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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/P46/018

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	02 Dec 2024	02 Dec 2024	☐
☐	CHMP Rapporteur Assessment Report	06 Jan 2025	20 Dec 2024	☐
☐	CHMP members comments	20 Jan 2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	23 Jan 2025	n/a	☐
☒	CHMP adoption of conclusions	30 Jan 2025	30 Jan 2025	☐

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1. Introduction

On 19 November 2024, the MAH submitted a completed paediatric study for dupilumab in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Efficacy and Safety data from this study with data cut-off (17 January 2024) have been evaluated during a recent variation procedure to add children from 1-12 years with a body weight of at least 15 kg to the indication for the treatment of eosinophilic oesophagitis (EoE).

A critical expert overview has not been provided, instead reference is made to the variation procedure EMEA/H/C/004390/II/0081.

2. Scientific discussion

2.1. Information on the development program

The Study *A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Dupilumab in Pediatric Patients with Active Eosinophilic Esophagitis* (R668-EE-1877) is part of the clinical development program of dupilumab in children and adolescents with EoE.

2.2. Information on the pharmaceutical formulation used in the study

- Dupilumab 150 mg/mL: Each 2.25 mL single-use, prefilled syringe with cap delivers 300 mg of study drug (2.0 mL of a 150 mg/mL solution)
- Dupilumab 175 mg/mL: Each 1.14 mL single-use, prefilled syringe with cap delivers 200 mg of study drug (1.14 mL of a 175 mg/mL solution)
- Dupilumab 150 mg/mL: Each 0.67 mL single-use, prefilled syringe with cap delivers 100 mg study drug (0.67 mL of a 150 mg/mL solution).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final study report for:

Study number: R668-EE-1877 (**Part C**)

Study Title: *A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Dupilumab in Pediatric Patients with Active Eosinophilic Esophagitis*

Study initiation date:	01 September 2020	(first signed informed consent).
First participant's first visit in Part C:	26 October 2022	
Study completion date:	14 May 2024	(last participant last visit).

The analyses presented in the report for Part C are based on the final database lock on **10 Jul 2024**.

In addition, the MAH submitted a study report addendum for **Part B** of the study.

First participant's first visit in Part B: 02 March 2021

The analyses presented in the report for Part B are based on a data cut-off date of 15 Jun 2023 and a database lock date of 13 Jul 2023. The addendum includes additional data from 2 participants who were ongoing in Part B of the study at the time of the Part B CSR data cut-off point.

No new or updated data for the completed **Part A** have been submitted.

2.3.2. Clinical study

R668-EE-1877

A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Dupilumab in Pediatric Patients with Active Eosinophilic Esophagitis

Description

Study R668-EE-1877 was a randomized, double-blind, placebo-controlled, multicenter, 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.

Following participant completion of the treatment period of Part B, participants could enter a 12-week follow-up period or continue into Part C to receive dupilumab in an open-label extension period after if eligible. Part C was designed to assess the long-term safety of repeat doses of the higher exposure dupilumab regimen (see *Treatments*).

Methods

Study participants

The study population consisted 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 at the start of Part A. Participants entering Part C with uninterrupted participation in the study were required to have completed the week 52 assessments of Part B, including the endoscopy with biopsies.

Treatments

In **Part B**, participants received a lower or a higher exposure regimen as originally assigned in Part A.

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

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

In **Part C**, all participants received an adapted higher exposure regimen, irrespective of prior randomization, as follows:

- 200 mg Q3W SC for participants weighing ≥5 to <15 kg
- 200 mg Q2W SC for participants weighing ≥15 to <30 kg

- 300 mg Q2W SC for participants weighing ≥30 to <40 kg
- 300 mg QW SC for participants weighing ≥40 kg

Objectives and endpoints

Part B

The overall primary and secondary study objectives and the endpoints applicable to Part B of the study (ie, 36-week extended active treatment period for participants who completed Part A) are summarized below.

