleep apnoea syndrome and Post procedural haemorrhage as not related to study drug. Post-procedural hemorrhage resolved the following day. Study treatment continued.

Asthma, severe in intensity, occurred in a participant on study day 153. The participant with history of asthma was admitted to ER and subsequently to ICU due to asthma exacerbation. The event resolved after corrective treatment (albuterol and oral prednisolone) the next day. The most recent dose of dupilumab 200 mg was on day 142. Study treatment continued. The event was considered not-related by the investigator.

Deaths

There were no TEAEs leading to death in Part A and Part B of study R668-EE-1877.

Treatment-Emergent Serious Adverse Events for Part C (cut-off date 17 January 2024)

As of the data cut-off date, 4 treatment-emergent SAEs were reported in 3/61 (4.9%) participants in the ≥15 to <30 kg weight tier. None of the SAEs led to discontinuation of study intervention. All the SAEs were reported as resolved and all were assessed as not related to study intervention by the Investigator. Of the 4 treatment-emergent SAEs, two of the reported PTs (Endoscopy intestinal and Oesophageal food impaction) were potentially linked to the underlying indication; both events resolved within one day of onset and were considered mild to moderate in severity and not related to the study drug. The participant who reported the PT Endoscopy intestinal also experienced an SAE of PT Perirectal abscess approximately 6 weeks prior in Part C (AE start date from first dose in Part C: study days 283 and 245, respectively) that was also considered not related to the study drug.

The remaining SAE concerned a participant who experienced a Cardiac arrest (verbatim: Cardiac asystole, requiring hospitalization for evaluation) on study day 550. The most recent dose of dupilumab 200 mg was on study day 540. Prior to the SAE, the participant experienced 2 non-serious AEs of Seizure that resolved the same day: the first was assessed as moderate in intensity (on study day 482, 68 days before the SAE and 5 days before 1st dupilumab dose in Part C), and the second was assessed as mild in intensity (on study day 545, 5 days before the SAE and 5 days after the 5th dose of dupilumab in Part C). Given these events, on day 550, 10 days after the 5th dose of dupilumab in Part C, a brain MRI under sedation with dexmedetomidine, and EEG were performed. No structural cause for the seizures was identified from the MRI. During the EEG, the ECG showed bradycardia and asystole, and the EEG showed slowing and suppression consistent with syncope from hypoperfusion. On study day 551, the participant was hospitalized for urgent work-up and an ECG and echocardiogram showed no abnormalities, laboratory assessments were normal, and work up for myocarditis was negative. On study day 554, an implantable cardiac monitor was inserted, dupilumab was administered, and the participant was discharged. The participant was to follow-up with electrophysiology (results not provided) and continued to receive dupilumab with no further episodes of bradycardia or asystole reported.

Table 39. Listing of Serious Adverse Events (Part C) (Data cut-off 17 Jan 2024)

Weight Tier in Part C	Patient ID/ Age (Year)/Sex	Preferred term/ *Verbatim term*	Study Day Start/ Stop[1]	Severity	Relationship to Study Intervention[2]	Outcome	Action Taken with Study Intervention
≥15 to <30 kg		Cardiac arrest/ *Cardiac asystole, requiring hospitalization for evaluation*	550 (178; 64)/ 554 (182; 68)	Moderate	Not related	Recovered/ resolved	Dose not changed
≥15 to <30 kg		Perirectal abscess / *Hospitalization due to perirectal abscess on left buttock*	610 (247; 245)/ 613 (250; 248)	Moderate	Not related	Recovered/ resolved	Dose not changed
≥15 to <30 kg		Endoscopy intestinal/ *Hospitalization for bowel prep for EGD, colonoscopy and EOA tomorrow*	648 (285; 283)/ 649 (286; 284)	Mild	Not related	Recovered/ resolved	Dose not changed
≥15 to <30 kg		Oesophageal food impaction / *Hospitalization due to suspected food impaction*	800 (428; 332)/ 801 (429; 333)	Moderate	Not related	Recovered/ resolved	Dose not changed

[1] Study day start and stop is relative to first dose of study intervention in Part A. The days within parenthesis are the start of event relative to the last dose in Part B and the first dose in Part C, respectively.
[2] The relationship of the AE to study drug as assessed by the investigator.
Abbreviations: AE=adverse event; ECG=electrocardiogram; EEG=electroencephalogram; F=female; ID=identification; MRI=magnetic resonance imaging; SAE=serious adverse event; SAF=safety analysis set.

Adverse events of special interest

Pre-specified adverse events of special interest (AESIs) in this study were: Anaphylactic reactions, Systemic hypersensitivity reactions, Helminthic infections, Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms), Any severe type of conjunctivitis or blepharitis, Keratitis, Severe injection site reactions, Herpes simplex infection, Arthralgia.

Adverse Events of Special Interest for Part A

In Part A, a total of 4 AESIS were reported; 1 (3.3%) participant in the lower exposure dupilumab group, 2 (5.4%) participants in the higher exposure dupilumab group, and 1 (2.9%) in the placebo group.

Table 40. Summary of Treatment-Emergent AESIs by AESI Category, SOC, and PT in R668-EE-1877 Part A (Part A SAF)

AESI Category SOC PT	Placebo (N=34)	Dupilumab Lower Exposure Dupilumab (N=30)	Dupilumab Higher Exposure Dupilumab (N=37)	Dupilumab Combined (N=67)
Number of such events	1	1	2	3
Number of patients with at least 1 such event, n (%)	1 (2.9%)	1 (3.3%)	2 (5.4%)	3 (4.5%)
Anaphylactic reactions	0	1 (3.3%)	1 (2.7%)	2 (3.0%)
Immune system disorders	0	1 (3.3%)	1 (2.7%)	2 (3.0%)
Anaphylactic reaction	0	1 (3.3%)	1 (2.7%)	2 (3.0%)
Herpes simplex infection	0	0	1 (2.7%)	1 (1.5%)
Infections and infestations	0	0	1 (2.7%)	1 (1.5%)
Herpes simplex	0	0	1 (2.7%)	1 (1.5%)
Arthralgia	1 (2.9%)	0	0	0
Musculoskeletal and connective tissue disorders	1 (2.9%)	0	0	0
Arthralgia	1 (2.9%)	0	0	0

MedDRA (Version 24.1) coding dictionary applied.
Sorted by decreasing frequency at all levels in the combined dupilumab group.
Abbreviations: AESI=adverse event of special interest; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAF=safety analysis set; SOC=system organ class.

The AESI in the placebo group was:

Arthralgia, mild in intensity, occurred in a participant on study day 10. Participant experienced mild, non-serious spontaneous right ankle pain; also had arthralgia of knees. AESI resolved the same day and was considered not related to the study intervention by the investigator. No relevant medical history was reported. The participant experienced two additional AESIs of in part B.

The AESI in the lower exposure dupilumab group was:

Anaphylactic reaction, moderate in intensity, classified as an SAE (see Section 5.5.5)

The AESI in the higher exposure dupilumab group were:

Herpes simplex, moderate in intensity, occurred in a participant on study day 66. Participant with a medical history of intermittent cold sores on different locations, but mostly on inside of lower lip, experienced an increased frequency since the start of the study. The event was non-serious, ongoing and considered related to the study intervention by the Investigator. Study intervention continued.

Anaphylactic reaction, severe in intensity, occurred in a participant on study day 31. Participant with a medical history of food and milk allergies, exercise-induced bronchospasm, and allergic rhinitis, experienced anaphylaxis after suspected exposure to dairy (milk). The event was non-serious, recovered on the same day after treatment with epinephrine, and was considered not related to the study intervention by the Investigator. Study intervention continued. No further events of anaphylaxis or hypersensitivity reactions were reported.

For all AESIs in Part A, no action was taken with study intervention. There were no AESIs of helminthic infections, severe conjunctivitis/blepharitis, keratitis, clinically symptomatic eosinophilia, or severe injection site reactions reported in Part A.

Adverse Events of Special Interest for Part B

In Part B, a total of 8 (8.2%) participants experienced a treatment-emergent AESI; 1 (5.6%) participant in the placebo/higher exposure dupilumab group, 3 (10.3%) participants in the lower exposure dupilumab/lower exposure dupilumab group, 4/37 (10.8%) participants in the higher exposure dupilumab/higher exposure dupilumab group.

Table 41. Summary of TEAEs of Special Interest by AESI Category, SOC, and PT During Part B 36-week Treatment Period (Part B SAF)

AESI Category System Organ Class Preferred Term	Placebo / Lower Exposure Dupilumab (N=14)	Placebo / Higher Exposure Dupilumab (N=18)	Placebo / Combined Dupilumab (N=32)	Lower Exposure Dupilumab / Lower Exposure Dupilumab (N=29)	Higher Exposure Dupilumab / Higher Exposure Dupilumab (N=37)	Combined Dupilumab (N=66)	Total (N=98)
Number of such events	0	2	2	3	4	7	9
Number of patients with at least one such event, n (%)	0	1 (5.6%)	1 (3.1%)	3 (10.3%)	4 (10.8%)	7 (10.6%)	8 (8.2%)
Arthralgia	0	1 (5.6%)	1 (3.1%)	0	2 (5.4%)	2 (3.0%)	3 (3.1%)
Musculoskeletal and connective tissue disorders	0	1 (5.6%)	1 (3.1%)	0	2 (5.4%)	2 (3.0%)	3 (3.1%)
Arthralgia	0	1 (5.6%)	1 (3.1%)	0	2 (5.4%)	2 (3.0%)	3 (3.1%)
Anaphylactic reactions	0	0	0	2 (6.9%)	0	2 (3.0%)	2 (2.0%)
Immune system disorders	0	0	0	2 (6.9%)	0	2 (3.0%)	2 (2.0%)
Anaphylactic reaction	0	0	0	2 (6.9%)	0	2 (3.0%)	2 (2.0%)
Systemic hypersensitivity reactions	0	0	0	1 (3.4%)	1 (2.7%)	2 (3.0%)	2 (2.0%)
Immune system disorders	0	0	0	1 (3.4%)	1 (2.7%)	2 (3.0%)	2 (2.0%)
Drug hypersensitivity	0	0	0	0	1 (2.7%)	1 (1.5%)	1 (1.0%)
Hypersensitivity	0	0	0	1 (3.4%)	0	1 (1.5%)	1 (1.0%)
Helminthic infections	0	0	0	0	1 (2.7%)	1 (1.5%)	1 (1.0%)
Infections and infestations	0	0	0	0	1 (2.7%)	1 (1.5%)	1 (1.0%)
Helminthic infection	0	0	0	0	1 (2.7%)	1 (1.5%)	1 (1.0%)

At each level of participant summarization, a participant is counted once if the participant reported one or more events.
MedDRA (Version 25.1) coding dictionary applied.
Sorted by decreasing frequency at all levels in the total group.
Abbreviations: AESI=adverse event of special interest; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAF=safety analysis set; SOC=system organ class; TEAE=treatment-emergent adverse event.

The AESIs in the placebo/higher exposure dupilumab group were:

Two AESIs of **Arthralgia**, mild in intensity, occurred in a participant on study days 150 and 183. Participant previously experienced arthralgia of right ankle and knees in Part A while on placebo. Both AESIs of Arthralgia in Part B resolved on the day of their onset without corrective treatment.

The AESIs in the lower exposure/lower exposure dupilumab group were:

Anaphylactic reaction, moderate in intensity, occurred in a participant on study day 198. Participant with medical history of multiple food allergies, including milk allergy, AD, and allergic rhinitis, experienced an anaphylactic reaction, following ingestion of a milk product, 21 days after the most recent dose of 200 mg dupilumab. Event resolved the same day following treatment with epinephrine and prednisolone.

Anaphylactic reaction, moderate in intensity, classified as SAE (see Section 5.5.5.)

