23 February 2023
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Dupixent

dupilumab

Procedure no: EMEA/H/C/004390/P46/010

Note

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

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Table of contents

1. Introduction

On 06 December 2022, the MAH submitted the Clinical Study Report (CSR) of Part B/C and Part A/C (Addendum 2) for study R668-EE-1774, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Part B/C and Part A/C for study R668-EE-1774 are part of a clinical development program. The extension application consisting of the Parts A, A/C and B CSRs of study R668-EE-1774 was submitted on 1 April 2022 in EoE Type II variation (EMEA/H/C/004390/II/0062 eCTD sequence 0160). The part B/C results made available subsequently were included in the response to request for supplementary information submitted on September (eCTD sequence 0173).

R668-EE-1774 study is part of the EoE PIP approved for Dupixent (EMEA-001501-PIP04-19-M02) and was subject to a positive partial compliance check on 25 February 2022 (EMA/8864/2022). A line listing of this study was included as an appendix at the end of the cover letter.

2.2. Information on the pharmaceutical formulation used in the study

Study Drug Name	Dupilumab	Placebo for Dupilumab
Type	Biologic	Not applicable
Dose Formulation	Liquid	Liquid
Unit Dose Strength(s)	Dupilumab 150 mg/mL. Each 2.0 mL single-use prefilled glass syringe with snap-off cap delivers 300 mg of study drug (2.0 mL of a 150 mg/mL solution)	Not applicable. Placebo matching dupilumab is prepared in the same formulation without the addition of protein (ie, active substance, anti-IL-4Rα monoclonal Ab).
Dosage Level(s)	300 mg QW or 300 mg Q2W for 28 weeks	Placebo Q2W (alternating with dupilumab Q2W) for 28 weeks[2]
Route of Administration	SC injection alternating among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site is not injected for 2 consecutive administrations	SC injection alternating among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site is not injected for 2 consecutive administrations
Use	Experimental	Placebo comparator so injection frequency was identical for both Q2W and QW groups
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling[1]	Provided in a single-use, prefilled glass syringe with snap-off cap (2.0 mL of a 150 mg/mL solution).	Provided in a single-use, prefilled glass syringe with snap-off cap (2.0 mL of placebo solution).
Current/Former Names	REGN668; Dupixent	Not applicable

Abbreviations: Ab=antibody; IL-4Rα=interleukin-4 receptor alpha; SC=subcutaneous; Q2W=once every other week; QW=once weekly.

[1] A medication numbering system was used to label blinded investigational study drug in Part B/C. Each immediate container and outer carton of study treatment were labeled per country-specific requirements.

[2] Participants randomized to dupilumab 300 mg Q2W received placebo on alternate weeks to maintain blinding.

No paediatric formulation has been used in Study R668-EE-1774.

In Part A and A/C Dupilumab 300 mg QW (or Placebo) has been administered.
In Part B and B/C Dupilumab 300 mg QW and Q2W (and Placebo) have been administered.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Part B/C and Part A/C (Addendum 2) of Study R668-EE-1774

2.3.2. Clinical study

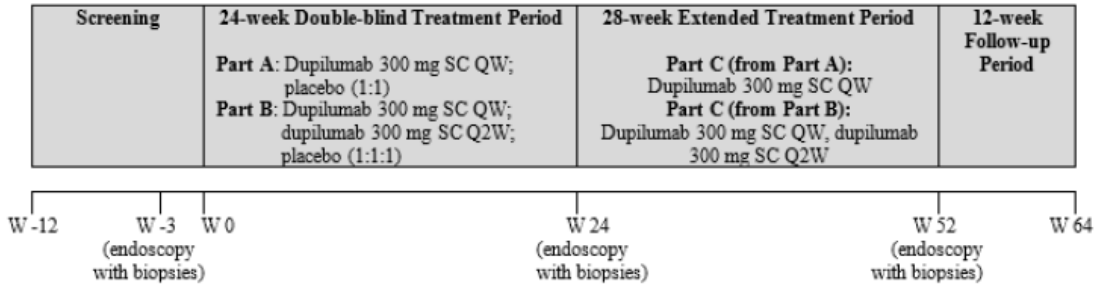
Clinical study R668-EE-1774

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

Description

Study R668-EE-1774 was a Phase 3, Randomized, 3-Part Study (Part A, B and C) to investigate the Efficacy and Safety of Dupilumab in Adults and Adolescent patients with eosinophilic esophagitis (EoE). Part A and Part B each consisting of a 24-week double-blind treatment period. Part C was a 28-week extended active treatment period.

Study 1 Flow Diagram (Parts A, B, and C)



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

Study R668-EE-1774 was conducted from 24 Sep 2018 (date of first consent to first screened participant in Part A) to 07 Jun 2022 (date of last visit in 12-week follow-up period for participants in Part B/C).

The Part A, A/C and B CSRs of R668-EE-1774 were submitted on 1 April 2022 in EoE Type II variation (EMEA/H/C/004390/II/0062 eCTD sequence 0160). The part B/C results made available subsequently were included in response to request for supplementary information submitted on 7 September (eCTD sequence 0173).

Part A/C (Addendum 2)

The results from the 28-week extended active treatment period (Part C) of Study R668-EE-1774 for participants who entered Part A were reported in the Part A/C clinical study report (CSR) (data cut-off

and database lock dated 18 Nov 2020 and 17 Dec 2020, respectively). At the time of the data cut-off for the Part A/C CSR, 66 participants had completed week 52 with 22 of these participants continuing in the follow-up period. Additionally, 6 participants were still in the extended active treatment period for Part A/C at the time of the data cut-off of 18 Nov 2020. Therefore, a total of 28 participants were ongoing at the 18 Nov 2020 data cut-off point.

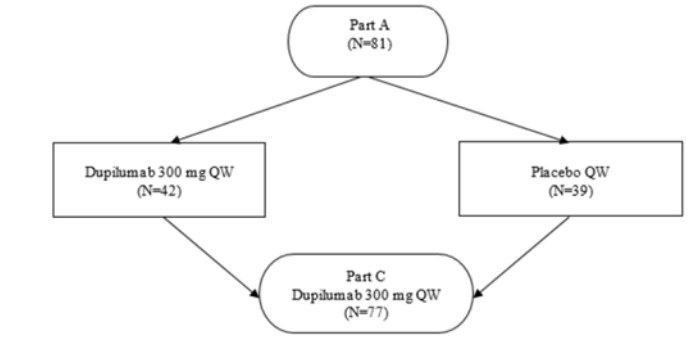
Among the 66 participants, 50 participants had follow-up period data that were reported in the Part A/C CSR. Individual patient data profiles containing data for the 6 participants collected from 18 Nov 2020 (data cut-off for Part A/C CSR) to 27 May 2021 (last participant last visit [LPLV]) were included in the first addendum to the R668-EE-1774 Part A/C CSR. The first addendum also included additional pharmacokinetic (PK) and antidrug antibody (ADA) data that were not available at the time of the data cut-off and additional database errata from Part A/C arising since the data cut-off for the Part A/C CSR.

Study R668-EE-1774 is now complete and the final database lock has occurred. Addendum 2 to the R668-EE-1774 Part A/C CSR includes the following information:

- A summary which includes the complete data for all 65 participants who completed the Part A/C 12-week follow-up period. This includes the post-treatment follow-up period data which was included in the Part A/C CSR and new data from the participants who were ongoing at the time of the data cut-off for the Part A/C CSR. Refer to Section 3.
- A summary of additional data collected following the initial week 52 database lock for the Part A/C CSR (on 17 Dec 2020). Several data points previously summarized in the Part A/C CSR have been updated based on additional data collected by the final database lock (on 14 Jul 2022).

Methods

Study 2 Design of Part A/C



Abbreviations: QW=once weekly

In Part A, participants were randomized to receive either placebo or dupilumab 300 mg SC once QW for 24 weeks. All participants who completed Part A and entered the extended active treatment period received dupilumab 300 mg QW for 28 weeks in Part A/C regardless of treatment in Part A (ie, placebo/dupilumab 300 mg QW or dupilumab 300 mg QW/dupilumab 300 mg QW). The participants who entered Part C after completing Part A then continued in the 12-week follow-up period. No study treatment was administered during the 12-week follow-up period.

Study participants

The study population of Part A/C consisted of adult males and females ≥18 years of age and adolescent males and females ≥12 to <18 years of age with EoE at the time of study entry into Part A. Participants who developed a serious or drug related adverse event during Parts A or B, which in the opinion of the investigator could indicate that continued treatment may have presented an unreasonable risk for the

participant, poor compliance or inability to complete required study assessments, became pregnant, prematurely discontinued from study, did not undergo endoscopy with biopsies prior to receiving rescue treatment or systemic hypersensitivity to dupilumab or the excipients were excluded.

Treatments

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

Objectives

The objective of the 12-week safety follow-up period was to assess the safety of dupilumab treatment in adult and adolescent participants with EoE after the 52 weeks of treatment.