Study Objectives	Endpoints Applicable to Part B
Primary Objective	Secondary Endpoints
• To demonstrate the efficacy of dupilumab treatment compared with placebo in pediatric patients with active EoE based on histologic improvement meeting validated histologic criteria	• 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) • Number of sign-free days during the 14-day period preceding week 52 as measured by the PESQ-C (for patients aged ≥1 to <12 years) • Change from baseline to week 52 in the proportion of total segments within a day (night, morning, afternoon, evening) with 1 or more EoE signs as measured by PESQ-C (for patients aged ≥1 to <12 years) • Change from baseline to week 52 in the proportion of days with 1 or more EoE symptoms as measured by PESQ-P (for patients aged ≥8 to <12 years)
Secondary Objectives	
• To assess efficacy of long-term (up to 160 weeks) dupilumab treatment • To assess safety, tolerability, and immunogenicity of long-term (up to 160 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 • To evaluate the concentration-time profile of functional dupilumab in serum in this population	

Study Objectives	Endpoints Applicable to Part B
	• Number of symptom-free days during the 14-day period preceding week 52 as measured by the PESQ-P (for patients aged ≥8 to <12 years) • Change from baseline to week 52 in the proportion of total segments within a day (night, morning, afternoon, evening) with 1 or more EoE symptoms as measured by PESQ-P (for patients aged ≥8 to <12 years) • 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 • **Change from baseline in body** weight for age percentile at week 52 • Change in body mass index for age z-score from baseline to week 52 for patients ≥2 years of age • Change in weight for age z-score from baseline to week 52 • Change in weight for height z-score from baseline to week 52 • Concentrations of functional dupilumab in serum by treatment regimen at each assessment time point from baseline to end of study • Incidence of TEAEs, SAEs, treatment-emergent AESIs, and TEAEs leading to permanent discontinuation of study treatment during the 36-week extended treatment period • Incidence of treatment-emergent ADA responses and titer during the 36-week extended treatment period

Part C

The study objectives and the endpoints applicable to Part C are summarized below.

Study Objectives	Endpoints Applicable to Part C
Secondary	
• To assess efficacy of long-term (up to 160 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 safety, tolerability, and immunogenicity of long-term (up to 160 weeks) dupilumab treatment • To assess the impact of dupilumab treatment on changes in weight and growth during the extended active period and open-label extension period of the study • To evaluate the concentration-time profile of functional dupilumab in serum in this population	• Proportion of participants achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf (400×) at week 100 and week 160 • Proportion of participants achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 100 and week 160 • Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 100 and week 160 • Absolute change in mean EoE grade score from the EoE-HSS from baseline to week 100 and week 160 • Absolute change in mean EoE stage score from the EoE-HSS from baseline to week 100 and week 160 • Absolute change in EoE-EREFS from baseline to week 100 and week 160 • Proportion of participants (with food elimination diet regimens at baseline) that have a re-introduction of a previously eliminated food group by week 100 and by week 160 • Normalized Enrichment Scores (NES) for the relative change from baseline to week 100 and 160 in the EoE diagnostic panel (EDP) transcriptome signature • NES for the relative change from baseline to week 100 and week 160 in the type 2 inflammation transcriptome signature

Study Objectives	Endpoints Applicable to Part C
	• Change in total score from baseline to week 160 as measured by the PEESSv2.0-caregiver version questionnaire • Change from baseline in body weight for age percentile up to week 160 • Change in body mass index for age z-score for participants ≥2 years of age from baseline to up to week 160 • Change in weight for age z-score from baseline to up to week 160 • Change in weight for height z-score from baseline to up to week 160 • Incidence of TEAEs during the 108-week open-label extension period • Incidence of treatment-emergent SAEs during the 108-week open-label extension period • Incidence of treatment-emergent AESIs during the 108-week open-label extension period • Incidence of TEAEs leading to permanent discontinuation of study treatment during the 108-week open-label extension period • Incidence of treatment-emergent ADA responses and titer during the 108-week open-label extension period • Concentrations of functional dupilumab in serum by treatment regimen at each assessment time point from baseline to end of study
Exploratory	
• To conduct exploratory research to study EoE and dupilumab mechanism of action in pediatric patients, including predictive biomarker discovery and/or validation • To explore impact of dupilumab on global impression of change and severity of disease	• Change in GIS-patient, caregiver, and clinician version score from baseline to up to week 160/EOT • Absolute change from baseline to week 100 and week 160 in EREFS (excluding stricture) • Absolute change from baseline to week 100 and week 160 in EREFS inflammation sub-score

Study Objectives	Endpoints Applicable to Part C
	• Absolute change from baseline to week 100 and week 160 in EREFS remodeling sub-score • Percent change in weight from baseline to week 100 and week 160.