Hypersensitivity, moderate in intensity, occurred in a participant on study day 298. Participant with medical history of AD, multiple food allergies, allergic rhinitis, and pollen allergy experienced stomachache, vomiting, coughing, and itching of face following a meal. AESI resolved the same day after treatment (epinephrine, oral diphenhydramine HCI, prednisone, and ondansetron). Study treatment continued.

The AESIs in the higher exposure/higher exposure dupilumab group were:

Arthralgia, mild in intensity, occurred in a participant on study day 303 (patient narrative). Participant experienced wrist and shoulder pain after a dresser fell on the participant's wrist and shoulder. The participant received ibuprofen and the AESI resolved the next day. Study treatment continued.

Drug Hypersensitivity, severe in intensity. occurred in a participant on study day 137. On study 133 (week 16 dose of dupilumab), the participant with a history of multiple food and other allergies, asthma, allergic rhinitis, and AD experienced pruritic, painful, red, mildly raised rash without systemic symptoms. The rash persisted despite topical treatment (triamcinolone and Aquaphor) and on study day 137 the event was reported as a possible adverse reaction to study intervention. After the study day 148, week 18 injection, the rash progressed, and study intervention was discontinued. The event resolved on study day 192.

Helminthic infection, mild in intensity, occurred in a participant on study day 369. Participant with a history of juvenile polyposis syndrome, eosinophilic colitis, and eosinophilic ileitis, underwent a colonoscopy, during which helminthic infection was diagnosed. Treated with albendazole. Strongyloides antibodies were 'minor at 0.9' and Toxocara antibodies were negative. Study treatment continued and the AESI resolved on study day 424. The event was considered as related to study treatment.

Arthralgia, moderate in intensity, occurred in a participant on study day 127. Participant with a history of intermittent joint pain, experienced mild and intermittent pain that became more intense and persistent in the wrist, elbow, and knees. Knee pain 'confirmed with MRI' and treated with naproxen. Study intervention continued and the AESI resolved on study day 330.

Study intervention was discontinued in one participant who experienced the AESI of Drug hypersensitivity. The events of Drug hypersensitivity and Helminthic infection were considered to be not related to study intervention by the investigator. There were no cases of clinically symptomatic eosinophilia, severe conjunctivitis or blepharitis, keratitis, severe injection site reactions, or herpes infections during Part B.

Adverse Events of Special Interest for Part C (cut-off date 17 January 2024)

As of the data cut-off date, during Part C, 8.2% (5/61) of participants experienced an AESI. All the reported AESIs were non-serious and did not lead to discontinuation of study intervention. The AESIs are summarized in Table 42 below. Two AESI were assessed as related to study drug by the investigator (PTs Arthralgia and Helminthic infection) while the remainder were considered not related to study drug.

Table 42. Listing of Serious Adverse Events of Special Interest (Part C) (Data cut-off 17 Jan 2024)

Weight tier in Part C	Patient ID/ Age (Year)/ Sex	Preferred term/ *Verbatim term*	Study Day Start/ Stop[1]	Severity	Serious	Relationship to Study Intervention[2]	Outcome	Action Taken with Study Intervention
≥15 to <30 kg		Anaphylactic reaction/ *Anaphylaxis*	543 (179; 39)/ 543 (179; 39)	Moderate	No	Not related	Recovered/ Resolved	Dose not changed
≥15 to <30 kg		Helminthic infection/ *Worms in the terminal ileum*	648 (285; 283)/ 650 (287; 285)	Moderate	No	Related	Recovered/ Resolved	Dose not changed
≥15 to <30 kg		Arthralgia/ *Arthralgia (Right elbow pain)*	847 (482; 298)/ 850 (485; 301)	Mild	No	Not related	Recovered/ Resolved	Dose not changed
≥15 to <30 kg		Arthralgia/ *Knee pains*	543 (174; 124)/ Ongoing	Mild	No	Related	Not Recovered/Not Resolved	Dose not changed
≥15 to <30 kg		Astigmatism / *Hyperopia/ Astigmatism*	679 (308; 280)/ Ongoing	Mild	No	Not related	Not Recovered/Not Resolved	Dose not changed

[1] Study day start and stop is relative to first dose in Part A. The days within parenthesis are the start of event relative to the last dose in Part B and the first dose in Part C, respectively.
[2] The relationship of the AE to study drug as assessed by the investigator.
Abbreviations: AD=atopic dermatitis; AE=adverse event; AESI=adverse event of special interest; IM=intramuscular; IV=intravenous; M=male; SAF=safety analysis set.

Other significant events

Injection Site Reactions (Part A & B)

In Part A, injection site reactions were reported in a higher proportion of participants in the lower exposure dupilumab group (10/30; 33.3%) and placebo group (11/34; 32.4%) than in the higher exposure dupilumab group (9/37; 24.3%) (Table 43). None of the injection site reactions were serious and none led to permanent discontinuation of study intervention. All injection site reactions were assessed as mild or moderate in intensity; no severe injection site reactions events were reported.

Table 43. Summary of Injection Site Reactions by PT During the R668-EE-1877 Part A 16-Week Treatment Period (Part A SAF)

		Dupilumab		
Preferred Term	**Placebo (N=34)**	**Lower Exposure Dupilumab (N=30)**	**Higher Exposure Dupilumab (N=37)**	**Combined (N=67)**
Number of such events	13	18	29	47
Number of patients with at least 1 such event, n (%)	11 (32.4%)	10 (33.3%)	9 (24.3%)	19 (28.4%)
Injection site reaction	7 (20.6%)	4 (13.3%)	4 (10.8%)	8 (11.9%)
Injection site erythema	1 (2.9%)	1 (3.3%)	4 (10.8%)	5 (7.5%)
Injection site pain	0	3 (10.0%)	0	3 (4.5%)
Injection site urticaria	0	1 (3.3%)	1 (2.7%)	2 (3.0%)
Injection site haemorrhage	1 (2.9%)	0	1 (2.7%)	1 (1.5%)
Injection site inflammation	0	0	1 (2.7%)	1 (1.5%)
Injection site irritation	0	0	1 (2.7%)	1 (1.5%)
Injection site mass	1 (2.9%)	0	1 (2.7%)	1 (1.5%)
Injection site oedema	0	0	1 (2.7%)	1 (1.5%)
Injection site swelling	1 (2.9%)	0	1 (2.7%)	1 (1.5%)
Injection site vesicles	0	1 (3.3%)	0	1 (1.5%)
Injection site bruising	1 (2.9%)	0	0	0

Preferred Term	Placebo (N=34)	Dupilumab		
		Lower Exposure Dupilumab (N=30)	Higher Exposure Dupilumab (N=37)	Combined (N=67)

At each level of patient summarization, a patient is counted once if the patient reported 1 or more events.
MedDRA (Version 24.1) coding dictionary applied.
Sorted by decreasing frequency at all levels in the combined dupilumab group.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAF=safety analysis set.

In Part B, injection site reactions were reported in 34.7% of participants (34/98). Injection site reactions were reported in a higher proportion of participants who had previously received placebo in Part A (50.0% in both the placebo/lower exposure dupilumab group and in the placebo/higher exposure dupilumab group) compared with those who had received dupilumab in Part A (24.1% in the lower exposure dupilumab/lower exposure dupilumab group and 29.7% in the higher exposure dupilumab/higher exposure dupilumab group).

None of the injection site reactions were serious or led to permanent discontinuation of study intervention. All injection site reactions were assessed as mild or moderate in intensity, with no severe events reported, and all resolved.

Table 44. Summary of Injection Site Reactions by PT During the R668-EE-1877 Part B 36-Week Treatment Period (Part B SAF)

Preferred Term	Placebo / Lower Exposure Dupilumab (N=14)	Placebo / Higher Exposure Dupilumab (N=18)	Placebo / Combined Dupilumab (N=32)	Lower Exposure Dupilumab / Lower Exposure Dupilumab (N=29)	Higher Exposure Dupilumab / Higher Exposure Dupilumab (N=37)	Combined Dupilumab (N=66)	Total (N=98)
Number of such events	43	26	69	26	27	53	122
Number of patients with at least 1 such event, n (%)	7 (50.0%)	9 (50.0%)	16 (50.0%)	7 (24.1%)	11 (29.7%)	18 (27.3%)	34 (34.7%)
Injection site reaction	4 (28.6%)	5 (27.8%)	9 (28.1%)	4 (13.8%)	5 (13.5%)	9 (13.6%)	18 (18.4%)
Injection site pain	3 (21.4%)	1 (5.6%)	4 (12.5%)	1 (3.4%)	1 (2.7%)	2 (3.0%)	6 (6.1%)
Injection site erythema	1 (7.1%)	2 (11.1%)	3 (9.4%)	0	0	0	3 (3.1%)
Injection site haemorrhage	1 (7.1%)	0	1 (3.1%)	0	2 (5.4%)	2 (3.0%)	3 (3.1%)
Injection site inflammation	0	0	0	2 (6.9%)	1 (2.7%)	3 (4.5%)	3 (3.1%)
Injection site oedema	0	1 (5.6%)	1 (3.1%)	1 (3.4%)	1 (2.7%)	2 (3.0%)	3 (3.1%)
Injection site swelling	1 (7.1%)	0	1 (3.1%)	0	2 (5.4%)	2 (3.0%)	3 (3.1%)
Injection site induration	0	1 (5.6%)	1 (3.1%)	0	0	0	1 (1.0%)
Injection site mass	0	0	0	0	1 (2.7%)	1 (1.5%)	1 (1.0%)
Injection site nodule	0	0	0	1 (3.4%)	0	1 (1.5%)	1 (1.0%)

At each level of participant summarization, a participant is counted once if the participant reported 1 or more events.
MedDRA (Version 25.1) coding dictionary applied.
Sorted by decreasing frequency at all levels in the Total group.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAF=safety analysis set.

Injection Site Reactions (Part C; cut-off date 17 January 2024)

As of the data cutoff date, TEAEs in the HLT Injection site reactions were reported in 18.0% (11/61) of participants. All were non-serious, assessed as mild in intensity and did not lead to study intervention discontinuation. The most commonly reported PTs were Injection site reaction (8.2%) and Injection site pain (4.9%). In 4 of the participants who experienced a TEAE within the HLT Injection site reactions, the TEAE was considered to be related to study intervention; all other injection site reaction events were considered by the investigator to be not related. There were no injection site reactions reported in the ≥5 to <15 kg and ≥40 kg weight tiers.

Conjunctivitis and Eye Disorder Events (Part A & B)

In Part A, there were 8 events coded under the conjunctivitis CMQ (broad) reported in 4 participants: 1 event of Conjunctivitis in 1/30 (3.3%) participant and 5 events of Eye irritation in 1/30 (3.3%) participant in the lower exposure dupilumab group, 1 event of Dry eye in 1/37 (2.7%) participant in the higher exposure dupilumab group, and 1 event of Conjunctivitis allergic in 1/34 (2.9%) participant in the placebo group. All these events were of mild or moderate intensity, non-serious, and did not lead to permanent discontinuation of study intervention.

Table 45. Number of Participants with Conjunctivitis CMQ (Broad) by PT During R668-EE-1877 Part A 16-Week Treatment Period (Part A SAF)

		Dupilumab		
Preferred Term	Placebo (N=34)	Lower Exposure Dupilumab (N=30)	Higher Exposure Dupilumab (N=37)	Combined (N=67)
Number of such events	1	6	1	7
Number of patients with at least 1 such event, n (%)	1 (2.9%)	2 (6.7%)	1 (2.7%)	3 (4.5%)
Conjunctivitis	0	1 (3.3%)	0	1 (1.5%)
Dry eye	0	0	1 (2.7%)	1 (1.5%)
Eye irritation	0	1 (3.3%)	0	1 (1.5%)
Conjunctivitis allergic	1 (2.9%)	0	0	0

At each level of patient summarization, a patient is counted once if the patient reported 1 or more events.
MedDRA (Version 24.1) coding dictionary applied.
Sorted by decreasing frequency at all levels in the combined dupilumab group
Broad conjunctivitis CMQ search includes 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; PT=preferred term; SAF=safety analysis set.