There were no efficacy objectives or endpoints defined for the 12-week follow-up period. However, the DSQ continued to be collected during the 12-week follow up period.

Outcomes/endpoints

The Main Endpoints from Part C were:

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

Sample size

Of the 77 participants who entered Part C from Part A, 65 participants (84.4%) completed the study (ie, completed Part A, Part A/C, and 12-week follow-up period) and 12 participants (15.6%) prematurely discontinued from the study. Eleven participants discontinued prior to the follow-up period and 1 participant prematurely discontinued during the follow-up period.

Randomisation and blinding (masking)

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

Part C: all patients who previously participated in Part A received 300 mg dupilumab (N=77) every week.

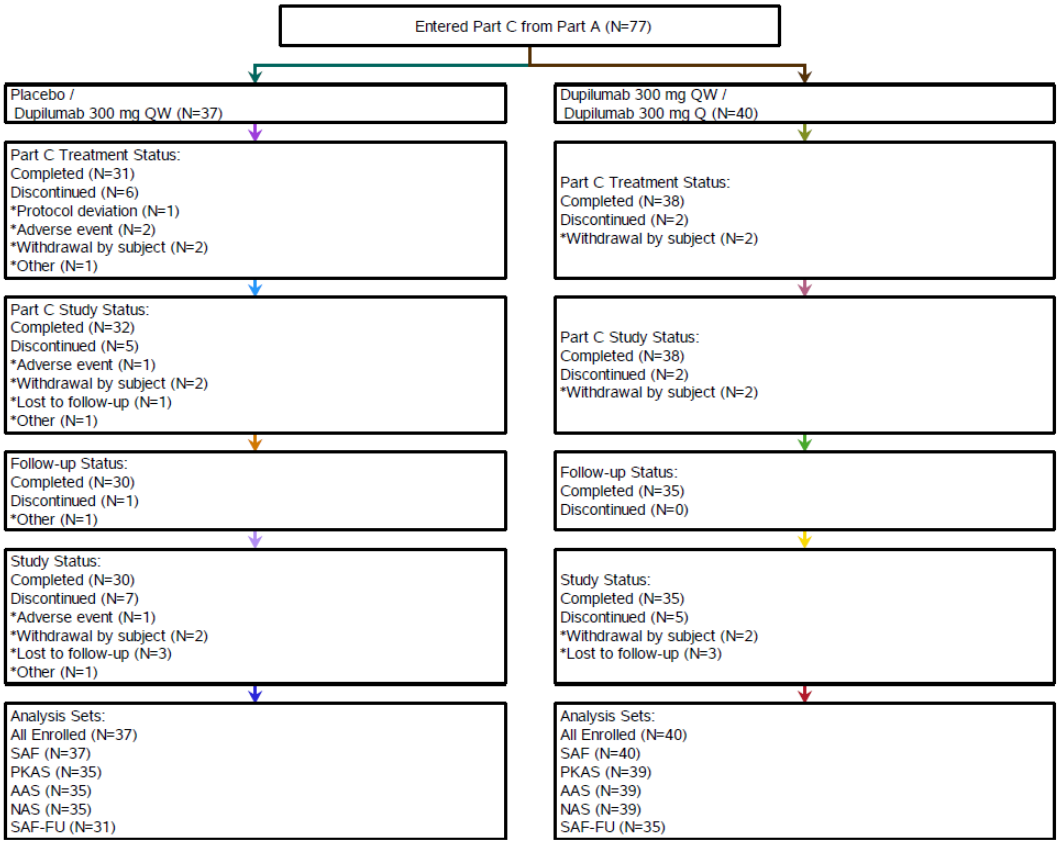
Statistical Methods

The statistical analysis plan (SAP) was not provided in the Article 46 submission. 1774ac-post-text-tables-ef-fu.pdf includes a descriptive tabulation of the results.

Results

Participant flow

Chart 1 Participant Disposition for Participants in the Part A/C Follow-up Period



Seventy-seven participants from Part A entered Part C of the study. Overall, 65 participants (84.4%) completed the study (Part A, Part A/C, and 12-week follow-up period) and 12 participants (15.6%) prematurely discontinued from the study. Eleven participants discontinued prior to the follow-up period and 1 participant prematurely discontinued during the follow-up period. The reasons for premature discontinuation from the study included lost to follow-up (7.8%), withdrawal by participant (5.2%), AE (1.3% with an AE of arthralgia) and other reasons (1.3%). The other reason for discontinuation was that the participant was not comfortable coming on-site for the week 52 esophagogastroduodenoscopy (EGD) procedure/clinic visit due to the Coronavirus Disease-2019 (COVID-19) pandemic.

Recruitment

24 Sep 2018 (date of first consent to first screened participant in Part A of the study) to 27 May 2021 (date of last participant last visit in the 12-week follow-up period for participants in Part A/C of the study).

The analyses presented in Addendum 2 are based on an end of study (final) database lock date of 14 Jul 2022.

Baseline data

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

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

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

Adolescents

In Part A, a total of 20 participants were adolescents (≥12 to <18 years of age). 11 adolescents were randomized to the dupilumab 300 mg QW and 9 to the placebo group. The mean age of the adolescent subgroup was 14.9 years. The majority were male (80.0%) and most participants were white (90.0%). The mean weight and BMI of adolescent participants was 58.9 kg and 20.8 kg/m2, respectively with 35.0% ≥60 kg. Baseline disease characteristics were generally balanced between the 2 treatment groups. The majority had previously used STCs for EoE (85.0%) and 10.0% had prior oesophageal dilations with a mean of 2.5 previous dilations.

Number analysed

37 subjects (22 dupilumab, 15 placebo subjects) included in absolute change from DSQ score (Part A) until week 64 (week 12 of follow-up). 37 subjects (22 dupilumab, 15 placebo subjects) included in absolute change from DSQ score (Part C) until week 64 (week 12 of follow-up).

Table 1 Summary of Study Analysis Set (All Randomized Participants in Part A Who Entered Part C)

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

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

Efficacy results

There were no efficacy objectives or endpoints defined for the 12-week follow-up period.

However, the DSQ continued to be collected during the 12-week follow up period. DSQ results for Part C are presented for all observed values regardless of rescue treatment use.

- **Absolute Change from Baseline in Dysphagia Symptom Questionnaire Total Score**

Absolute Change from Part A Baseline

The DSQ total score was calculated based on the daily responses over a 14-day period. A minimum of 8 diary entries was required for each 14-day period to derive a standardized DSQ total score.

In the dupilumab 300 mg QW/dupilumab 300 mg QW group, the mean absolute change from the Part A baseline was −21.95 at the Part A/C baseline (N=35) and −24.27 points (15.261) at week 52 (N=30). These findings show that dysphagia symptoms continued to improve with an additional 28 weeks of treatment with dupilumab 300 mg QW.

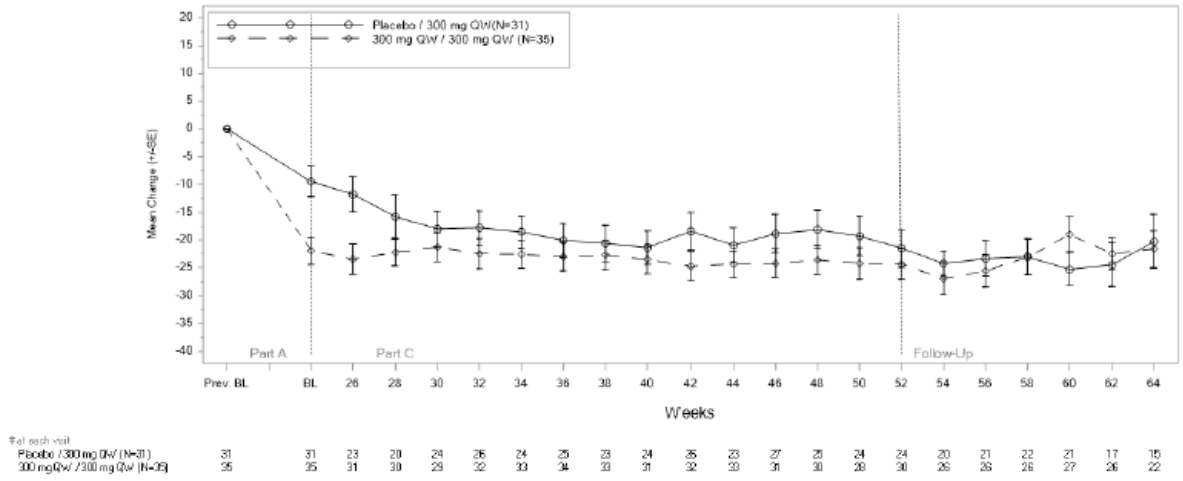
A similar improvement can be seen for the placebo/dupilumab 300 mg QW group, the mean absolute change in DSQ total score from the Part A baseline was −9.43 points at the Part A/C baseline (N=31) and −21.53 points at week 52 (N=24).