Note: There was no primary efficacy endpoint for Part C of the study. All secondary endpoints assessed in Part C were summarized with descriptive statistics based on weight group at the start of Part C. No formal statistical hypothesis testing was performed.
Abbreviations: ADA=anti-drug antibody; AESI=adverse event of special interest; EDP=EoE diagnostic panel; EoE=eosinophilic esophagitis; EoE-EREFS=Eosinophilic Esophagitis-Endoscopic Reference Score; EoE-HSS=EoE Histology Scoring System; eos/hpf =eosinophils/high-power field; GIC=Global Impression of Change; GIS=Global Impression of Severity; NES=Normalized Enrichment Score; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Sample size

The planned sample size was a total of approximately 90 patients (1:1:1 ratio, 30 patients in the higher dupilumab exposure group, 30 patients in the lower dupilumab exposure group, and 30 patients in the placebo group).

Randomisation and blinding (masking)

Randomization during Part A was stratified by weight at baseline (≥5 kg to <15 kg, ≥15 kg to <30 kg, or ≥30 kg to <60 kg). There was no additional randomization step for Part B or Part C. Part C of the study was open-label.

Statistical Methods

Secondary endpoints in Part C, up to week 160, were analyzed descriptively at given visits. For the purposes of this Part C CSR, endpoints are primarily summarized at week 100, since the number of participants with assessments at later visits was small. In Part C, descriptive analysis is presented by weight group, since all participants were on the same weight-tiered dupilumab treatment regimen (open-label treatment).

Results

Participant flow

Of the 102 participants who were randomized into Part A of the study, 98 participants (32 placebo, 29 lower exposure dupilumab, and 37 higher exposure dupilumab) entered Part B and 97 of those completed the week 52 visit in Part B. Of those, 61 participants (2 weighing ≥5 to <15 kg, 38 weighing ≥15 to <30 kg, 17 weighing ≥30 to <40 kg, and 4 weighing ≥40 kg at entry in Part C) entered Part C and are included in the current analysis.

Overall, 25 participants (14 weighing ≥15 to <30 kg and 11 weighing ≥30 to <40 kg) of the 61 who entered Part C completed the end of study visit prior to entering Part C (ie, re-entry participants) and are included in the current analysis. The median time off treatment for re-entry participants was 216 days, ranging from 112 to 445 days. The other 36 participants in the Part CSAF entered Part C directly (either after completion of the Part B treatment period or during the Part B follow-up period).

Of note, none of the participants completed the week 160 visit, as dupilumab became commercially available for pediatric participants and this was a pre-specified reason for treatment completion in the study protocol, which allowed for participants to transition to commercial dupilumab once it was

approved in the participant's country. Overall, of the 61 participants who entered Part C, 8/61 (13.1%) completed the study including Part C treatment and follow-up periods. 53/61 (86.9%) participants did not complete the study including both the Part C treatment and follow-up periods (ie, did not have a final EOS visit). Most of these participants (46/61 [75.4%]) did not complete the study because they did not agree to enter or did not complete the 12-week follow-up period, since they would be required to be off treatment in this period and the therapy was available commercially.

Baseline data

Demographics

In Part B, the majority of participants were male (76.5%), and most participants were White (82.7%) and not Hispanic or Latino (89.8%). Most participants were from the US (99.0%), with 1.0% from Canada. The mean (SD) age of participants was 7.0 (3.08) years with 33.7% of participants ≥1 to <6 years of age and 66.3% of participants ≥6 to <12 years of age. The mean (SD) weight of participants when entering Part A was 26.8 (11.09) kg with 15.3% of participants ≥5 to <15 kg, 52.0% of participants ≥15 to <30 kg, and 32.7% of participants ≥30 to <60 kg.

The mean (SD) weight of participants when entering Part A was 22.5 (7.54) kg with a mean weight of 10.7 (1.20) kg in the ≥5 to <15 kg group, 18.5 (4.10) kg in the ≥15 to <30 kg dupilumab group, 29.4 (3.43) kg in the ≥30 to <40 kg dupilumab group, and 37.3 (3.07) kg in the ≥40 kg dupilumab group.

In Part C, the majority of participants were male (47/61 [77.0%]), and most participants were White (52/61 [85.2%]) and not Hispanic or Latino (54/61 [88.5%]). Most participants were from the US (60/61 [98.4%]), with 1 participant from Canada. The mean (SD) age of participants at study entry was 6.3 (2.82) years with 24/61 (39.3%) of participants ≥1 to <6 years of age and 37/61 (60.7%) of participants ≥6 to <12 years of age.

The mean (SD) weight of participants when entering Part C was 27.2 (9.61) kg with a mean weight of 13.7 (0.42) kg in the ≥5 to <15 kg group, 21.9 (4.80) kg in the ≥15 to <30 kg dupilumab group, 35.8 (3.11) kg in the ≥30 to <40 kg dupilumab group, and 47.8 (7.53) kg in the ≥40 kg dupilumab group.