In Part B, there were no AESIs of conjunctivitis (severe TEAEs of conjunctivitis; see 5.5.6). Overall, 11/98 (11.2%) participants reported 17 events in the summary using the conjunctivitis CMQ (broad). The PT of Conjunctivitis was reported in 6/98 [6.1%] participants. All events of Conjunctivitis were non-serious, mild in intensity (except for 1 moderate event in the lower exposure dupilumab/lower exposure dupilumab group), none led to permanent discontinuation of study intervention, all resolved, and all but 1 event were considered not related to the study intervention by the investigator. Events other than PT Conjunctivitis, using the conjunctivitis CMQ (broad), that were reported in <5% of participants included Ocular hyperaemia (3/98 (3.1%)), Conjunctivitis allergic (2/98 (2.0%)), Eye pruritus (2/98 (2.0%)), Dry eye (1/98 (1.0%)).

Table 46. Number of Participants with Conjunctivitis CMQ (Broad) by PT During R668-EE-1877 Part B 36-Week Treatment Period (Part B SAF)

PT	Placebo / Lower Exposure Dupilumab (N=14)	Placebo / Higher Exposure Dupilumab (N=18)	Placebo / Combined Dupilumab (N=32)	Lower Exposure Dupilumab / Lower Exposure Dupilumab (N=29)	Higher Exposure Dupilumab / Higher Exposure Dupilumab (N=37)	Combined Dupilumab (N=66)	Total (N=98)
Number of such events	2	3	5	11	1	12	17
Number of patients with at least 1 such event, n (%)	2 (14.3%)	2 (11.1%)	4 (12.5%)	6 (20.7%)	1 (2.7%)	7 (10.6%)	11 (11.2%)
Conjunctivitis	0	1 (5.6%)	1 (3.1%)	4 (13.8%)	1 (2.7%)	5 (7.6%)	6 (6.1%)
Ocular hyperaemia	0	0	0	3 (10.3%)	0	3 (4.5%)	3 (3.1%)
Conjunctivitis allergic	1 (7.1%)	1 (5.6%)	2 (6.3%)	0	0	0	2 (2.0%)
Eye pruritus	1 (7.1%)	0	1 (3.1%)	1 (3.4%)	0	1 (1.5%)	2 (2.0%)
Dry eye	0	1 (5.6%)	1 (3.1%)	0	0	0	1 (1.0%)

At each level of patient summarization, a patient is counted once if the patient reported 1 or more events.
MedDRA (Version 25.1) coding dictionary applied.
Sorted by decreasing frequency at all levels in the total group
Broad conjunctivitis CMQ search includes 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; PT=preferred term; SAF=safety analysis set.

Conjunctivitis and Eye Disorder Events (Part C; cut-off date 17 January 2024)

Based on the conjunctivitis CMQs (broad), 4 participants (6.6%; 4/61) in the ≥15 to <30 kg weight tier reported a TEAE of Conjunctivitis and 1 in the ≥5 to <15 kg weight tier reported a TEAE of Eye pruritus. In 2 participants who reported Conjunctivitis the events were mild in intensity and in 1 participant the event was moderate in intensity. All Conjunctivitis PT events were non-serious, did not lead to discontinuation of the study intervention, and were assessed by the investigator as unrelated to study intervention. The event of Eye pruritus was mild and non-serious and was considered related to study intervention by the Investigator. No keratitis TEAEs were reported.

Infections (Including Adverse Events Related to COVID-19)

Part A

In the SOC of Infections and infestations, the incidence of TEAEs was numerically lower in the dupilumab groups, ie, (36.7% [11/30] in the lower exposure dupilumab group and 35.1% [13/37] in the higher exposure dupilumab group) than in the placebo group (41.2% [14/34]). No SAEs, TEAEs of severe intensity, or TEAEs that led to permanent withdrawal of study intervention were reported in this SOC.

The most frequently reported HLTs (≥5%) were Coronavirus infections and Upper respiratory tract infections; in the higher exposure dupilumab group, Coronavirus infections, Viral infections NEC, and Upper respiratory tract infections; and in the placebo group, Upper respiratory tract infections, Viral infections NEC, Ear infections, and Molluscum contagiosum viral infections.

There was a higher incidence of TEAEs in the HLT of Upper respiratory tract infections in the placebo group (20.6%) versus the dupilumab groups (10.0% in lower exposure dupilumab group and 5.4% in

the higher exposure dupilumab group). 3 participants (8.8%) in the placebo group reported a PT of Upper respiratory tract infection compared to 1 participant (3.3%) in the lower exposure and no participants in the higher exposure dupilumab groups; the same proportions were also reported for the PT of Sinusitis.

Overall, the main HLT driving the incidence of events in the Infections and infestations SOC was Coronavirus infections in the dupilumab groups and Upper respiratory tract infections in the placebo group.

Table 47. Summary of TEAEs in the Primary SOC Infections and Infestations by HLT and PT Reported in ≥5% of Participants in any Treatment Group During the R668-EE-1877 Part A 16-Week Treatment Period (Part A SAF)

		Dupilumab		
Primary SOC **HLT** **PT**	**Placebo (N=34)**	**Lower Exposure Dupilumab (N=30)**	**Higher Exposure Dupilumab (N=37)**	**Combined (N=67)**
Infections and infestations	14 (41.2%)	11 (36.7%)	13 (35.1%)	24 (35.8%)
Coronavirus infections	0	9 (30.0%)	6 (16.2%)	15 (22.4%)
COVID-19	0	9 (30.0%)	5 (13.5%)	14 (20.9%)
Viral infections NEC	4 (11.8%)	1 (3.3%)	5 (13.5%)	6 (9.0%)
Gastroenteritis viral	1 (2.9%)	0	4 (10.8%)	4 (6.0%)
Viral upper respiratory tract infection	2 (5.9%)	0	0	0
Upper respiratory tract infections	7 (20.6%)	3 (10.0%)	2 (5.4%)	5 (7.5%)
Nasopharyngitis	2 (5.9%)	1 (3.3%)	2 (5.4%)	3 (4.5%)
Sinusitis	3 (8.8%)	1 (3.3%)	0	1 (1.5%)
Upper respiratory tract infection	3 (8.8%)	1 (3.3%)	0	1 (1.5%)
Ear infections	2 (5.9%)	1 (3.3%)	0	1 (1.5%)
Ear infection	2 (5.9%)	0	0	0
Molluscum contagiosum viral infections	2 (5.9%)	0	0	0
Molluscum contagiosum	2 (5.9%)	0	0	0

At each level of patient summarization, a patient is counted once if the patient reported 1 or more events.
MedDRA (Version 24.1) coding dictionary applied.
Sorted by decreasing frequency at all levels in the combined dupilumab group.
Abbreviations: HLT=high-level term; MedDRA=Medical Dictionary for Regulatory Activities; NEC=not elsewhere classified; PT=preferred term; SAF=safety analysis set; SOC=system organ class.

The study was conducted during the COVID-19 pandemic (during the waves of the Delta and Omicron variants) and COVID-19 vaccines were not approved for use in pediatric patients at the begin of Part A.

There was a higher incidence of TEAEs with a PT of COVID-19 in the dupilumab groups (30.0% [9/30] in the lower exposure dupilumab group and 13.5% [5/37] in the higher exposure dupilumab group) and no incidence in the placebo group (0.0% [0/34]). The majority of participants experienced events of COVID-19 that were mild in intensity (2 participants in the lower exposure dupilumab group experienced TEAEs of COVID-19 of moderate intensity). None of the events of COVID-19 infection were serious TEAEs or required hospitalization or oxygen supplementation, and study intervention was not discontinued.

By age subgroup, there was a higher incidence of TEAEs of COVID-19 in participants aged ≥1 to <6 years (lower exposure: 36.4% [4/11]; higher exposure: 28.6% [4/14]) than in participants aged ≥6 to <12 years (26.3% [5/19] and 4.3% 1/23], respectively), while the number of participants per subgroup was small and does not allow clear conclusions.

Part B

In the SOC of Infections and infestations, the incidence of TEAEs was 68.4% (67/98) overall and varied between 61.1% (placebo/higher exposure), 62.1% (lower exposure/lower exposure), 70.3% (higher exposure/higher exposure) and 85.7% (placebo/lower exposure). All infection-related TEAEs were mild or moderate in intensity; none were severe. None led to permanent discontinuation of study intervention. There was 1 SAE in the SOC of Infections and infestations (HCoV-OC43 infection; see Section 5.5.5) that was considered not-related to study treatment.

The most frequently reported HLTs (≥10%) were Coronavirus infections (26.5% overall), Upper respiratory tract infections (24.5%), Viral infections NEC (15.3%), and Influenza viral infections (12.2%).

Table 48. Summary of TEAEs in the Primary SOC Infections and Infestations by HLT and PT Reported in ≥5% of Participants in any Treatment Group During R668-EE-1877 Part B 36-Week Treatment Period (Part B SAF)

Primary SOC HLT PT	Placebo / Lower Exposure Dupilumab (N=14)	Placebo / Higher Exposure Dupilumab (N=18)	Placebo / Combined Dupilumab (N=32)	Lower Exposure Dupilumab / Lower Exposure Dupilumab (N=29)	Higher Exposure Dupilumab / Higher Exposure Dupilumab (N=37)	Combined Dupilumab (N=66)	Total (N=98)
Infections and infestations	12 (85.7%)	11 (61.1%)	23 (71.9%)	18 (62.1%)	26 (70.3%)	44 (66.7%)	67 (68.4%)
Coronavirus infections	2 (14.3%)	5 (27.8%)	7 (21.9%)	8 (27.6%)	11 (29.7%)	19 (28.8%)	26 (26.5%)
COVID-19	2 (14.3%)	5 (27.8%)	7 (21.9%)	7 (24.1%)	11 (29.7%)	18 (27.3%)	25 (25.5%)
Upper respiratory tract infections	3 (21.4%)	5 (27.8%)	8 (25.0%)	9 (31.0%)	7 (18.9%)	16 (24.2%)	24 (24.5%)
Upper respiratory tract infection	2 (14.3%)	1 (5.6%)	3 (9.4%)	7 (24.1%)	2 (5.4%)	9 (13.6%)	12 (12.2%)
Croup infectious	0	1 (5.6%)	1 (3.1%)	1 (3.4%)	2 (5.4%)	3 (4.5%)	4 (4.1%)
Nasopharyngitis	0	0	0	1 (3.4%)	3 (8.1%)	4 (6.1%)	4 (4.1%)
Sinusitis	1 (7.1%)	1 (5.6%)	2 (6.3%)	1 (3.4%)	0	1 (1.5%)	3 (3.1%)
Pharyngitis	0	1 (5.6%)	1 (3.1%)	1 (3.4%)	0	1 (1.5%)	2 (2.0%)
Rhinitis	0	2 (11.1%)	2 (6.3%)	0	0	0	2 (2.0%)
Tonsillitis	0	1 (5.6%)	1 (3.1%)	0	0	0	1 (1.0%)
Viral infections NEC	2 (14.3%)	3 (16.7%)	5 (15.6%)	6 (20.7%)	4 (10.8%)	10 (15.2%)	15 (15.3%)
Gastrointestinal viral infection	1 (7.1%)	1 (5.6%)	2 (6.3%)	2 (6.9%)	0	2 (3.0%)	4 (4.1%)
Respiratory tract infection viral	1 (7.1%)	1 (5.6%)	2 (6.3%)	1 (3.4%)	1 (2.7%)	2 (3.0%)	4 (4.1%)
Viral upper respiratory tract infection	0	0	0	3 (10.3%)	1 (2.7%)	4 (6.1%)	4 (4.1%)
Gastroenteritis viral	0	0	0	0	2 (5.4%)	2 (3.0%)	2 (2.0%)
Ear infection viral	0	1 (5.6%)	1 (3.1%)	0	0	0	1 (1.0%)
Viral infection	0	1 (5.6%)	1 (3.1%)	0	0	0	1 (1.0%)