Absolute Change from Part A Baseline

The mean DSQ total score at week 64 (end of the 12-week follow-up period) increased when compared to the mean score at week 52, suggesting a worsening in dysphagia once treatment is stopped.

The mean DSQ total score at week 52 and at week 64 by treatment group were dupilumab 300 mg QW/dupilumab 300 mg QW group: 7.73 at week 52 (N=30) and 9.72 at week 64 (N=22); placebo/dupilumab 300 mg QW group: 11.81 at week 52 (N=24) and 13.74 at week 64 (N=15).

Figure 1 Mean (±SE) of Absolute Change in DSQ Total Score from Part A Baseline to Week 64, All Observed Values Regardless of Rescue Treatment Use (Part A/C Follow-up Period SAF)



Abbreviations: BL=baseline; DSQ=Dysphagia Symptom Questionnaire; QW=once weekly; SAF=safety analysis set; SE=standard error.

Absolute Change from Part A/C Baseline (ie, week 24)

In the dupilumab 300 mg QW/dupilumab 300 mg QW group, the mean absolute change in DSQ total score from the Part A/C baseline was −2.35 points at week 52 (N=30). In the placebo/dupilumab 300 mg QW group, the mean absolute change in DSQ total score from the Part A/C baseline was −10.79 at week 52 (N=24). These findings show improvement in DSQ total score with dupilumab 300 mg QW during the extended active treatment period.

Adolescents

In Part A/C, 3 of 9 (33.3%) adolescent participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group and 6/8 (75.0%) in the placebo/dupilumab 300 mg QW group achieved a peak 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 improvement in DSQ total score with continued treatment during Part C. The mean change from the Part A baseline (36.21) was -24.80 points at the Part C baseline (week 24; N=10) and −25.57 points at week 52 (N=6). Adolescent participants in the placebo/dupilumab 300 mg QW group who started dupilumab treatment in Part C showed progressive improvement. The mean change from the Part A baseline (36.04) was -25.45 points at week 52 (N=5).

Safety results

Table 2 Overall Summary of Number of Participants with TEAEs During Follow-up Period (Part A/C Follow-up Period SAF)

	Placebo/ Dupilumab 300 mg QW (N=31)	Dupilumab 300 mg QW/ Dupilumab 300 mg QW (N=35)	Total (N=66)
Any TEAE, n (%)	6 (19.4%)	6 (17.1%)	12 (18.2%)
Any drug related TEAE, n (%)	0	1 (2.9%)	1 (1.5%)
Maximum intensity for any TEAE, n (%)			
Mild	5 (16.1%)	4 (11.4%)	9 (13.6%)
Moderate	1 (3.2%)	2 (5.7%)	3 (4.5%)
Severe	0	0	0
Any TEAE death, n (%)	0	0	0
Any TE SAE, n (%)	0	0	0

After the database lock, 1 SAE of Pneumonia mycoplasmal in 1 participant in the dupilumab 300 mg QW/dupilumab 300 mg QW group was reported. The event started 70 days after the 52nd and last dose of the study drug and became an SAE 73 days after the last dose of the study drug.
Abbreviations: AE=adverse event; QW=once weekly; SAE=serious adverse event; SAF=safety analysis set; TEAE=treatment-emergent adverse event.

Overall, 12 participants (18.2%) had treatment-emergent adverse events (TEAEs) during the follow up period (Table 2). One participant in the dupilumab 300 mg QW/dupilumab 300 mg QW group reported 2 TEAEs (Preferred Term [PT]: Nausea and Constipation) mild in severity and assessed by the investigator as related to the study drug. The remainder of the TEAEs were assessed by the investigators as not related to the study drug.

Overall, the system organ classes (SOCs) with >5% incidence were Gastrointestinal disorders and Infections and infestations. Within these SOCs, all TEAEs were reported in 1 participant (1.5%) each and were either mild or moderate in severity. No severe TEAEs were reported for any participant during the Part A/C follow-up period.

No treatment-emergent serious adverse events (SAEs) were reported during the Part A/C follow up period at the time of the first database lock. After the final database lock (14 Jul 2022), 1 SAE of Pneumonia mycoplasmal was reported in 1 participant in the dupilumab 300 mg QW/dupilumab 300 mg QW group. The adverse event (AE) started as a non-serious AE 70 days after the 52nd and last dose of the study drug and became an SAE (because it required hospitalization) 73 days after the last dose of study drug. The SAE was moderate in intensity and assessed as not related to study drug by the study investigator. The outcome of the SAE was reported as recovering/resolving. The SAE was reported by the site after the participant's participation in the study had ended. The participant did not complete the study per protocol due to being lost to follow-up after completing week 52.

No deaths were reported during the Part A/C follow-up period.

CHMP comment

The submitted Addendum 2 summarizes the complete data for the Part A/C 12-week follow-up period and updates to data reported in Part A/C CSR versus data collected through final database lock (14 Jul 2022). No new safety findings were identified during the follow-up period or from updates in the data. The changes to the Part A/C data are considered not clinically relevant and are generally consistent with the previous results and conclusions reported. These updates have no impact on the conclusions regarding the efficacy and safety of the dupilumab 300 mg QW for the treatment of adult and adolescent participants with EoE.

PART B/C

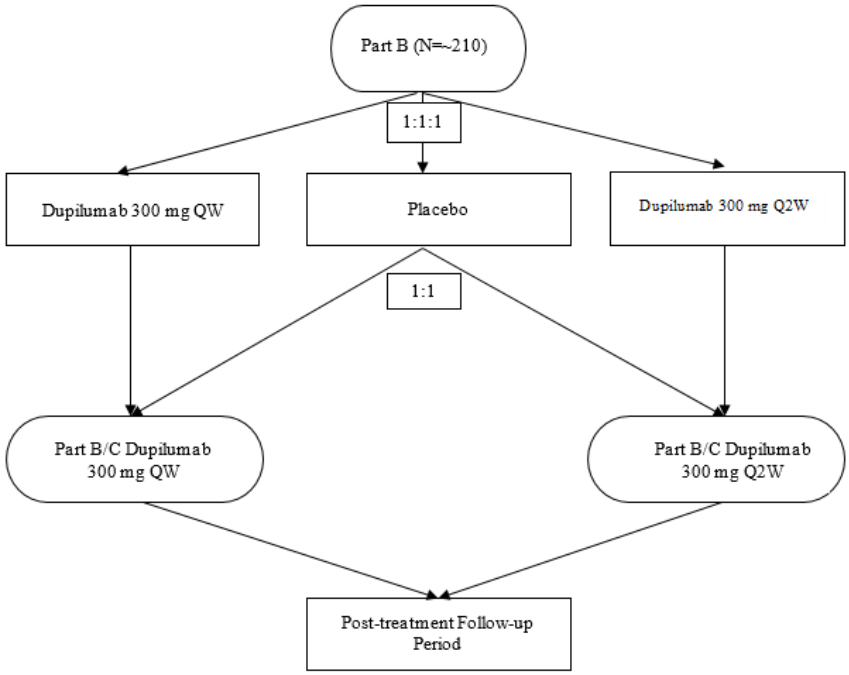
Part B/C of the study assessed the maintenance of efficacy over the 52-week treatment period for participants who received dupilumab 300 mg QW or 300 mg Q2W during both Part B and Part B/C and the treatment effect for participants who received 24 weeks of placebo during Part B and switched to 28 weeks of treatment with dupilumab 300 mg QW or Q2W during Part B/C. All endpoints in Part B/C were considered secondary.

The secondary endpoints were assessed at week 52, 1 week after the last dose of study drug during the extended active treatment period.

Methods

After completing the randomized, double-blind, placebo-controlled 24-week treatment period (Part B), eligible participants could enter a 28-week extended active treatment period (Part C). Participants who were randomized to placebo during Part B were re-randomized in a 1:1 ratio to receive dupilumab 300 mg once weekly (QW) or dupilumab 300 mg every 2 weeks (Q2W; with matching placebo alternating with dupilumab doses) in Part B/C, and those who were randomized to dupilumab in Part B remained on the same dupilumab dose regimen (300 mg QW or Q2W) in Part B/C.

Figure 2 Study Design - Part B, Part B/C, and Follow-up Period



Efficacy assessments were performed at specified time points and included an oesophageal endoscopy with biopsies for histologic assessments including intraepithelial eosinophil count and EoE Histology Scoring System (EoEHSS, EoE-EREFS) performed by the investigator during the endoscopy to assess oesophageal mucosal inflammatory and remodelling features. Patient-reported outcomes including Dysphagia Symptom Questionnaire (DSQ) were completed daily to assess the frequency and severity of dysphagia, EoE Impact Questionnaire (EoE-IQ) to assess disease-specific health-related quality of life and EoE Symptom Questionnaire (EoE-SQ) to assess the frequency and severity of symptoms other than dysphagia and swallowing pain.

The impact of dupilumab on disease markers, including markers associated with the EoE disease process or markers of type 2 inflammation was assessed. In addition, circulating biomarkers of type 2 inflammation, which are believed to be relevant to the pathophysiology of EoE were assessed.