Primary SOC HLT PT	Placebo / Lower Exposure Dupilumab (N=14)	Placebo / Higher Exposure Dupilumab (N=18)	Placebo / Combined Dupilumab (N=32)	Lower Exposure Dupilumab / Lower Exposure Dupilumab (N=29)	Higher Exposure Dupilumab / Higher Exposure Dupilumab (N=37)	Combined Dupilumab (N=66)	Total (N=98)
Influenza viral infections	4 (28.6%)	1 (5.6%)	5 (15.6%)	4 (13.8%)	3 (8.1%)	7 (10.6%)	12 (12.2%)
Influenza	4 (28.6%)	1 (5.6%)	5 (15.6%)	4 (13.8%)	3 (8.1%)	7 (10.6%)	12 (12.2%)
Eye and eyelid infections	1 (7.1%)	1 (5.6%)	2 (6.3%)	6 (20.7%)	1 (2.7%)	7 (10.6%)	9 (9.2%)
Conjunctivitis	0	1 (5.6%)	1 (3.1%)	4 (13.8%)	1 (2.7%)	5 (7.6%)	6 (6.1%)
Eye infection	0	0	0	2 (6.9%)	0	2 (3.0%)	2 (2.0%)
Hordeolum	1 (7.1%)	0	1 (3.1%)	0	0	0	1 (1.0%)
Ear infections	1 (7.1%)	2 (11.1%)	3 (9.4%)	0	4 (10.8%)	4 (6.1%)	7 (7.1%)
Ear infection	1 (7.1%)	1 (5.6%)	2 (6.3%)	0	2 (5.4%)	2 (3.0%)	4 (4.1%)
Otitis media	0	1 (5.6%)	1 (3.1%)	0	2 (5.4%)	2 (3.0%)	3 (3.1%)
Streptococcal infections	1 (7.1%)	1 (5.6%)	2 (6.3%)	2 (6.9%)	0	2 (3.0%)	4 (4.1%)
Pharyngitis streptococcal	1 (7.1%)	1 (5.6%)	2 (6.3%)	2 (6.9%)	0	2 (3.0%)	4 (4.1%)
Infections NEC	0	1 (5.6%)	1 (3.1%)	0	1 (2.7%)	1 (1.5%)	2 (2.0%)
Groin infection	0	1 (5.6%)	1 (3.1%)	0	0	0	1 (1.0%)
Skin structures and soft tissue infections	1 (7.1%)	0	1 (3.1%)	0	0	0	1 (1.0%)
Impetigo	1 (7.1%)	0	1 (3.1%)	0	0	0	1 (1.0%)

At each level of participant summarization, a participant is counted once if the participant reported 1 or more events.
MedDRA (Version 25.1) coding dictionary applied.
Sorted by decreasing frequency at all levels in the Total group.
Abbreviations: HLT=high-level term; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAF=safety analysis set; SOC=system organ class.

The most commonly reported PTs in the SOC of Infections and infestations overall were COVID 19 in 25.5% (25/98) of participants, Upper respiratory tract infection in 12.2% (12/98) of participants, and Influenza in 12.2% (12/98) of participants. The incidence of TEAEs with a PT of COVID-19 across the treatment groups was similiar (placebo/higher exposure: 27.8% [5/18]; lower exposure/lower exposure: 24.1% [7/29]; higher exposure/higher exposure 29.7% [11/37]) except for the placebo/lower exposure group with an incidence of 14.3% (2/14). None of the COVID-19 TEAEs led to study intervention discontinuation. There were 2 participants (1 in the placebo/lower exposure dupilumab group and 1 in the higher exposure dupilumab/higher exposure dupilumab group) who interrupted study intervention due to moderate COVID-19 infections; both participants were on Q2W dosing and missed the week 24 and week 34 dose, respectively. Both participants went on to complete study treatment. All COVID-19 TEAEs resolved.

By age subgroup, there was a similar incidence of TEAEs of COVID-19 overall (24.2% [8/33] in participants aged ≥1 to <6 years and 26.2% [17/65] in participants aged ≥6 to <12 years).

Respiratory Tract Infections (Including Adverse Events Related to COVID-19) (Part A and Part B)

When examined by the Upper respiratory tract infection cluster (Upper respiratory tract infection HLT plus PTs containing the word "COVID-19"), incidences were similar across treatment groups in both Part A (20.6% in the placebo group and 26.9% in the combined dupilumab group) and in Part B (just over 40% in both the placebo/combined dupilumab group and the dupilumab/combined dupilumab group).

In the Infections and infestations SOC in the combined dupilumab group, the exposure-adjusted incidence rate was lower in Part B (101.68) versus Part A (132.34), and this trend was also seen for TEAEs of COVID-19 (40.13 and 70.61, respectively).

Based on its mechanism of action, dupilumab is not expected to increase the risk of COVID-19 infection. The main immunologic mechanism to combat SARS COV-2 infection is through neutralizing antibodies; dupilumab has been shown not to interfere with the induction of IgG antibodies in studies evaluating whether there is an interaction between dupilumab and vaccination, nor does dupilumab impact the persistence of IgG isotypes important in antiviral responses.

Considering the imbalance in the number of patients reporting COVID-19-related TEAEs in the dupilumab treatment groups in Part A of the of study R668-EE-1877 and COVID-19 TEAEs reported most frequently overall in Part B of the study, a comprehensive review of COVID-19 reports received throughout the dupilumab clinical trial program coupled with a review of postmarketing data, as well as the published literature and external safety databases, was performed. The totality of available evidence does not support a causal relationship between COVID-19 infection and dupilumab. However, this observation of COVID-19 imbalance was included in the PI.

Part C (cut-off date 17 January 2024)

As of the data cutoff date, the overall incidence of TEAEs in the SOC of Infections and infestations was 50.8% (31/61 participants), with similar incidences in each weight tier. The most commonly reported HLTs (incidence ≥5% overall) were Upper respiratory tract infections (in 50.8%; 31/61 of participants), Viral infections NEC (in 18.0% of participants; 11/61 participants), Streptococcal infections (in 16.4%; 10/61 participants), Ear infections (in 6.6%; 4/61 participants), Coronavirus infections and Eye and eyelid infections (both in 6.6%; 4/61 participants). The most commonly reported PTs were Pharyngitis streptococcal (in 16.4%; 10/61 participants), Upper respiratory tract infection (in 13.1%; 8/61 participants), Gastroenteritis viral (in 8.2%; 5/61 participants) and Croup infectious and Ear infection (both in 6.6%; 4/61 participants). TEAEs of PT COVID-19 were reported in 4.9% (3/61) of participants.

Time to occurrence of COVID-19 infections after start of dupilumab treatment (Part A and Part B)

An additional analysis pertaining to the time to occurrence of COVID-19 infections (using COVID-19 SMQ (Narrow) search criteria) after the start of dupilumab treatment for Part A and Part B was provided during the procedure. No consistent trend or dose-dependent pattern emerged between initiation of higher or lower exposure dupilumab dosage regimens and the development of COVID-19 in either part of the study. Of the 40 participants who had a COVID-19 event in Part A or B of Study R668-EE-1877, only 4 participants had more than one COVID-19 event. No trend has been identified in the time to occurrence of these events and no notable difference was observed in the clinical presentation of COVID-19 reinfection relative to the first episode in dupilumab-treated participants with EoE aged <11 years.

Table 49. Overview of the time to onset of first occurrence of COVID-19 related events in Study R668-EE-1877 Part A

TTO* (approx. weeks)	Count of COVID-19 related events# from first dupilumab dose in Part A
≤4 weeks *(17-24 days after part A start)*	2
>5 weeks and ≤8 weeks *(36-50 days after part A start)*	3
>9 weeks and ≤12 weeks *(66-86 days after part A start)*	3
>13 weeks and ≤18 weeks *(99-123 days after part A start)*	6
Total event count (first occurrence) in Part A	**14**

* The time to onset (TTO) refers to time between the start day of dupilumab treatment and the onset of COVID-19 related event, using the SMQ (N) COVID-19. The number of days were rounded to the applicable whole number of weeks.
# Of note, no COVID-19 related events were reported in the placebo group of R668-EE-1877 Part A.

Table 50. Overview of the time to onset of first occurrence of COVID-19 related events in Study R668-EE-1877 Part B

	Count of COVID-19 related events from first dose of dupilumab in Part B		
TTO* (approx. weeks)	**Placebo/ Combined Dupilumab Group**	**Combined Dupilumab Group**	**Overall**
≤8 weeks *(121-173 days after part A start)*	3	4	7
>9 weeks and ≤12 weeks *(184-190 days after part A start)*	1	1	2
>13 weeks and ≤20 weeks *(223-261 days after part A start)*	1	6	7
>21 weeks and ≤30 weeks	1	4	5

	Count of COVID-19 related events from first dose of dupilumab in Part B		
TTO* (approx. weeks)	**Placebo/ Combined Dupilumab Group**	**Combined Dupilumab Group**	**Overall**
(263-320 days after part A start)			
>31 weeks *(338-373 days after part A start)*	1	3	4
Total event count (first occurrence) in Part B	**7**	**18**	**25**

*The time to onset (TTO) refers to time between the start day of dupilumab treatment from Part B first dose and the onset of COVID-19 related event, using the SMQ (N) COVID-19 (includes participants who may have reported a COVID-19 related event during Part A of the study). The number of days were rounded to the applicable whole number of weeks.

Participants with potential new infection or re-infection during course of study

No information is available on the occurrence of previous COVID-19 infections prior to the baseline study visit to conclude if the COVID-19 events reported during study Part A were truly reflective of a potential new infection. Irrespective of whether the patient experienced a new or a recurrence of a previous COVID-19 infection, all such events were mild to moderate in intensity, had resolved and were considered not related to the study drug by the Investigator. Of note, Study R668-EE-1877 was conducted during the COVID-19 pandemic (during the waves of the Delta and Omicron variants) and COVID-19 vaccines were not approved for use in pediatric patients until early in Part B (and later for children aged <5 years).

Regarding potential reinfections during the study, natural immunity due to previous COVID-19 infection has been previously shown to last up to 1 year before beginning to wane, although some strains and variants, such as Omicron, appear to exhibit greater immune escape, making reinfection more common. Previous studies have evaluated the risk of reinfection at least 90 days after the primary infection. For this analysis, the MAH conservatively considered a reinfection of COVID-19 if a participant reported more than one COVID-19 related event during Part A and/or Part B irrespective of the time elapsed between the first and subsequent episodes.

Immunologic view on COVID-19 infections

Among patients with EoE, a prior study reported in the literature has shown that both adult and pediatric patients with EoE have significantly lower gene expression levels of ACE2 and TMPRSS2 in the esophagus than adults without EoE. Although the respiratory tract is the main entry point for SARS-CoV-2 virus, the gastrointestinal tract is considered an additional entry portal for infection. These data may suggest that children, including those with EoE, and adults with EoE, may be at lower risk for SARS-CoV-2 infections than adults without EoE. The MAH performed RNA sequencing on esophageal biopsies taken pre- and post-dupilumab treatment in the EoE studies (R668-EE-1774 and R668-EE-1877) to evaluate the effects of dupilumab on gene expression. In this analysis, dupilumab normalized the gene expression in the esophageal epithelium of pediatric and adult both patients, including expression of EPCAM, a marker of normal epithelium, as well as the SARS-CoV-2 receptor ACE2 and co-receptor TMPRSS2 that are required for viral entry. The change in the expression of the latter two

genes were however less than a two-fold increase relative to healthy controls, a typical threshold to aid identification of biologically meaningful changes in gene expression; no threshold has been established however for the evaluation of changes in ACE2 and/or TMPRSS2 expression specifically. It is speculated that these slight increases in ACE2 and TMPRSS2 expression are likely reflective of normalization of esophageal gene expression in EoE patients by dupilumab.

Based on its mechanism of action, dupilumab is not expected to increase the risk of COVID-19. Blockade of IL4/13 immune pathway by dupilumab should remove suppression of the Th1 axis and help against viral infections. In vitro and in vivo research reported in the literature suggests that type 2 cytokines, particularly IL-13, reduce the risk of SARS-CoV-2 infection in the airway epithelium. However, these studies did not look at the impact of dupilumab treatment, ie, IL-13 blockade, on the risk of SARS-CoV-2, nor the impact of type 2 cytokines on the gastrointestinal epithelium, a site of particular relevance to the EoE population.

A number of literature articles discuss the impact of ketogenesis on COVID-19 outcomes. The literature suggests that diet, in particular a ketogenic diet, may positively impact COVID-19 outcomes and limit viral levels of SARS-CoV-2 in the human body, thereby mitigating the infection. No literature publications were identified that examined the incidence of COVID-19 in patients on a ketogenic diet compared to those not on a ketogenic diet or those with impaired ketogenesis to make conclusions. In addition, the mainstay dietary intervention recommended for the management of EoE remains food elimination diets, ketogenic diets are not currently recommended as a dietary approach to manage symptoms of EoE which limits the relevance of any potential impact of ketogenesis on COVID-19 for the population under study.

Adverse drug reactions

To qualify as an ADR, any TEAE PT in Part A had to fulfill all of the following criteria:

- Incidence ≥1% in the dupilumab group with a difference ≥1% over placebo
- Lower bound of the 95% CI for Cox hazard ratio in dupilumab versus placebo >1

The identified TEAEs were then further evaluated by medical judgment for potential inclusion as ADRs.

Less frequent PTs were also evaluated to see if any PT could qualify as an ADR based on pathobiologic mechanisms or medical judgment.

There were no TEAEs in which the lower bound of the 95% CI for the Cox hazard ratio in dupilumab versus placebo was greater than 1. The medical review did not identify any new ADRs in addition to what has been already established for adult and adolescent patients with EoE.

Laboratory findings

Hematology

In Parts A and B, there were no clinically meaningful trends in shifts from baseline in hematology parameters in all treatment groups.

Blood eosinophils

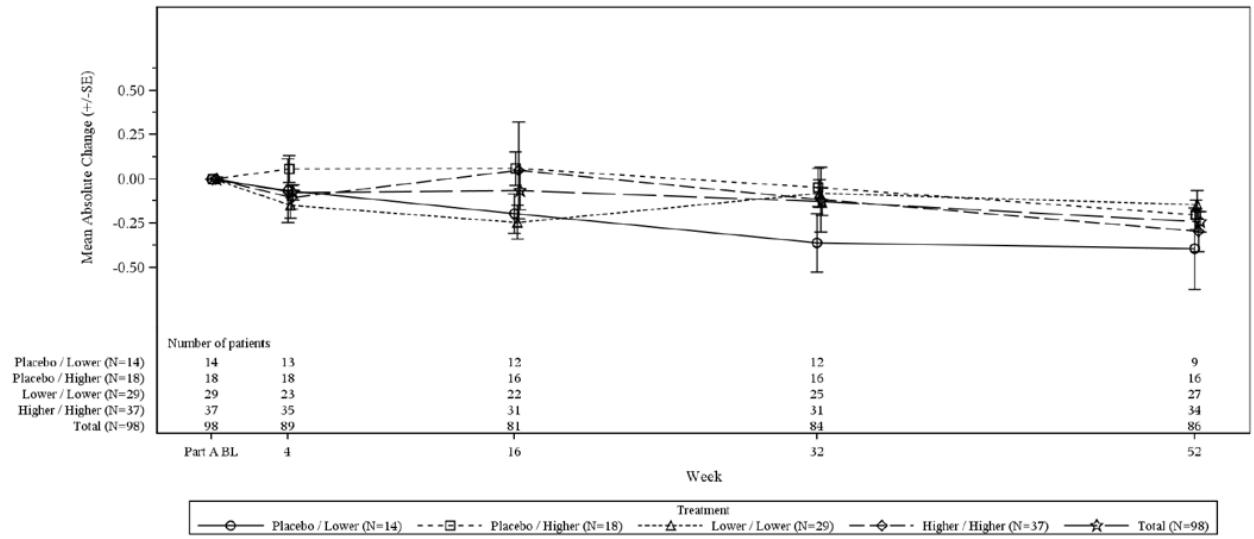
In Part A, mean decreases from baseline were observed at week 16 in the lower exposure dupilumab and placebo groups with greater mean decreases in the lower exposure dupilumab group. Median eosinophil counts were similar at baseline (0.570×10^9/L in the lower exposure dupilumab group, 0.650×10^9/L in the higher exposure dupilumab group, and 0.575×109/L in the placebo group) and

decreased across the 3 treatment groups, with larger median decreases in the lower exposure dupilumab (-0.155×10^9/L) and higher exposure dupilumab groups (-0.130×10^9/L) than in the placebo group (-0.065×10^9/L) at week 16. In the higher exposure dupilumab group, there was an upward trend in mean values at week 16 due to one participant with a maximum change from baseline value (7.600×10^9/L) which resulted in a mean increase (0.0484×10^9/L) versus a median decrease (-0.130×10^9/L) from baseline; the event was reported as a PCSV in 1 participant (eosinophil count of 8×10^9/L at week 16).

In Part B, median eosinophil values at Part B baseline were 0.3850×10^9/L in the placebo/lower exposure dupilumab group, 0.7700×10^9/L in the placebo/higher exposure dupilumab group, 0.3300×10^9/L in the lower exposure/lower exposure dupilumab group, and 0.5300×10^9/L in the higher exposure/higher exposure dupilumab group. There were median decreases from Part B baseline at week 52 in all treatment groups except the lower exposure dupilumab/lower exposure dupilumab group where there was a slight median increase of 0.0700×10^9/L; the largest median decreases were seen in the 2 groups that had previously received placebo in Part A (-0.2100×10^9/L in the placebo/lower exposure dupilumab group and -0.3450×10^9/L in the placebo/higher exposure dupilumab group) versus -0.1800×10^9/L in the higher exposure dupilumab/higher exposure dupilumab group.

Mean changes throughout Parts A and B in the Part B SAF are shown below.

Figure 30. Mean (+/-SE) of Hematology (White Blood Cells) from Part A Baseline in Part A and Part B (Part B – Safety Analysis Set) (Eosinophils 10Λ9/L)



Chemistry

In Parts A and B, there were no clinically meaningful trends towards an increase or decrease in mean or median values over time in any treatment group for any chemistry parameter.

In Parts A and B, there were no clinically meaningful trends in shifts from baseline in chemistry parameters in all treatment groups; sporadic cases of normal-to-high and normal-to-low shifts from baseline in some chemistry parameters were observed in all treatment groups.

Urinalysis

In Parts A and B, there were no clinically meaningful trends towards an increase or decrease in mean or median values over time in any treatment group for any urinalysis parameter.

In Parts A and B, there were no clinically meaningful trends in shifts from baseline in urinalysis parameters in all treatment groups.

Vital Signs / Physical Findings

In Parts A and B, there were no clinically meaningful trends towards an increase or decrease in mean or median values over time in any treatment group for any vital sign measurements, nor in the incidence of treatment-emergent PCSVs for vital signs.
There were no clinically meaningful differences in shifts from baseline in physical examination findings (in Part A) or findings at week 52 (in Part B) in all treatment groups.

Immunogenicity

The ADA incidence was low in children ≥1 to <12 years of age with EoE who received dupilumab treatment in Study R668-EE-1877 Parts A and/or B. Across all dupilumab groups, two participants (2.0%) experienced a treatment-emergent ADA response. Both ADA responses occurred during Part A, one in a higher exposure dupilumab participant and the other in a placebo-treated participant.

In Part A, 1 participant in the higher exposure dupilumab group (1/37, 2.7%) experienced a treatment emergent ADA response that was low titer and of indeterminate duration. This participant reported no serious or severe TEAEs, AESIs, or TEAEs leading to study intervention discontinuation. All TEAEs reported by this participant (Injection site reaction [2 occurrences], Diarrhoea, Nausea, Vomiting, Chest discomfort, Abdominal pain upper [2 occurrences], and Pyrexia) were mild in intensity and resolved the same day they were reported. Only the events of Injection site reaction were considered related to study intervention. For this participant, concentrations of dupilumab were within the range observed for ADA negative participants.

One participant in the placebo/higher exposure dupilumab group (1/18, 5.6%) was missing a predose ADA sample at baseline and exhibited a low titer response in all samples collected in Part A (during placebo treatment); therefore, this participant was considered to have a persistent, treatment-emergent ADA response. This participant had a negative ADA response in Part B and was negative for NAb in Parts A and B.

In Part B, no participants developed a new treatment-emergent or treatment-boosted ADA response to dupilumab, and all participants were negative for NAbs.

Safety in special populations

Safety in Subgroups

Safety data of Parts A and B, were analysed by subgroups (age groups, sex, duration of EoE, baseline weight, prior use of STCs, history of AD, history of asthma, history of allergic rhinitis, history of food allergy, and whether the participants had an inadequate response, were intolerant, and/or had a contraindication to STCs). There were no clinically meaningful differences in the subgroup analyses. However, participant numbers in subgroups were small.

Table 51. Summary of TEAEs Reported by ≥2 Participants in any Treatment Group by Primary SOC and PT During Part A 16-week Treatment Period by Age Groups (Part A SAF)

≥1 to <6 years

Primary System Organ Class Preferred Term	Placebo (N=8)	Dupilumab Lower Exposure Dupilumab (N=11)	Dupilumab Higher Exposure Dupilumab (N=14)	Dupilumab Combined (N=25)
Number of such events	32	43	34	77
Number of patients with at least one such event, n (%)	8 (100%)	10 (90.9%)	11 (78.6%)	21 (84.0%)
Infections and infestations	5 (62.5%)	5 (45.5%)	8 (57.1%)	13 (52.0%)
COVID-19	0	4 (36.4%)	4 (28.6%)	8 (32.0%)
Gastroenteritis viral	0	0	3 (21.4%)	3 (12.0%)
Ear infection	2 (25.0%)	0	0	0
Viral upper respiratory tract infection	2 (25.0%)	0	0	0
Skin and subcutaneous tissue disorders	4 (50.0%)	4 (36.4%)	4 (28.6%)	8 (32.0%)
Eczema	1 (12.5%)	2 (18.2%)	0	2 (8.0%)
Rash	0	0	2 (14.3%)	2 (8.0%)
General disorders and administration site conditions	2 (25.0%)	3 (27.3%)	4 (28.6%)	7 (28.0%)
Injection site reaction	2 (25.0%)	1 (9.1%)	1 (7.1%)	2 (8.0%)
Respiratory, thoracic and mediastinal disorders	2 (25.0%)	2 (18.2%)	2 (14.3%)	4 (16.0%)
Cough	1 (12.5%)	2 (18.2%)	0	2 (8.0%)
Gastrointestinal disorders	4 (50.0%)	3 (27.3%)	0	3 (12.0%)
Diarrhoea	0	2 (18.2%)	0	2 (8.0%)
Constipation	2 (25.0%)	0	0	0
Vomiting	3 (37.5%)	0	0	0