Change(s) in Study Conduct

Five protocol amendments were published during the study. All changes in the conduct of the study were implemented by protocol amendments.

Of note, the purpose of protocol amendment 4, finalized on 16 Apr 2020) was to protect participant safety and data integrity during the Coronavirus Disease-2019 (COVID-19) pandemic by allowing for certain study procedures to occur at delayed time points and/or outside of the clinic environment. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19 were to be documented as being related to COVID-19 and remain in effect only for the duration of the public health emergency. Protocol Amendment 5, finalized on 06 Nov 2020, clarified that any additional analysis and methods required to investigate the impact of the COVID 19 pandemic, including extended dosing, on the safety evaluation would be specified in the statistical analysis plan (SAP).

Study participants

The study population consisted of adult males and females ≥18 years of age and adolescent males and females ≥12 to <18 years of age with EoE at the time of study entry into Part B.

At the start of Part B, study participants were required to have a confirmed diagnosis of EoE that was not responsive to high-dose proton pump inhibitor (PPI) therapy. Participants who were receiving PPIs during the screening period and eligible to enrol in the study were to continue a stable high-dose PPI regimen during the study. All participants were required to have an oesophageal endoscopy with biopsies at the baseline visit, which demonstrated ≥15 intraepithelial eos/hpf in at least 2 of 3 oesophageal regions (proximal, mid, and distal). Study participants were also required to have a history of an average of at least 2 episodes of dysphagia per week in the 4 weeks prior to screening, and at least 4 episodes of dysphagia in the 2 weeks prior to baseline. Participants must also have completed at least 11 of 14 days of the DSQ eDiary data entry in the 2 weeks prior to the baseline visit and have a baseline DSQ score ≥10.

Participants who completed Part B of the study could have either entered Part B/C (28-week extended active treatment period) or continued into a 12-week follow-up period. Excluded from Part B/C were participants who developed a serious adverse event (SAE) and/or AE related to the study drug during Part B, prematurely withdrawn during Part B due to a protocol violation, became pregnant during Part B, prematurely discontinued from study drug due to an AE, did not undergo endoscopy with biopsies prior to receiving rescue treatment or systemic hypersensitivity to dupilumab or the excipients.

Treatments

All participants entering Part B/C from Part B received dupilumab 300 mg, regardless of randomized treatment received during Part B. Participants who were randomized to placebo during Part B were re-randomized in a 1:1 ratio to receive dupilumab 300 mg QW or dupilumab 300 mg Q2W with matching placebo alternating with dupilumab doses so the injection frequency was identical for both groups for regimen-blinding purposes in Part B/C, and those who were randomized to one of the dupilumab dose regimens in Part B remained on the same dupilumab dose regimen in Part B/C. No treatment was administered during the 12-week follow-up period.

Part B/C study drug treatment was extended for 15 participants beyond the planned 28-week treatment period (>28 injections). Protocol Amendment 4 allowed participants to continue Part B/C study drug treatment beyond the planned 28-week treatment period if the week 52 endoscopy with biopsies was delayed due to the COVID-19 pandemic.

Exposure:

Overall, the mean treatment compliance during Part B/C was high (98.86%) with a mean number of study drug administrations (injections) during Part B/C of 26.6 and mean treatment duration of 190.6 days. Mean dupilumab treatment duration inclusive of during both Part B and Part B/C of the study was 310.0 days.

Objectives and endpoints

Objectives (Part B/C)	Secondary Endpoints (Part B/C)[1]
Primary	
• To assess the safety and efficacy of dupilumab treatment in adult and adolescent participants with EoE after up to 52 weeks of treatment as assessed by histological and clinical measures.	• Proportion of participants achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 52 • Absolute change in DSQ score from baseline to week 52 • Absolute change in EoE-EREFS from baseline to week 52 • Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 52 • Absolute change in EoE Grade Score from the EoEHSS from baseline to week 52 • Absolute change in EoE Stage Score from the EoEHSS from baseline to week 52 • Proportion of participants achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 52 • Proportion of participants achieving peak esophageal intraepithelial eosinophil count of ≤1 eos/hpf at week 52 • Percent change in DSQ from baseline to week 52 • NES for the relative change from baseline to week 52 in the EDP transcriptome signature • NES for the relative change from baseline to week 52 in the type 2 inflammation transcriptome signature • Absolute change from baseline to week 52 in health-related QOL as measured by EoE-IQ • Absolute change from baseline to week 52 in severity and/or frequency of EoE symptoms other than dysphagia • Proportion of participants who receive rescue medications or procedures during the treatment period
Secondary	
• To evaluate the safety, tolerability, and immunogenicity of dupilumab treatment for up to 52 weeks in adult and adolescent participants with EoE • To explore the relationship between dupilumab concentration and responses in adult and adolescent participants with EoE, using descriptive analyses • To evaluate the effects of dupilumab on transcriptomic signatures associated with EoE and type 2 inflammation • To demonstrate the efficacy of dupilumab treatment compared to placebo after up to 52 weeks of treatment in adult and adolescent patients with EoE who have previously received swallowed topical corticosteroids	

[1] Note: There were no primary efficacy endpoints for Part B/C of the study. All endpoints above were considered secondary endpoints for Part B/C. Secondary endpoints assessed in Part B/C (through week 52) were summarized with descriptive statistics. No formal statistical hypothesis testing was performed.
Abbreviations: DSQ=Dysphagia Symptom Questionnaire; EDP=eosinophilic esophagitis diagnostic panel; EoE=eosinophilic esophagitis; EoE-EREFS=Eosinophilic Esophagitis-Endoscopic Reference Score; EoEHSS=Eosinophilic Esophagitis Histology Scoring System; EoE-IQ=Eosinophilic Esophagitis Impact Questionnaire; eos/hpf =eosinophils/high-power field; NES=Normalized Enrichment Scores; QOL=quality of life

Sample size

Of the 240 participants who were randomized into Part B of the study, 227 participants (74 placebo, 74 dupilumab 300 mg QW, and 79 dupilumab 300 mg Q2W) entered Part B/C from multiple global sites.

Randomisation and blinding (masking)

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

Of the patients who previously participated in Part B, those who received dupilumab in Part B continued their dosing regimen in Part C and those who received placebo were randomised to either dosing regimen.

Participants who received 300 mg Q2W in Part B also continued with matching placebo alternating with dupilumab doses so the injection frequency was identical for both groups for regimen-blinding purposes.

Statistical Methods

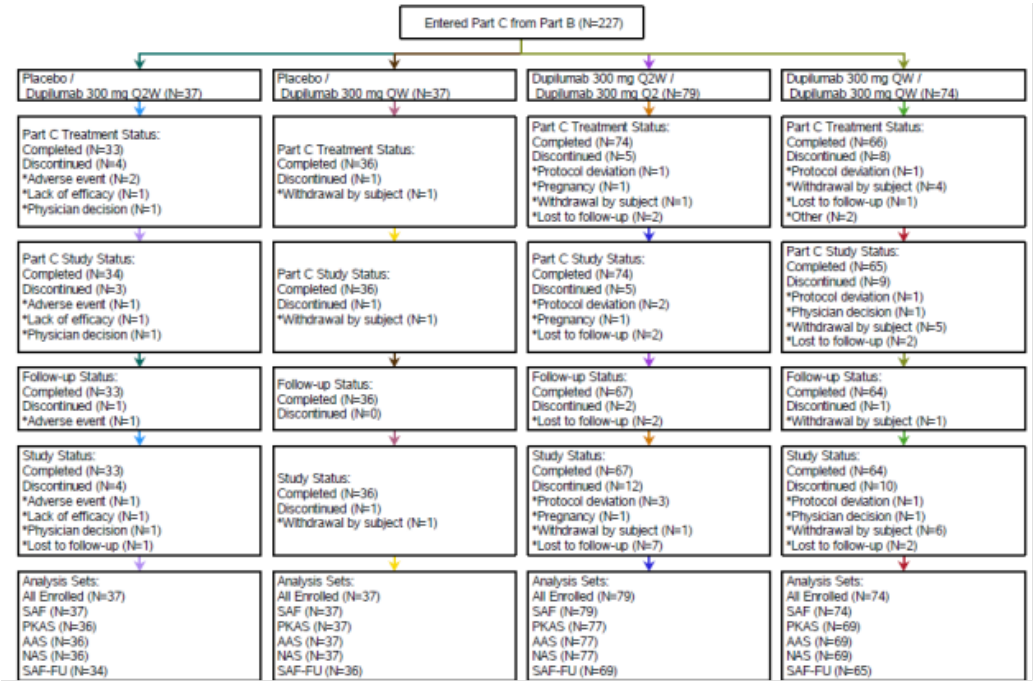
The co-primary and secondary endpoints assessed at week 24 during Part B were assessed at week 52 as secondary endpoints for the extended treatment period (Part B/C) and summarized with descriptive statistics based on the treatment assignment in the double-blind treatment period, as well as the extended active treatment assignment for participants previously in the placebo group (i.e., placebo/dupilumab 300 mg QW, placebo/dupilumab 300 mg Q2W, dupilumab 300 mg QW/dupilumab 300 mg QW, and dupilumab 300 mg Q2W/dupilumab 300 mg Q2W).