≥6 to <12 years

Primary System Organ Class Preferred Term	Placebo (N=26)	Dupilumab Lower Exposure Dupilumab (N=19)	Dupilumab Higher Exposure Dupilumab (N=23)	Dupilumab Combined (N=42)
Number of such events	94	63	65	128
Number of patients with at least one such event, n (%)	23 (88.5%)	16 (84.2%)	16 (69.6%)	32 (76.2%)
General disorders and administration site conditions	10 (38.5%)	8 (42.1%)	8 (34.8%)	16 (38.1%)
Injection site reaction	5 (19.2%)	3 (15.8%)	3 (13.0%)	6 (14.3%)
Injection site erythema	1 (3.8%)	1 (5.3%)	3 (13.0%)	4 (9.5%)
Fatigue	0	0	2 (8.7%)	2 (4.8%)
Injection site pain	0	2 (10.5%)	0	2 (4.8%)
Gastrointestinal disorders	7 (26.9%)	7 (36.8%)	5 (21.7%)	12 (28.6%)
Vomiting	3 (11.5%)	1 (5.3%)	3 (13.0%)	4 (9.5%)
Abdominal pain upper	0	2 (10.5%)	1 (4.3%)	3(7.1%)
Nausea	0	2 (10.5%)	1 (4.3%)	3 (7.1%)
Diarrhoea	1 (3.8%)	0	2 (8.7%)	2 (4.8%)
Gastrooesophageal reflux disease	0	2 (10.5%)	0	2(4.8%)
Abdominal pain	3 (11.5%)	0	1 (4.3%)	1 (2.4%)
Infections and infestations	9 (34.6%)	6 (31.6%)	5 (21.7%)	11 (26.2%)
COVID-19	0	5 (26.3%)	1 (4.3%)	6 (14.3%)
Nasopharyngitis	2 (7.7%)	0	1 (4.3%)	1 (2.4%)
Sinusitis	2 (7.7%)	1 (5.3%)	0	1 (2.4%)
Upper respiratory tract infection	2 (7.7%)	0	0	0
Skin and subcutaneous tissue disorders	4 (15.4%)	7 (36.8%)	2 (8.7%)	9 (21.4%)
Rash	2 (7.7%)	3 (15.8%)	1 (4.3%)	4 (9.5%)
Urticaria	0	2 (10.5%)	1 (4.3%)	3 (7.1%)
Nervous system disorders	2 (7.7%)	5 (26.3%)	2 (8.7%)	7 (16.7%)
Headache	1 (3.8%)	3 (15.8%)	1 (4.3%)	4 (9.5%)
Dizziness	2 (7.7%)	1 (5.3%)	1 (4.3%)	2 (4.8%)
Respiratory, thoracic and mediastinal disorders	5 (19.2%)	4 (21.1%)	1 (4.3%)	5 (11.9%)
Rhinitis allergic	1 (3.8%)	2 (10.5%)	0	2 (4.8%)
Eye disorders	3 (11.5%)	2 (10.5%)	1 (4.3%)	3 (7.1%)
Eye swelling	1 (3.8%)	2 (10.5%)	0	2 (4.8%)
Psychiatric disorders	4 (15.4%)	2 (10.5%)	1 (4.3%)	3 (7.1%)
Fear of injection	2 (7.7%)	1 (5.3%)	0	1 (2.4%)
Immune system disorders	2 (7.7%)	1 (5.3%)	0	1 (2.4%)
Seasonal allergy	2 (7.7%)	0	0	

Table 52. Overall Summary of Number of Patients with Treatment-Emergent Adverse Events (TEAE) during Part B 36-week Treatment Period by Age Groups (Part B SAF)

≥1 to <6 years

	Placebo / Lower Exposure Dupilumab (N=4)	Placebo / Higher Exposure Dupilumab (N=4)	Placebo / Combined Dupilumab (N=8)	Lower Exposure Dupilumab / Lower Exposure Dupilumab (N=11)	Higher Exposure Dupilumab / Higher Exposure Dupilumab (N=14)	Combined Dupilumab (N=25)	Total (N=33)
Any TEAE, n (%)	4 (100%)	4 (100%)	8 (100%)	11 (100%)	13 (92.9%)	24 (96.0%)	32 (97.0%)
Any drug related TEAE, n (%)	4 (100%)	0	4 (50.0%)	3 (27.3%)	3 (21.4%)	6 (24.0%)	10 (30.3%)
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 (50.0%)	2 (50.0%)	4 (50.0%)	6 (54.5%)	7 (50.0%)	13 (52.0%)	17 (51.5%)
Moderate	1 (25.0%)	2 (50.0%)	3 (37.5%)	5 (45.5%)	5 (35.7%)	10 (40.0%)	13 (39.4%)
Severe	1 (25.0%)	0	1 (12.5%)	0	1 (7.1%)	1 (4.0%)	2 (6.1%)
Any TEAE death, n (%)	0	0	0	0	0	0	0
Any TE SAE, n (%)	1 (25.0%)	0	1 (12.5%)	2 (18.2%)	1 (7.1%)	3 (12.0%)	4 (12.1%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0	0	0	0	0	0
Any TEAE of Special Interest (AESI)	0	0	0	2 (18.2%)	1 (7.1%)	3 (12.0%)	3 (9.1%)

≥6 to <12 years

	Placebo / Lower Exposure Dupilumab (N=10)	Placebo / Higher Exposure Dupilumab (N=14)	Placebo / Combined Dupilumab (N=24)	Lower Exposure Dupilumab / Lower Exposure Dupilumab (N=18)	Higher Exposure Dupilumab / Higher Exposure Dupilumab (N=23)	Combined Dupilumab (N=41)	Total (N=65)
Any TEAE, n (%)	10 (100%)	11 (78.6%)	21 (87.5%)	17 (94.4%)	21 (91.3%)	38 (92.7%)	59 (90.8%)
Any drug related TEAE, n (%)	4 (40.0%)	6 (42.9%)	10 (41.7%)	5 (27.8%)	8 (34.8%)	13 (31.7%)	23 (35.4%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	0	0	0	0	1 (4.3%)	1 (2.4%)	1 (1.5%)
Maximum intensity for any TEAE, n (%)							
Mild	5 (50.0%)	4 (28.6%)	9 (37.5%)	7 (38.9%)	12 (52.2%)	19 (46.3%)	28 (43.1%)
Moderate	5 (50.0%)	7 (50.0%)	12 (50.0%)	10 (55.6%)	8 (34.8%)	18 (43.9%)	30 (46.2%)
Severe	0	0	0	0	1 (4.3%)	1 (2.4%)	1 (1.5%)
Any TEAE death, n (%)	0	0	0	0	0	0	0
Any TE SAE, n (%)	0	0	0	1 (5.6%)	1 (4.3%)	2 (4.9%)	2 (3.1%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0	0	0	0	0	0
Any TEAE of Special Interest (AESI)	0	1 (7.1%)	1 (4.2%)	1 (5.6%)	3 (13.0%)	4 (9.8%)	5 (7.7%)

Discontinuation due to adverse events

In Part A, 2/34 (5.9%) participants in the placebo group experienced a TEAE leading to permanent withdrawal of study intervention: Fear of injection and Anxiety (related to study intervention) in one participant each.

In Part B, 1/98 (1.0%) participant in the higher exposure dupilumab/higher exposure dupilumab group, experienced a TEAE leading to permanent withdrawal of study intervention: a non-serious, severe TEAE of Drug hypersensitivity. This event was also an AESI.

Post marketing experience

A cumulative search with a data lock point of 28 March 2023 was performed in the Sanofi dupilumab global safety database to identify all post-marketing case reports describing use of dupilumab in patients <12 years of age with EoE (Dupilumab is approved in children ≥6 months for AD and ≥6 years for asthma). There were 201 post-marketing case reports involving patients <12 years of age, for whom the EoE was reported as one of the indications. Of the 201 case reports received, 196 were non-serious and 5 case reports were serious.

1 of the 5 serious case reports was a fatal case report (anaphylactoid reaction following administration of total parenteral nutrition), received from a health care provider in the US and involved a pediatric patient with severe food allergies, who was treated with DUPIXENT pre-filled pen, 300 mg SC Q4W, for AD and EoE.

The majority of the post-marketing cases reported use of dupilumab in patients <12 years of age (use in unapproved indication) without any associated AE(s). Consequently, the most frequently reported events were within the SOC of Injury, poisoning, and procedural complications, with the most common PTs being Off-label use and Product use issue. In case reports where the use of DUPIXENT in patients <12 years of age was associated with an event(s), the most frequently reported events were injection site reactions (mainly represented by PTs Injection site pain and Injection site swelling), coding to a SOC of General disorders and administration site conditions.

2.5.1. Discussion on clinical safety

The MAH seeks the extension of indication of dupilumab for the treatment of children with EoE within the age range of ≥1 to <12 years. The current approval for the EoE indication covers the treatment of adults and adolescents ≥12 years and ≥40kg with a recommended dose of 300 mg SC administered by weekly injections. Approval for treatment of children for other indications exist for asthma (6 to 11 years) and atopic dermatitis (6 months to 5 years; 5 to 11 years) both with specific dose regimens defined by body weight.

Safety data for the herein discussed application are derived from study **R668 EE-1877**. The study assessed the safety and efficacy of dupilumab in children ≥1 to <12 years of age with EoE over a 16-week randomized, double-blind, placebo-controlled treatment period (**Part A**) and a 36-week extended active treatment period (**Part B**) in children ≥1 to <12 years of age with EoE. The study was conducted in pediatric participants from the US (99%) and from Canada (1%). An additional **Part C** (open-label extension period up to 108 weeks) is ongoing and preliminary safety data from this study part (cut-off date of 17 January 2024) have been provided during the procedure. Overall, separated safety data for Part A, Part B, and Part C were provided by the MAH and no integrated analyses of

safety data was performed which is considered is acceptable. Descriptive statistics were presented for analyses of safety parameters.

In Part A, participants were randomized to either one of two weight-tiered dupilumab regimens (higher exposure and lower exposure) or matching placebo and were treated for 16 weeks. The two dupilumab regimens evaluated were intended to approximate the 300 mg weekly dosing already used in adults and adolescents. In the following Part B, all participants (including initial placebo-treated participants) were treated with dupilumab and received weight-tiered dupilumab as assigned in Part A. Of note, the 300 mg QW dosing has been so far only approved in the EoE indication and the proposed dosing regimen for children ≤12 years would lead to the steady-state exposures largely exceeding those used for the other pediatric indications for which dupiluman is currently approved (ie. asthma and atopic dermatitis) (see PK assessment; 5.3).

In Part A, 101 participants received study intervention (placebo: 34; lower exposure: 30; higher exposure: 37) and the majority completed Part A (98/101) and subsequently entered Part B of the study. Most of participants (n=94) finally completed the entire combined treatment duration of 52 weeks (Part A + Part B). Around 2/3 of participants were exposed for ~1 year to dupilumab while the remaining 1/3 of subjects that had initially received placebo in Part A received dupilumab in Part B (36 weeks) only. The overall mean (SD) treatment duration of participants treated with one of the two dupilumab regimes in both parts of the study (combined dupilumab: 67) was 366.1 (51.55). 94.0% of dupilumab-treated participants had a cumulative treatment duration ≥357 days (≥51 weeks). 82.4% of participants treated with dupilumab only in Part B (placebo/combined dupilumab group) had a cumulative treatment duration of ≥245 days (≥35 weeks).

The mean (SD) age of participants was 7.1 (3.05) years. The majority of participants had an age between ≥6 - <12 years (69/102; 67.6%). The remaining participants 33/102 (32.4%) were in the younger age group of ≥1 - <6 years. Of note, the number of young children with an age of 1 year was very low (1-2 per treatment group). There were only three participants in each group with an age between 1 and 2 years. The number of participants in the lowest weight group ≥5 to <15 kg was also limited (15/102; 14.7%). No participant had a weight below 10kg. A large number of participants had a history of atopic/allergic diseases such as food allergy (81.4%), allergic rhinitis (76.5%), asthma (54.9%) and atopic dermatitis (53.9%) which is typical for the EoE disease.