For continuous endpoints, in addition to summary of change from the Part B baseline, summary of change from the Part B/C baseline was provided to assess the maintenance of effect with continued treatment of dupilumab from the end of Part B (Week 24) through the end of Part B/C (Week 52) in the dupilumab 300 mg QW/dupilumab 300 mg QW and dupilumab 300 mg Q2W/dupilumab 300 mg Q2W groups.

Results

Participant flow

Chart 2 Participant Disposition for Participants in the Part B/C Follow-up Period



Continuation into Part B/C

Of the 240 participants who were randomized into Part B of the study, 227 participants (74 placebo, 74 dupilumab 300 mg QW, and 79 dupilumab 300 mg Q2W) entered Part B/C and were included in the current analysis. The remaining 13 participants (5 placebo, 6 dupilumab 300 mg QW, and 2 dupilumab 300 mg Q2W) did not participate in Part B/C.

Reasons for not participating in Part B/C were:

- Developed an AE deemed related to study drug and/or SAE in Part B (1 dupilumab 300 mg QW [Breast cancer] and 1 dupilumab 300 mg Q2W [Rhabdomyolysis] participants)
- Withdrew from Part B due to a protocol violation, poor compliance, or inability to complete required study assessments (1 dupilumab 300 mg QW participant)
- Prematurely discontinued from study drug due to an AE during Part B (2 placebo [Hepatic enzyme increased and Oral herpes], 1 dupilumab 300 mg QW [Hypermobility syndrome and Myalgia], and 1 dupilumab 300 mg Q2W [Congenital coronary artery malformation and Dyspnoea] participants);
- Other reasons including:
  - COVID-19 restrictions causing continued delay in visit 11 and psychosocial acopia (1 placebo participant)
  - Withdrawn consent due to AE (PT of Oral herpes [verbatim term: worsening cold sore] considered related to study drug; 1 placebo participant)
  - Did not complete visit 11/week 24 (1 placebo participant decided to stop due to COVID-19 pandemic)
  - Did not receive study drug (1 placebo participant)
  - Withdrawn consent (2 dupilumab 300 mg QW participants).

Part B/C Study Treatment Completion Status

All 227 participants from Part B who continued into Part B/C were treated with at least 1 dose of dupilumab 300 mg SC during Part B/C (37 placebo/dupilumab 300 mg QW, 37 placebo/dupilumab 300 mg Q2W, 74 dupilumab 300 mg QW/dupilumab 300 mg QW, and 79 dupilumab 300 mg Q2W/dupilumab 300 mg Q2W) and were included in the Part B/C SAF. Most participants (209/227, 92.1%) completed 52 weeks of study treatment (ie, 24 weeks of study drug in Part B plus 28 weeks of study drug in Part B/C). Eighteen of 227 participants (7.9%) discontinued study drug during Part B/C. The most frequent reason for discontinuation of study treatment was withdrawal by participant (1 placebo/dupilumab 300 mg QW, 4 dupilumab 300 mg QW/dupilumab 300 mg QW, and 1 dupilumab 300 mg Q2W/dupilumab 300 mg Q2W participants).

Two participants discontinued study treatment due to AEs ([PTs: Aspartate aminotransferase increased, Alanine aminotransferase increased, and Blood creatine phosphokinase increased] and [PT: Joint noise]), both in the placebo/dupilumab 300 mg Q2W group. One participant, in the dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group, discontinued study treatment due to the COVID-19 pandemic (ie, physician decision due to COVID-19).

Study Completion Status

Of the 227 participants who entered Part B/C, 200 (88.1%) completed the study (defined as completing Part B, Part B/C, and 12-week follow-up period) and 27 (11.9%) discontinued the study, including 4 participants who discontinued the study during the 12-week follow-up period. The most frequent reasons for discontinuing from the study were lost to follow-up and withdrawal by participant. One participant, in the placebo/dupilumab 300 mg Q2W group, discontinued the study during the follow-up period due to an AE (PT of Joint noise). No participant discontinued from the study due to the COVID-19 pandemic.

Adolescents

Of the 227 participants who entered Part B/C, 75 were adolescents (≥12 to <18 years of age). Of these 75 adolescent participants, 71 completed 52 weeks of study drug and 4 discontinued study drug during Part B/C. Three of these adolescent participants were in the dupilumab 300 mg QW/dupilumab 300 mg QW group (withdrawal by participant [1], protocol violation [1], Other [missed visit 18] [1]) and 1 was in the dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group (withdrawal by participant [1]) discontinued study drug during Part B/C.

Of the 75 adolescent participants, 67 completed the study, and 9 discontinued the study. Of the 9 adolescent participants who discontinued the study, 3 participants were in the dupilumab 300 mg QW/dupilumab 300 mg QW group (withdrawal by participant [n=2], protocol violation [n=1]), 5 participants were in the dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group (protocol violation [n=1], lost to follow-up [n=3], withdrawal by participant [n=1]), and 1 participant was in the placebo/dupilumab 300 mg Q2W group (lost to follow-up).

Recruitment

Study Period was from 12 Aug 2019 (date of first consent for first screened participant in Part B) to 07 Jun 2022 (date of last visit in 12-week follow-up period for participants in Part B/C). The analyses presented in the report are based on an end of study (final) database lock date of 14 Jul 2022.

Baseline data

Demographic and baseline characteristics of participants at study entry (Part B) for participants included in Part B/C of the study were generally balanced across treatment groups and similar to a typical EoE patient population published in the literature with respect to sex, ethnicity, and race.

Demographic and baseline characteristics for participants who enrolled in Part B/C were also consistent with those for participants from the Part B.

Overall, the majority of participants in Part B/C were male (63.9%) and most participants were White (90.7%) and not Hispanic or Latino (94.3%). The mean age of these participants at study entry was 28.1 years with 33.0% of participants ≥12 to <18 years of age, 45.4% of participants ≥18 to <40 years of age, and 20.7% of participants ≥40 to <65 years of age.

Two participants (0.9%) were ≥65 years of age. Most participants were from the US with 81.5%, with 4.0% from Australia, 3.5% from Canada, 3.1% from Italy, 2.6% from Spain, 1.8% from Netherlands, 1.3% from Belgium, 0.9% from Germany, 0.9% from UK and 0.4% from France.

The placebo/dupilumab 300 mg Q2W group had a higher percentage of male participants (81.1%) than in the placebo/dupilumab 300 mg QW (64.9%), dupilumab 300 mg QW/dupilumab 300 mg QW (64.9%), or dupilumab 300 mg Q2W/dupilumab 300 mg Q2W (54.4%) groups. The placebo/dupilumab 300 mg QW group had a smaller percentage of participants <60 kg (10.8%) than in the placebo/dupilumab 300 mg Q2W (21.6%), dupilumab 300 mg QW/dupilumab 300 mg QW (28.4%), or dupilumab 300 mg Q2W/dupilumab 300 mg Q2W (27.8%) groups.

Baseline disease characteristics at study entry (i.e., Part B baseline) indicated a highly symptomatic population, often refractory to other therapies, with the majority of participants having previously used STCs for the treatment of EoE (74.0%) and approximately one-third of participants having prior oesophageal dilations (35.2%) with a mean of 2.4 previous dilations. Overall, 28.6% had a history of both STC used for the treatment of EoE and prior oesophageal dilation.

Only 30.8% reported STCs as being effective for EoE. Overall 49.3% had a history of an inadequate response, intolerance, and /or contraindication to STCs. Approximately 70% of participants were receiving PPIs at the time of randomization. More than one-half of participants (59.9%) had been on a food elimination diet in the past.

The mean peak eosinophil count of 3 oesophageal regions (proximal, mid, and distal) at the Part B baseline was 86.8 eos/hpf. The mean EREFS total score at Part B baseline was 7.1 points. The mean DSQ score at the Part B baseline was 36.6, indicating substantial dysphagia symptom burden. The mean number of days with dysphagia at the Part B baseline was 10.7 days out of 14 days, with more than two-thirds of participants (70.5%) having dysphagia for ≥10 out of 14 days.

A number of participants in the SAF had other type 2 co-morbidities, including atopic dermatitis (26.4%), asthma (43.6%), and allergic rhinitis (63.4%).

At the start of Part B/C, the mean peak oesophageal intraepithelial eosinophil count of 3 oesophageal regions was higher in the placebo/dupilumab 300 mg QW and Q2W groups than in the dupilumab 300 mg QW/dupilumab 300 mg QW and dupilumab 300 mg Q2W/dupilumab 300 mg Q2W groups consistent with the clinically and statistically significant reduction in peak eosinophil score at the end of Part B. At the start of Part B/C, the mean DSQ total scores were higher in the placebo/dupilumab 300 mg QW, placebo/dupilumab 300 mg Q2W, and dupilumab 300 mg Q2W/dupilumab 300 mg Q2W groups than in the dupilumab 300 mg QW/dupilumab 300 mg QW group. These findings demonstrate the clinically and statistically significant symptomatic improvement in dysphagia symptoms observed after treatment with dupilumab 300 QW at the end of Part B.

Number analysed

Table 3 Summary of Study Analysis Set (All Randomized Participants in Part B Who Entered Part B/C)

	Placebo / Dupilumab 300 mg Q2W	Placebo / Dupilumab 300 mg QW	Placebo / Dupilumab	Dupilumab 300 mg Q2W / Dupilumab 300 mg Q2W	Dupilumab 300 mg QW / Dupilumab 300 mg QW	Dupilumab Combined	Total
Patients entered Part C, n [1]	37	37	74	79	74	153	227
Patients Included in the Safety Analysis Set (SAF), n(%)	37/37 (100%)	37/37 (100%)	74/74 (100%)	79/79 (100%)	74/74 (100%)	153/153 (100%)	227/227 (100%)
Patients Who Entered the Safety Follow-up Period after Part C, n(%)	34/37 (91.9%)	36/37 (97.3%)	70/74 (94.6%)	69/79 (87.3%)	65/74 (87.8%)	134/153 (87.6%)	204/227 (89.9%)
Patients included in the PK Analysis Set (PKAS), n(%)	36/37 (97.3%)	37/37 (100%)	73/74 (98.6%)	77/79 (97.5%)	69/74 (93.2%)	146/153 (95.4%)	219/227 (96.5%)
Patients included in the ADA Analysis Set (AAS), n(%)	36/37 (97.3%)	37/37 (100%)	73/74 (98.6%)	77/79 (97.5%)	69/74 (93.2%)	146/153 (95.4%)	219/227 (96.5%)
Patients included in the Neutralizing Antibodies Analysis Set (NAS), n(%)	36/37 (97.3%)	37/37 (100%)	73/74 (98.6%)	77/79 (97.5%)	69/74 (93.2%)	146/153 (95.4%)	219/227 (96.5%)

Note: Percentages are based on number of enrolled patients.
[1] It is the number of patients enrolled Part C from Part B (ie, Part B/C)
Abbreviations: AAS=anti-drug antibody analysis set; ADA=anti-drug antibody; NAS=neutralizing antibody analysis set; PKAS=pharmacokinetic analysis set; Q2W=once every 2 weeks; QW=once weekly; SAF=safety analysis set

Efficacy results

The results of Part B/C have been submitted and discussed during the Extension of indication procedure for EoE.

Results for Part B/C are presented for all observed values regardless of rescue treatment use.

Table 4 Results for Secondary Efficacy Endpoints at Part B/C Baseline (end of Part B [i.e. Week 24]) and Week 52 (end of Part B/C), All Observed Values Regardless of Rescue Treatment Use (Part B/C SAF)

	EE-1774 Part C[B] (Week 52) (N=227)			
Endpoints at Week 52[a] using OC regardless of rescue treatment	Placebo/ Dupilumab 300 mg q2w (N=37)	Placebo/ Dupilumab 300 mg qw (N=37)	Dupilumab 300 mg q2w/ Dupilumab 300 mg q2w (N=79)	Dupilumab 300 mg qw/ Dupilumab 300 mg qw (N=74)
Proportion of Peak Eos Count ≤6/hpf, n/N1 (%)	23/32 (71.9%)	25/37 (67.6%)	54/73 (74.0%)	**55/65 (84.6%)**
Absolute Change in DSQ total score [0-84], Mean (SD), [N1]	-23.69 (13.737), [27]	-27.25 (11.457), [24]	-20.87 (16.387), [52]	**-30.26 (15.389), [54]**
% change in DSQ total score [0-84], Mean (SD), [N1]	-71.01 (37.256), [27]	-78.13 (31.003), [24]	-61.19 (44.447), [52]	**-80.74 (32.866), [54]**
% change in peak eos count, Mean (SD), [N1]	-91.20 (13.037), [32]	-84.21 (42.169), [37]	-84.78 (40.973), [73]	**-95.85 (4.037), [65]**

Absolute Change in EoEHSS mean grade score [0-3], Mean (SD), [N1]	-0.779 (0.4292), [32]	-0.906 (0.3936), [37]	-0.838 (0.4039), [73]	**-0.968 (0.4293), [65]**
Absolute Change in EoEHSS mean stage score [0-3], Mean (SD), [N1]	-0.710 (0.3783), [32]	-0.871 (0.3510), [37]	-0.809 (0.3434), [73]	**-0.932 (0.3730), [65]**
Absolute Change in EREFS total score [0-18] (local reads), Mean (SD), [N1]	-4.3 (3.21), [31]	-6.1 (3.60), [37]	-5.2 (3.40), [73]	**-5.3 (2.85), [63]**
Peak Eos Count <15/hpf, n/N1 (%)	28/32 (87.5%)	29/37 (78.4%)	61/73 (83.6%)	**65/65 (100%)**
NES for EDP, median, [N1]	-2.39, [8]	-2.58, [14]	-2.65, [32]	**-2.72, [27]**
NES for T2INF, median, [N1]	-1.83, [8]	-1.96, [14]	-1.96, [32]	**-1.98, [27]**

Abbreviations: DSQ=Dysphagia Symptom Questionnaire; EDP= the EoE diagnostic panel; EoE=eosinophilic esophagitis; EoEHSS=EoE Histology Scoring System; EREFS=Endoscopic Reference Score; NES=Normalized Enrichment Scores; Q2W=every 2 weeks; QW=every week; SD=standard deviation; T2INF=type 2 inflammation signature.
N=number of patients enrolled in Part C from Part B; N1=number of patients with observed data.

a For endpoints measured by absolute or % change, changes were calculated from study baseline (ie, start of Part B).

Results from Part B/C support the long-term efficacy of dupilumab 300 mg in adult and adolescent participants with EoE.

Efficacy with the dupilumab 300 mg QW dosing regimen observed at the Part B/C baseline continued to improve during Part B/C (dupilumab 300 mg QW/dupilumab 300 mg QW group). While 64.9% of participants treated with dupilumab 300 mg QW in Part B achieved peak oesophageal intraepithelial eosinophil count ≤6 eos/hpf at the Part B/C baseline (Week 24) this increased to 84.6% after 52 weeks, and remarkably, 100% of participants on this regimen achieved <15 eos/hpf after 52 weeks of treatment (89.2% after 24 weeks). Similarly, DSQ total scores continued to improve (mean decrease from Part B baseline) in the dupilumab 300 mg QW/ dupilumab 300 mg QW group from −25.99 at the Part B/C baseline (ie, week 24) to −30.26 at week 52.

In addition, participants who received placebo in Part B achieved improvements in efficacy after 28 weeks on dupilumab 300 mg QW in Part B/C (placebo/dupilumab 300 mg QW group) that were similar to improvements observed for participants who received 24 weeks of dupilumab 300 mg QW treatment during Part B.

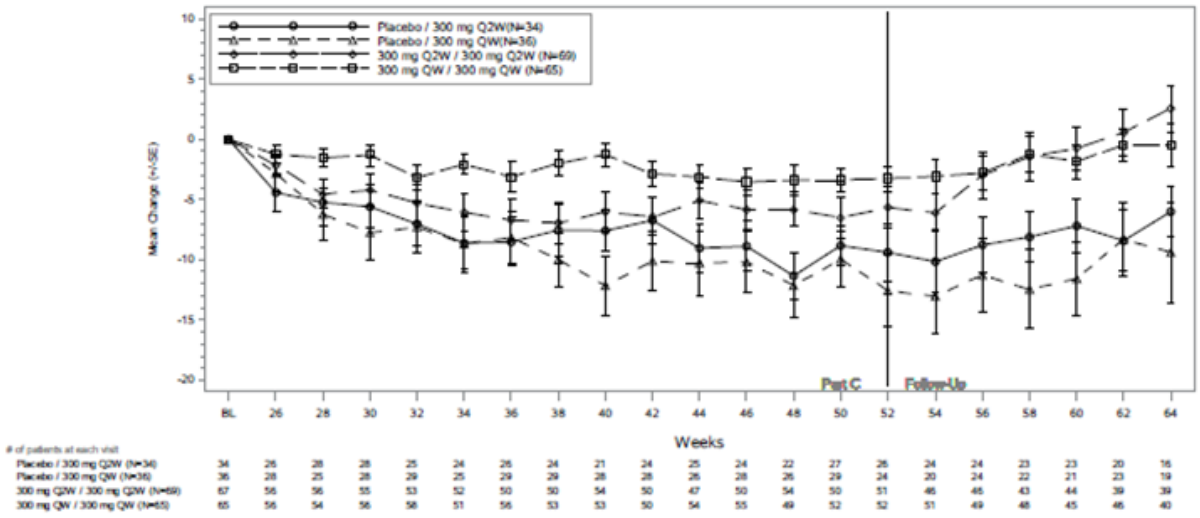
Except for dysphagia, the predominant symptom of EoE, the magnitude of improvements in other histologic, endoscopic, and molecular outcomes after 24 weeks of treatment with dupilumab 300 mg Q2W were similar to those observed with dupilumab 300 mg QW. After 24 weeks of treatment, the dupilumab Q2W dosing regimen showed numerically less improvement in dysphagia symptoms compared with the dupilumab 300 mg QW regimen. During Part B/C, continued treatment with dupilumab 300 mg Q2W showed improvement in dysphagia and maintenance of effect on histologic, endoscopic, and molecular measures at week 52. Except for dysphagia, the magnitude of improvements with continued treatment with dupilumab 300 mg Q2W in Part B/C were consistent with those observed with the dupilumab 300 mg QW/dupilumab 300 mg QW dosing regimen. A reason for this difference was discussed during the Extension of indication procedure. The reason for the disparate results of the two different dupilumab dosing regimens for the co-primary endpoint of peak oesophageal intraepithelial eosinophil count (≤6/hpf defining a histologic remission) and the DSQ (a validated tool to measure the frequency and severity of dysphagia) could not be finally identified, although it is known that dupilumab has a broader pharmacologic effect than influencing eosinophil infiltration to oesophageal mucosa alone. One hypothesis may be that, in addition to the effect compartment for the drug effect on infiltration of eosinophils in the oesophageal mucosa, the drug effect on dysphagia may be modulated by a different effect compartment (e.g., muscularis layer, oesophageal nervous plexus).