Given the rarity of the disease, the small size of the safety population is understandable. However, number of pediatric patients especially in the youngest age and weight groups is very limited. Overall, safety data for the entire safety population and subgroups can only be evaluated in a descriptive manner and the placebo-controlled treatment period of Part A is restricted to 16 weeks, which limits the safety evaluation.

In Part A, the incidence of all TEAES was 92.1% in the placebo group and 86.7% or 73.0% for the lower and higher exposure dupilumab regimen, respectively. The majority of TEAEs were mild or moderate. Two participants in the placebo group discontinued treatment due to TEAEs of anxiety or fear of injection, respectively. The most common TEAE by SOC were Infections and infestations, General disorders and administration site conditions, Skin and subcutaneous tissue disorders and Gastrointestinal disorders. By PT, the most frequent TEAE reported in dupilumab groups was COVID-19 (30.0% in the lower exposure dupilumab group and 13.5% in the higher exposure dupilumab group). In the placebo group, the most frequently reported PT was Injection site reaction (20.6%). In the SOC Infections and infestations, although the overall incidence was numerically higher in the placebo group

(placebo: 41.2%; combined dupilumab: 35.8%), there was a striking number of COVID-19 infections in participants receiving dupilumab (14/67; 20.9%) while no case was reported in the placebo group.

In Part B, an overall similar AE profile with regard to TEAE by SOC and PT was observed. The incidence of TEAEs was 92.9% in total study population with slight variations between the 4 different dupilumab treatment groups (83.3% to 100%). Again, a high number of participants with injection site reactions was observed in all treatment groups (total: 18/98; 18.4%) and about 20% of participants experienced COVID 19 infections across the different treatment groups.

In the placebo-controlled Part A of study R668 EE-1877, the incidences of TEAEs in the SOC of Infections and infestations were similar between placebo (14/34; 41.2%) and dupilumab-treated participants (24/67; 35.8%). However, a pronounced incidence of COVID-19 infections (14/67; 20.9%) was observed in the dupilumab-treated groups (lower exposure 9/30 (30.0%); higher exposure: 5/37 (13.5%) while no case of COVID-19 occurred in the placebo group. Section 4.8 of the SmPC was updated to reflect that COVID-19 , sinusitis, and upper respiratory tract infection was numerically higher with dupilumab compared to placebo. Most of COVID-19 infections were mild in intensity (2 participants in the lower exposure dupilumab group experienced TEAEs of COVID-19 of moderate intensity). None of the events were serious. There was no increase of upper respiratory tract infections as compared to placebo in general. The same observation was made for the adult and adolescent EoE population (9 cases of COVID- 19 in dupilumab-treated participants (n=161) and no event in the placebo group in Part B of study R668-EE-1774). The fact that high incidences of COVID-19 infections have been observed twice in adults and children with EoE in independent placebo-controlled study parts points to a potential relationship of COVID-19 infections after dupilumab treatment in patients with EoE. In order to address this concern, a comprehensive review of COVID-19 reports received throughout the dupilumab clinical trial program coupled with a review of post marketing data as well as the published literature and external safety databases, was performed by the MAH which does not indicate a general increase of COVID-19 infections in the other dupilumab indications. In addition, the MAH has provided an analysis of time to occurrence of COVID-19 infections after start of dupilumab for Part A and Part B. No clear trend for the time to occurrence of the first COVID-19 is apparent in Part A or Part B of the study. The number of re-infections was low. Also, the MAH has further discussed COVID-19 infections in EoE considering the current immunologic understanding of EoE, dupilumab's effect on type 2 cytokines and diet of the participants with COVID-19 infections. This discussion provided further arguments for not considering a causal relationship between COVID-19 infections and dupilumab treatment. Blockade of the IL4/13 immune pathway should remove suppression of the Th1 axis and help against viral infections, thus should not increase the risk for COVID-19. In addition, in the EoE studies, the overall incidence of upper respiratory tract infections (including COVID-19 events) was similar between treatment groups. COVID-19 events were mild or moderate in severity and non-serious. Still, some level of uncertainty remains and COVID-19 infections will be monitored in future PSURs to gain more insights in the "potential" interplay between dupilumab and COVID-19 infections in EoE.

In both study parts, there was a high number of injection site reactions throughout all treatment groups (Part A: placebo: 7/34, 20.6%; combined dupilumab: 8/67, 11.9%; Part B: placebo/combined dupilumab: 28.1%; combined dupilumab: 13.6%). Events of injection site pain and injection site erythema were also observed. None of the injection site reactions were serious or led to permanent discontinuation of study intervention. All injection site reactions were assessed as mild or moderate in intensity, with no severe events reported, and all resolved. The relatively high frequency of injections site reactions in children with EoE is similar to what has been observed for the adult and adolescent

EoE population. Injection site reactions (including erythema, oedema, pruritus, pain, swelling, and bruising) are known ADRs for dupilumab and are already included in the product information.

In Part A, treatment-emergent SAEs were reported for 3 participants (all treated with dupilumab). In Part B, treatment-emergent SAEs were reported for 6 participants (2 of them had already experienced an SAE in part A). All of the events resolved and were considered not related to the study treatment. This evaluation is endorsed. Some of the SAEs in Part A and B are likely attributed to the high prevalence of atopic/allergic conditions in the studied EoE study population.

No death events occurred in Part A and Part B.

Adverse events of special interest including anaphylactic reactions, hypersensitivity, different infections (e.g. conjunctivitis, blepharitis, keratitis, herpes) and arthralgia were evaluated in Part A and Part B. In Part A, the number of participants with AESIs was overall low. A total of 3 events (3.5%) in individual participants treated with dupilumab were reported. Two events of anaphylaxis occurred, one in the lower and one in the higher exposure dupilumab group. Both events were, however, unrelated to dupilumab (exposure to milk in allergic participants). There was one event of herpes simplex (higher exposure group) that was considered related to dupilumab. In Part B, the total number of participants with AESIs was 8 (8.2%). Two events of anaphylactic reactions (one serious) occurred in two individual participants with known milk allergy after exposure to milk. One drug hypersensitivity reaction in the higher exposure group considered related to dupilumab led to discontinuation of study intervention. One related event of helminthic infections occurred in one participant in the higher exposure group. Overall, the AESI profile observed in study R668-EE-1877 appears consistent with the already known AESI profile of dupilumab throughout the different adult and pediatric indications.

In Part A, there were 7 events coded under the conjunctivitis CMQ (broad) reported in 3 participants treated with dupilumab. In Part B, overall 11 participants reported 17 conjunctivitis events using CMQ (broad) criteria. All the events were of mild or moderate intensity, non-serious, and did not lead to permanent discontinuation of study intervention. No event of severe conjunctivitis (AESI) was reported.

No events of clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms) were reported in Part A and Part B. Blood eosinophil slightly decreased over time with different patterns between treatment groups. No pronounced transient increase in blood eosinophils as seen for other dupilumab indications was observed for the pediatric EoE population which is similar to what has been already observed in adult and adolescent EoE patients. No significant safety findings with regard to the laboratory evaluation were observed in study R668-EE-1877. The incidence of treatment emergent ADAs throughout Part A and Part B was low (2/98; 2.04%) and appears similar to the known ADA profile of dupilumab. Section 4.8 of SmPC has been updated accordingly.

No indications for a pronounced difference in the incidence of AEs within pre-defined subgroups (age, weight, gender, EoE disease characteristics and pre-existing atopic/allergic conditions) was observed in study R668 EE-1877. No apparent difference in the occurrence of AEs was also observed for the lower or higher exposure dupilumab regimen. However, as discussed for the baseline demographics above, the low number of participants within the subgroups largely limits firm conclusions and must be considered and remains a limitation when interpreting subgroup data.

Additional safety data from Part C with a data cut-off date of 17 January 2024 have been provided by the MAH during the procedure. A total of 61 participants transitioned to Part C with the majority included in the ≥15 kg to <30 kg weight group (n=38) and the 30 kg to <40kg weight group (n=17). A total of 4 participants had a body weight of ≥40kg, thus receiving the 300 QW dosing. Only 2

participants had a body weight below 15 kg. Around 80 percent of the participants had an exposure of at least 1.5 years which was equally distributed between the weight groups.

Overall, the safety profile obtained within Part C (including the occurrence of AESIs) appears similar to what has been already observed during Part A and B of the study R668-EE-1877. There was no death event. A total of 4 treatment-emergent SAEs were reported in 3 participants, all in the ≥15 to <30 kg weight group. All SAEs were considered not-related to dupilumab. There was a notable event of a cardiac arrest in one patient for which additional information have been presented by the MAH that support the assessment of this event as not related to dupilumab treatment. The event did not lead to treatment discontinuation and the participant continued to receive treatment. Of note, only sparse clinical safety data are available from Part C of study R668-EE-1877 for the high exposure dose regimen in participants with a body weight below 15 kg. Only 2 participants in the ≥5 to <15 kg weight group received the 200 mg Q3W dose regimen which again limits firm conclusion on the long-term safety profile in this weight group.

Overall, the limited safety data of Part A, B, and C for the high exposure dose regimen in participants with a body weight below 15 kg are not sufficient to conclude on the safety profile for this weight group**.** As a result, the indication to patients with EoE has been restricted to patients with a body weight ≥15kg.

2.5.2. Conclusions on clinical safety

The safety profile of dupilumab in the paediatric EoE population with a body weight greater than 15 kg is overall consistent with the so far known safety profile of dupilumab in the adult and adolescent EoE population.

2.5.3. 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

2.6. Update of the Product information

As a consequence of this new indication, 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.

Changes were also made to the PI to bring it in line with the current QRD template, SmPC guideline and other relevant guideline(s).

2.6.1. 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 applicant proposed an extension of the already authorised indication for the treatment of EoE in children (from 1 year onwards). The changes in the package leaflet are minor and the key safety messages are not affected. Therefore, no consultation with target patient groups is required.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Eosinophilic esophagitis (EoE) is a serious, rare, chronic, type 2 inflammatory, allergic/immune-mediated disease of the esophagus. The disease is characterized by local eosinophilic inflammation of the esophagus leading to symptoms of oesophageal dysfunction. EoE 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 oesophageal eosinophilia leading to symptoms of oesophageal dysfunction. Eosinophilic esophagitis is a chronic, type 2 inflammatory, immune-mediated disease of the oesophagus which results in fibrostenosis of the esophagus if left untreated. The primary clinical manifestations of EoE in adults and children over 10 years of age are dysphagia and food impaction.

Clinical, histological and molecular evidence also suggests that EoE has the same underlying pathogenesis in different age groups. Histologic, biomarker and genetic studies have demonstrated a generally similar pattern of inflammation and genetic abnormalities across age groups. Thus, the differences observed in the presentation of EoE symptomatology and endoscopic findings between pediatric and adult patients (eg, less dysphagia and fewer remodelling features in pediatric patients) likely reflect different durations of disease. Despite the differences in symptom presentation between age groups, the pathological hallmark of the disease across all ages is eosinophil-predominant inflammation of the mucosa. Patients with EoE have increased levels of oesophageal inflammatory infiltrates, including eosinophils, T-lymphocytes, mast cells, and basophils, as well as increased expression of type 2-associated chemokines and cytokines, such as eotaxin-3, IL-4, IL-5, and IL-13 in oesophageal biopsies (Abonia, 2012) (Blanchard, 2007) (Blanchard, 2006) (Bullock, 2007) (Mishra, 2009) (O'Shea, 2018) (Sherrill, 2014) (Straumann, 2001) (Wen, 2013).