Treatment effects on dysphagia, histologic, endoscopic, and molecular measures at week 52 in the placebo/dupilumab 300 mg Q2W group showed a similar trend to the treatment effects observed at the

Part B/C baseline for participants who received dupilumab 300 mg Q2W during Part B. However, participants treated with dupilumab 300 mg Q2W who switched from placebo treatment in Part B achieved a lower level of improvement in dysphagia compared with placebo participants who were re-randomized to treatment with dupilumab 300 mg QW in Part B/C.

The DSQ total score was the only efficacy outcome that was collected after week 52 to the end of the study (week 64). As observed from the follow-up period, there was worsening of DSQ total score from week 52 to week 64 in all treatment groups when dupilumab treatment was stopped, suggesting an increase in disease activity. However, it is not clear at what point after treatment discontinuation worsening of DSQ total score was seen. The persistence in effect of about 8 weeks post dosing is expected based on the PK profile of dupilumab.

Figure 3 1/1C-bf Mean (+/-SE) of Absolute Change in DSQ Total Score From Part C Baseline to Week 64, All Observed Values Regardless of Rescue Treatment Use (Follow-up Period Safety Analysis Set – Patients in Part B Who Entered Follow-Up After Part C)



For other secondary efficacy endpoints of patient-reported outcomes, including measures to assess non-dysphagia symptoms (EoE-SQ) and disease-specific health-related QOL (EoE-IQ), numerical improvements from the Part B baseline were observed at week 52 in participants treated with dupilumab 300 mg QW and to a lesser extent Q2W during Part B/C.

Similar effects on efficacy as observed for the overall population were demonstrated for the subgroup of adolescent participants and for the subgroups of participants with prior use of STCs and participants who were inadequately controlled by, or were intolerant to, or had contraindications to STCs.

These findings provide clinical evidence of the durability of the histological response, symptomatic response, endoscopic response and molecular outcomes in adult and adolescent participants with EoE after treatment with dupilumab 300 mg QW for up to 52 weeks. These findings also demonstrated the robust efficacy with 28 weeks of dupilumab 300 mg QW following 24 weeks of placebo treatment.

Adolescents

The dupilumab 300 mg QW/dupilumab 300 mg QW treated group demonstrated continued improvement in the proportion of adolescent participants who achieved a peak oesophageal intraepithelial eosinophil count ≤6 eos/hpf in all 3 regions of the esophagus (histologic remission) at Week 52. At baseline of Part C (Week 24), 66.7% of adolescent participants treated with dupilumab 300 mg QW achieved histologic remission. The results from Part B/C show continued improvement with 81.8% adolescent participants achieving histological remission at Week 52. The dupilumab 300 mg

Q2W/dupilumab 300 mg Q2W group also demonstrated sustained improvement. Overall 53.8% of participants treated with dupilumab 300 mg Q2W achieved histologic remission at Week 24, with 60.0% achieving histological remission in all 3 regions at Week 52.

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

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

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

Overall the 300 mg QW dosing regimen showed higher efficacy in achieving histological remission and the reduction of dysphagia burden in the adolescent participants.

Safety results

Safety was evaluated in participants who received at least 1 dose of study drug.

Table 5 Overall Summary of Number of Participants with TEAEs During Part B/C 28-Week Treatment Period (Part B/C SAF)

	Placebo / Dupilumab 300 mg Q2W (N=37)	Placebo / Dupilumab 300 mg QW (N=37)	Placebo / Dupilumab (N=74)	Dupilumab 300 mg Q2W / Dupilumab 300 mg Q2W (N=79)	Dupilumab 300 mg QW / Dupilumab 300 mg QW (N=74)	Dupilumab Combined (N=153)	Total (N=227)
Any TEAE, n (%)	22 (59.5%)	23 (62.2%)	45 (60.8%)	56 (70.9%)	51 (68.9%)	107 (69.9%)	152 (67.0%)
Any drug related TEAE, n (%)	12 (32.4%)	7 (18.9%)	19 (25.7%)	25 (31.6%)	14 (18.9%)	39 (25.5%)	58 (25.6%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	2 (5.4%)	0	2 (2.7%)	0	0	0	2 (0.9%)
Maximum intensity for any TEAE, n (%)							
Mild	8 (21.6%)	17 (45.9%)	25 (33.8%)	42 (53.2%)	32 (43.2%)	74 (48.4%)	99 (43.6%)
Moderate	14 (37.8%)	4 (10.8%)	18 (24.3%)	13 (16.5%)	18 (24.3%)	31 (20.3%)	49 (21.6%)
Severe	0	2 (5.4%)	2 (2.7%)	1 (1.3%)	1 (1.4%)	2 (1.3%)	4 (1.8%)
Any TEAE death, n (%)	0	0	0	0	0	0	0
Any TE SAE, n (%)	0	2 (5.4%)	2 (2.7%)	0	3 (4.1%)	3 (2.0%)	5 (2.2%)
Any TE SAE leading to discontinuation of study drug permanently, n (%)	0	0	0	0	0	0	0

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

The proportion of participants who experienced a TEAE across the treatment groups ranged from 59.5% in the placebo/dupilumab 300 mg Q2W group to 70.9% in the dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group. By PT, the most frequent TEAEs reported overall (in ≥5% of participants) were Injection site reaction (13.7%), Injection site pain (8.4%), Injection site erythema (6.6%), and COVID-19 (7.9%). The majority of TEAEs were mild or moderate in intensity. The proportions of participants experiencing a treatment-related TEAE was 18.9% in participants receiving dupilumab QW in Part B/C (placebo/dupilumab 300 mg QW and dupilumab 300 mg QW/dupilumab 300 mg QW groups) and higher in those receiving dupilumab Q2W in Part B/C (32.4% in the placebo/dupilumab 300 mg Q2W group and 31.6% in the dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group).

No deaths were reported during Part B/C.

Treatment-emergent SAEs were reported in the dupilumab 300 mg QW/dupilumab 300 mg QW group by PT: Diarrhoea and Rectal tenesmus (2 SAEs in 1 participant), Enterocolitis infectious (1 participant) and Chest pain (1 participant) and in the placebo/dupilumab 300 mg QW group Vomiting (1 participant) and Cellulitis (1 participant). None of the SAEs were assessed to be related to study drug by the investigator. None of these SAEs lead to permanent discontinuation of the study drug.

There were no TEAEs leading to permanent discontinuation of the study drug in any of the dupilumab/dupilumab groups or in the placebo/dupilumab 300 mg QW group. In the placebo/dupilumab 300 mg Q2W group, there were 2 participants with TEAEs leading to permanent discontinuation of the study drug (Joint noise in 1 participant and Aspartate aminotransferase increased, Alanine aminotransferase increased, and Blood creatine phosphokinase increased in another participant). The TEAE of Joint noise was assessed by the investigator to be related to study drug, while the other TEAEs were assessed as unrelated. There was no pattern among the reported SAEs or TEAEs leading to permanent discontinuation of study drug identified to suggest any relationship to dupilumab treatment.

TEAEs within the Infections and infestations SOC were closely examined to determine if there was an association of TEAEs with dupilumab use. The most frequently reported PT in this SOC was COVID-19 (7.9% overall) followed by Nasopharyngitis (4.4%) and Urinary tract infection (2.6%). All other PTs in this SOC were reported in <2% of participants overall.