3.1.2. Available therapies and unmet medical need

Current treatment options for both adults and pediatric patients with EoE consists of food elimination diets, use of STCs and high-dose PPI therapy. Jorveza (budesonide orodispersible tablets) has been approved in the EU for the treatment of EoE in adults.

About 25% of patients may have significant ongoing symptoms, despite treatment with dietary modification and corticosteroids.

Recently, Dupilumab 300 mg SC QW has been approved in the EU for the treatment of adult and pediatric patients aged 12 years and older, weighing at least 40 kg, with EoE.

No approved medicinal product is available for the treatment of EoE in children <12 years of age or for adolescents <40 kg.

3.1.3. Main clinical studies

One pivotal study has been conducted. Study R668-EE-1877 is a phase 3 study consisting of 3 parts. Part A (a 16-week randomized, double-blind, placebo-controlled treatment period) and Part B (a 36-

week extended active treatment period) have been completed while Part C (an open-label extension period) is ongoing with a 12-week follow-up period.

In Part A, the 16-week, double-blind, placebo-controlled treatment period, participants receiving higher exposure dupilumab were assigned based on baseline body weight to 100 mg Q2W (≥5 to <15 kg), 200 mg Q2W (≥15 to 30 kg) and 300 mg Q2W (≥30 to <60 kg). Participants receiving lower exposure dupilumab were assigned based on baseline body weight to 200 mg Q4W (≥5 to <15 kg), 300 mg Q4W (≥15 to <30 kg) and 200 mg Q2W (≥30 to <60 kg).

After completion of Part A, participants continued to a 36-week extended treatment period (Part B). Participants in the dupilumab groups received the same treatment as in Part A, while participants who received placebo were switched to higher exposure or lower exposure dupilumab according to the exposure regimen assigned at randomization. Individual weight-tiered doses within each treatment group were adjusted, if needed, based on body weight at week 16 and also at week 32 if body weight increased to a higher tier.

3.2. Favourable effects

Overall, 67.6% of participants in the higher exposure dupilumab group in Part A achieved peak oesophageal intraepithelial eosinophil count ≤6 eos/hpf at week 16 (primary endpoint). These results were maintained with 62.9% after 52 weeks with continued treatment in Part B. Furthermore, 83.8% of participants in higher exposure dupilumab group achieved <15 eos/hpf after 16 weeks of treatment, which was maintained at 85.7% after 52 weeks. A similar improvement was seen in week 52 for patients, who switched from placebo to the higher exposure dupilumab treatment in week 16.

Similar to the histologic improvements, effects on efficacy were observed for endoscopic improvements in the oesophagus, where participants in the higher exposure dupilumab/higher exposure dupilumab group showed endoscopic improvements at week 16, which were further improved at week 52. Participants who received placebo in Part A and were switched to 36 weeks of treatment with higher exposure dupilumab during Part B of the study also achieved similar endoscopic improvements.

3.3. Uncertainties and limitations about favourable effects

The number of participants was low, especially in the weight group of less than 15 kg and no patient with less than 10 kg was enrolled (except for one patient that had 9.8 kg at baseline). Therefore, only a weight-limit for patients with a body weight of at least 15 kg is considered justified. The MAH has thus revised the wording of the indication accordingly.

Furthermore, the study was not designed and powered to show symptomatic improvement. It is unclear whether the higher histologic and endoscopic improvement seen in the higher exposure dupilumab group will translate in symptomatic benefit for the patients. However, due to the fact that clinical, histological and molecular evidence suggests that EoE has the same underlying pathogenesis in different age groups and histologic, biomarker and genetic studies have demonstrated a generally similar pattern of inflammation and genetic abnormalities across age groups, a similar benefit of the treatment with a higher dupilumab dosing regimen as seen in the adolescent and adult study R668-EE-1774 can be assumed for all age groups.

3.4. Unfavourable effects

In Part A, the incidence of all TEAEs during Part A was 92.1% in the placebo group and 86.7% or 73.0% for the lower and higher exposure dupilumab regimen, respectively. The majority of TEAEs

were mild or moderate. The most common TEAEs by SOC were Infections and infestations, General disorders and administration site conditions, Skin and subcutaneous tissue disorders and Gastrointestinal disorders. In Part B, an overall similar AE profile with regard to TEAEs by SOC and PT was observed.

In Part A, treatment-emergent SAEs were reported for 3 individual participants (all treated with dupilumab). In Part B, treatment-emergent SAEs were reported for 6 individual participants. All of the events resolved and were considered not related to the study treatment. No death events occurred in Part A and Part B.

In Part A, the number of participants with AESIs was overall low. A total of 4 events (4.5%) in individual participants were reported, including 1 event in one placebo patient. There was one event of herpes simplex (higher exposure group) that was considered related to dupilumab. In Part B, the total number of participants with AESIs was 8 (8.2%). One drug hypersensitivity reaction in the higher exposure group considered related to dupilumab led to discontinuation of study intervention. One related event of helminthic infections occurred in one participant in the higher exposure group. Overall, the AESI profile observed in study R668-EE-1877 appears consistent with the already known AESI profile of dupilumab throughout the different adult and paediatric indications.

In the placebo-controlled Part A, a pronounced incidence of COVID-19 infections (20.9%) was observed in the dupilumab-treated groups (lower exposure: 30.0%; higher exposure: 13.5%) while no case of COVID-19 occurred in the placebo group. Most of COVID-19 infections were mild in intensity (2 participants in the lower exposure dupilumab group experienced TEAEs of COVID-19 of moderate intensity). None of the events were serious. There was no increase of upper respiratory tract infections as compared to placebo in general. In Part B, the incidence of COVID-19 infections was similar between the treatment groups (placebo/combined dupilumab: 21.9%; combined dupilumab: 27.3%).

In both study parts, there was a high number of participants with injection site reactions throughout all treatment groups (Part A: placebo: 20.6%; combined dupilumab: 11.9% / Part B: placebo/combined dupilumab: 28.1%; combined dupilumab: 13.6%). Events of injection site pain and injection site erythema were also observed. None of the injection site reactions were serious or led to permanent discontinuation of study intervention. All injection site reactions were assessed as mild or moderate in intensity, with no severe events reported, and all resolved. Injection site reactions (including erythema, oedema, pruritus, pain, swelling, and bruising) are known ADRs for dupilumab.

3.5. Uncertainties and limitations about unfavourable effects

Data on the long-term safety for the higher exposure regimens proposed for the treatment of EoE are limited. Higher incidences of COVID-19 infections have been observed in study R668 EE-1877 but also for adults and adolescents with EoE (study R668-EE-1774). As some level of uncertainty on the potential relationship between COVID-19 infections and dupilumab treatment in children with EoE still remains, COVID-19 infections will be closely monitored post approval i.e. in future PSURs.

3.6. Effects Table

Table 53. Effects Table for Dupixent in children ≥1 to <12 years with eosinophilic esophagitis (EoE) (data cut-off: 17-Jan-2023)

Effect	Short description	Unit	DUPI*[1]	PCB	Uncertainties / Strength of evidence	References
Favourable Effects						
≤6 eos/-	Proportion of Participants	%	Higher exposure	2.9	p<0.0001	CSR Part A

Effect	Short description	Unit	DUPI*[1]	PCB	Uncertainties / Strength of evidence	References
hpf at Week 16	Achieving Peak Esophageal Intraepithelial Eosinophil Count ⩽6 eos/hpf at Week 16		group: 67.6			
<15 eos/hpf at week 16	Proportion of Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count of <15 eos/hpf	%	Higher exposure group: 83.8	2.9	p<0.0001	CSR Part A
EoE-HSS Mean Grade Score	Absolute Change from Baseline in EoE-HSS Mean Grade Score	p	Higher exposure group: -0.879	0.023	p<0.0001	CSR Part A
Unfavourable Effects						
TEAE	Injection site reactions	%	11.9	20.6	All Mild or moderate Known ADR	R668 EE-1877 Part A (SAF)
	Injection site erythema	%	7.5	2.9		
	Injections site pain	%	4.5	0		
	Headache	%	7.5	2.9	all of mild intensity	
	COVID-19	%	20.9	0	Mostly mild, no severe event; disease-specific dupilumab-related mechanism possible	
	Injection site reactions	%	18.4	-*[2]	All Mild or moderate Known ADR	R668 EE-1877 Part B (SAF)

Abbreviations: ADR, adverse drug reaction; DUPI, dupilumab; PBC, placebo;

Notes: *[1] participants received either a higher or lower exposure dose regimen
*[2] in part B all participants received dupilumab

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Eosinophilic esophagitis is a chronic, type 2 inflammatory, immune-mediated disease of the oesophagus which results in fibrostenosis of the esophagus if left untreated. No approved medicinal product is available for the treatment of EoE in children <12 years of age or for adolescents <40 kg. In study R668-EE1877, 67.6% of participants in the higher exposure dupilumab group in Part A achieved peak oesophageal intraepithelial eosinophil count ≤6 eos/hpf at week 16 (primary endpoint; placebo group 2,9%), which is considered clinically meaningful. These results were maintained with 62.9% after 52 weeks with continued treatment in Part B. Furthermore, 83.8% of participants in higher exposure dupilumab group achieved <15 eos/hpf after 16 weeks of treatment (placebo group 2,9%), which was maintained at 85.7% after 52 weeks. Although the study was not designed and powered to show symptomatic improvement and it is unclear whether the higher histologic and endoscopic improvement seen in the higher exposure dupilumab group will translate in symptomatic benefit for the patients, the histological and molecular evidence suggests that EoE has the same underlying

pathogenesis in different age groups and a similar benefit of the treatment with a higher dupilumab dosing regimen as seen in the adolescent and adult study R668-EE-1774 can be assumed for all age groups.

The safety profile of dupilumab in children <12 years as observed in study R668 EE-1877 (Part A and B) appears to be principally similar as compared to adults and adolescents with EoE and other approved dupilumab indications. Given the limited number of participants, especially in the lowest weight and the youngest age group (≥5 to <15 kg; 1-2 years of age) firm safety conclusions for the high exposure dose regimen in children with low body weight could not be made. As such, the MAH agreed to restrict the indication to patients with a body weight of ≥15 kg.

A high number of participants with injection site reactions was observed with dupilumab but also with placebo treatment. All injection site reactions were assessed as mild or moderate in intensity, with no severe events reported, and all resolved. Similar observations have been also made for adult and adolescent EoE population previously. Injection site reactions (including erythema, oedema, pruritus, pain, swelling, and bruising) are known ADRs for dupilumab and are already included in the product information. Higher incidences of COVID-19 infections have been observed in Part A of study R668 EE-1877 and also previously for adult and adolescent EoE patients. COVID 19 infections in EoE will be closely monitored in future PSURs.

3.7.2. Balance of benefits and risks

The single pivotal study provides evidence of efficacy of dupilumab in the treatment of paediatric EoE. The proposed posology is weight tiered. Efficacy was demonstrated in children weighing at least 15 kg.

Results for the histologic endpoints in study R668-EE-1877 show that the higher exposure dupilumab regimen led to significant reduction in signs of inflammation. The study was not powered and designed to show improvement in symptoms which is considered difficult in this age group. However, it was demonstrated that a similar benefit of the treatment can be expected for all age groups. The higher exposure regimen appears to have an acceptable safety profile in patients with a body weight ≥15 kg and is consistent between adolescent and adults EoE.

3.8. Conclusions

The overall B/R of Dupixent is positive for the treatment of eosinophilic esophagitis in adults, adolescents and children aged 1 year and older, weighing at least 15 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.

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 children aged 1 year and older, weighing at least 15 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy based on final results from study R668-EE-1877 (Part A, Part B, and Part A Addendum) - A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Dupilumab in Pediatric Patients with Active Eosinophilic Esophagitis. 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.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0541/2022 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-Var.0081'

Attachments

1. Product information as adopted by the CHMP on 19 September 2024.

Appendix

1. CHMP AR on similarity dated 19 September 2024.