The majority of TEAEs in this SOC were mild (18.5%) or moderate (6.6%) in intensity and all were assessed as not related to the study drug. Two participants (0.9% overall) experienced severe events in this SOC category (PTs: COVID-19 and Cellulitis). Both events were assessed as not related to study drug. The Cellulitis event was considered serious, as well as a PT of Enterocolitis. No TEAEs that led to permanent withdrawal of the study drug were reported in this SOC in any group. There was no pattern among the reported events in this SOC identified to suggest any relationship to dupilumab treatment.

A review of COVID-19 cases throughout the dupilumab program clinical database, post-marketing data, as well as the published literature did not reveal a systemic imbalance in COVID-19 TEAEs

During Part B/C of the study, 3.1% of the participants overall had an AESI. One participant each in the placebo/dupilumab 300 mg Q2W group (2.7%; PT of Anaphylactic reaction), the placebo/dupilumab 300 mg QW group (2.7%; PT of Arthralgia), and dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group (1.3%; PT of Oral herpes), and 4 participants in the dupilumab 300 mg QW/dupilumab 300 mg QW group (5.4%; all PTs of Arthralgia).

All the AESIs were non-serious and assessed by the investigator to be not related to the study drug. The study drug was continued in all cases, except in 1 participant for which it was reported unknown.

Overall, 24.5% experienced TEAEs during the 12-week post-treatment follow-up period. The majority of TEAEs were mild or moderate in intensity. One participant (in the dupilumab 300 mg QW/dupilumab 300 mg QW group) had a treatment-related TEAE (mild Rash) during the follow-up period.

No deaths were reported during the follow-up period.

One SAE was reported during the follow-up period in 1 participant in the placebo/dupilumab 300 mg Q2W group (Open globe injury in 1 participant). After database lock, another 2 SAEs in 1 participant in the dupilumab 300 mg Q2W/dupilumab 300 mg Q2W group were reported (Generalized anxiety disorder and Substance use disorder). The events were severe in intensity, assessed by the investigator as not related to study drug and the events resolved before the end of the follow-up period.

There was no consistent trend towards an increase or decrease in mean or median values over time from the Part B/C baseline for any haematology or chemistry parameter except eosinophil counts. Mean eosinophil counts at Part B/C baseline were higher in participants previously receiving placebo than dupilumab, with larger mean changes from the Part B/C baseline at week 52 in the placebo/dupilumab 300 mg QW (−0.1697×109/L) and placebo/dupilumab 300 mg Q2W (−0.1800×109/L) groups than in the dupilumab 300 mg QW/dupilumab 300 mg QW (−0.0332×109/L) and dupilumab 300 mg Q2W/dupilumab 300 mg Q2W (−0.0014×109/L) groups.

Otherwise, there were no clinically meaningful changes or differences between the treatment groups observed for chemistry, haematology, urinalysis laboratory values, vital signs, ECG, or physical examination findings.

Adolescents

During the Extension of indication procedure for EoE the data from 75 adolescent participants with EoE up to 1 year (exposure from Part B and Part C combined) were already submitted and discussed.

Table 6 Overall Summary of Number of Adolescent Participants (≥12 to <18 Years of Age) with TEAEs During Part B/C 28-Week Treatment Period (Part B/C SAF)

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

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

The incidence of all TEAEs reported in adolescent participants during Part B/C of the study was similar across the treatment groups (69.2% to 73.3%). Most TEAEs in adolescent participants were mild or moderate in intensity. Two treatment-emergent SAEs were reported by 1 adolescent participant in the dupilumab 300 mg QW/dupilumab 300 mg QW group (Diarrhoea, Rectal tenesmus); these SAEs were assessed by the investigator as unrelated to the study drug. No adolescent participant experienced a TEAE that led to permanent study drug discontinuation during Part B/C of the study.

During the Extension of indication procedure for EoE the MAH submitted the data from 75 adolescent participants with EoE up to 1 year (exposure from Part B and Part C combined).

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

The most commonly affected system organ class (SOC) in adolescents was General disorders and administration site conditions with 33.3% (25/75 adolescent participants), while the placebo/dupilumab 300 mg QW group had the lowest incidence (20.0%). This SOC incidence was mostly driven by various injection site reaction preferred terms (PTs) including injection site reaction (17.3% of adolescent participants), injection site pain (10.7% of adolescent participants), injection site erythema (5.3% of adolescent participants), and injection site swelling (5.3% of adolescent participants). The proportion of participants with serious adverse events (SAEs) was low with 1 adolescent participant (1.3%) reporting a SAE in the dupilumab 300 mg QW/dupilumab 300 mg QW group.

CHMP comment

The results from Part B/C have already been submitted and extensively discussed during the Extension of Indication for EoE. The SmPC has been modified to address all issues that have been identified in this procedure.

For further discussion of the results see below and EoE Type II variation (EMEA/H/C/004390/II/0062 eCTD sequence 0160).

2.3.3. Discussion on clinical aspects

The study design of the Phase 3 Study R668-EE-1774 carried out as separate sequential independent parts was adequate.

Addendum 2 summarizes the complete data for the Part A/C 12-week follow-up period for Part A/C participants and updates to data reported in Part A/C CSR versus data collected through final database lock (14 Jul 2022). No new safety findings associated with dupilumab in adult and adolescent participants with EoE were identified during the follow-up period or from updates in the data. The changes to the Part A/C data are considered minor and are generally consistent with the previous findings and conclusions reported. These updates did not impact the overall conclusions regarding the efficacy or safety of dupilumab for the treatment of EoE in adult and adolescent participants as previously reported.

The results from Part C (A/C and B/C) of Study R668-EE-1774 show that the improvements in signs and symptoms of EoE in participants with substantial disease burden achieved during Part A and B were maintained or even further improved with long-term treatment through week 52. In addition, participants who switched from placebo to dupilumab 300 mg QW in Part C showed similar improvement as participant treated with dupilumab in the previous study parts. The dupilumab 300 mg QW dosing regimen is therefore considered to have meaningful benefit for patients with EoE.

In contrast, in Part B/C dupilumab 300 mg Q2W did not show improvements in clinical symptoms or health-related QoL compared with placebo, even though the magnitude of improvements in all histologic, endoscopic, and molecular endpoints of EoE were similar to those observed with the dupilumab 300 mg QW dosing regimen.

The safety of the Dupilumab 300 mg QW dosing regimen has already been evaluated in different trials. Approximately 3,000 participants have been exposed to dupilumab 300 mg QW mainly in the AD indication. No new safety signals associated with the use of dupilumab in participants with EoE were identified. The overall safety profile was consistent with that seen in multiple other indications in the dupilumab development program (AD, asthma, and CRSwNP).

The SOC with the highest incidence of TEAEs across all treatment groups was General disorders and administration site conditions. Injection site swelling and Injection site bruising met the criteria for

ADRs based on the safety pool results. Injection site reactions, including injection site swelling, are already identified ADRs for other approved indications for dupilumab. Although these TEAEs were of mild to moderate intensity, there was a high incidence especially in the adolescent participants.

The rate of Serious Adverse Events and Adverse Events leading to discontinuation was low in all treatment groups and no clear pattern was identified indicating a relationship to the study treatment.

Overall, the safety profile in adult participants is adequately evaluated and consistent with the safety profile of 300 mg QW reported in other indications. In adolescent participants, the rates of TEAEs are higher in adolescents compared to the adults and most SAEs were reported in this age group. The 300 mg QW dose of dupilumab has not been administered to adolescents outside of study R668-EE-1774.

Data from 10 adolescent participants with eosinophilic esophagitis (EoE) in Study Part A/C and 75 adolescent participants in Study Part B/C, who completed 52 weeks on dupilumab 300 mg every week (QW), were submitted. These participant numbers are considered important especially in the context of a rare disease like EoE. The data confirmed a broadly similar safety profile in adolescents with EoE to that seen in adults with EoE, even though slightly higher rates of TEAE are suggested.

3. CHMP overall conclusion and recommendation

The benefit risk of the 300mg weekly dose in adults and adolescents can be considered positive for up to 52 weeks of treatment.

The results from Part B/C have already been submitted and discussed during the EoE Type II variation (EMEA/H/C/004390/II/0062 eCTD sequence 0160). The SmPC has been modified to address issues that have been identified.

☒ Fulfilled:

No regulatory action required.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies (EoE)

Product Name: Dupixent Active substance: Dupilumab

Study title	Study number	Date of completion	Date of submission of final study report
A Phase 3, Randomized, 3-Part Study to Investigate the Efficacy and Safety of Dupilumab in Adult and Adolescent Patients with Eosinophilic Esophagitis	R668-EE-1774 Part A/C Addendum 2 and B/C	14 July 2022 (final database lock)	06 December 2022
A Phase 3, Randomized, 3-Part Study to Investigate the Efficacy and Safety of Dupilumab in Adult and Adolescent Patients with Eosinophilic Esophagitis	R668-EE-1774 Part A, B and A/C	Part A 20 May 2020 (database lock) Part B 30 Sep 2021 (database lock) Part A/C 17 Dec 2020 (database lock CSR)	01 April 2022