Baseline Disease Characteristics at Study Entry

At Part A baseline, mean (SD) duration of EoE overall was 3.69 (2.757) years. In most participants overall (43/61 [70.5%]), the duration of EoE was less than 5 years. The mean (SD) age at EoE onset overall was 3.3 (2.22) years.

At study entry, 8/61 (13.1%) participants had a resolved atopic/allergic condition, but all participants (61/61; 100.0%) had at least 1 active atopic/allergic condition in addition to EoE . The most frequently reported current allergic conditions were food allergy (49/61; 80.3%) and allergic rhinitis (45/61; 73.8%). Over one-half of participants (35/61; 57.4%) reported a current history of AD and 29/61; 47.5% reported a current history of asthma.

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 at the start of Part C are shortly described in the following: The mean (SD) PEESS score at Part C baseline was 21.2 (17.58), decreased from 40.0 (18.46) at Part A baseline. At Part C baseline the mean (SD) GIS-C, GIS-P, and GIS-Clin were 1.2 (0.46), 1.2 (0.43), and 1.2 (0.48), respectively. Each of these parameters decreased from Part A baseline mean (SD) GIS-C, GIS-P, and GIS-Clin values of 1.9 (0.84), 1.5 (0.66), and 2.4 (0.87). At Part C baseline, the mean (SD)

peak eosinophils count of 3 esophageal regions (proximal, mid, and distal) was 9.6 (16.40) eos/hpf, decreased from Part A baseline (75.2 [35.46] eos/hpf). The mean (SD) eosinophils count of 3 esophageal regions was 5.1 (9.02) eos/hpf, decreased from Part A baseline (57.0 [28.47] eos/hpf). The mean (SD) EoE-EREFS total score at baseline of Part C was 2.0 (2.06) points, decreased from Part A baseline (6.8 [2.37] points). At Part C baseline 24 (39.3%) participants had a blood peripheral eosinophil count ≥0.50 giga/L decreased from 37 (60.7%) at Part A baseline.

Number analysed

The **Part B** SAF is the basis for the Part B efficacy and safety analyses. All 98 participants who entered Part B were included in the SAF.

Safety and efficacy analyses for **Part C** of the study were based on the SAF. All 61 participants who entered Part C received at least 1 dose of high exposure dupilumab in Part C and were included in the Part C SAF (see Table 1 below).

Table 1 - Part C – Safety Analysis Set

Geographic Region	Date of First Consent	Date of Last Visit in Part C	Number of Participants Enrolled	Treatment Group (Part C)	Safety Analysis Set (SAF)
Total	01FEB2021	12MAR2024	61	Total	61
				>=5-<15 kg	2
				>=15-<30 kg	38
				>=30-<40 kg	17
				>=40 kg	4

Efficacy results

Part B

Additional week 52 efficacy data for 2 participants that were not available at the time of the Part B database lock (ie, peak esophageal intraepithelial eosinophil count, EoE-EREFS, and EoE-HSS stage and grade scores) are presented in the Part B study report addendum. PESQ-C data, which were collected via diaries and do not require a site visit, were missing for both participants at week 52 due to patient noncompliance (ie, <8 e-diary entries during the 14-day period).

One Participant in the placebo/higher exposure dupilumab group (for whom treatment was ongoing at the time of the database lock for the Part B CSR) and one participant in the higher exposure dupilumab/higher exposure dupilumab group (had completed study intervention but not the week 52 visit at the time of data cutoff due to health issues [non-COVID-19 infection]) had records for eosinophil count, EoE-EREFS, and EoE-HSS at week 52 added to the EDC system after the Part B database lock.

Efficacy results for the two additional participants are shown below.

Table 2 - Part C – Results for Efficacy Endpoints at Week 52 (End of Part B) (Part B SAF)

Efficacy Endpoints	Placebo/Higher Exposure Dupilumab (N=18)[b]	Participant[c,e] #840023006	Higher Exposure Dupilumab / Higher Exposure Dupilumab (N=37)[b]	Participant[d,e] #840023007
Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 52, n (%)	9/17 (52.9%)	Non-responder	22/35 (62.9%)	Non-responder
Peak esophageal intraepithelial eosinophil count (eos/hpf) at week 52, mean (SD)	17.82 (25.635) (N1=17)	72 (baseline=60)	7.09 (9.859) (N1=35)	17 (baseline=65)
Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 52, mean (SD)[a]	-76.83 (41.228) (N1=17)	20.00	-90.97 (14.482) (N1=35)	-73.85
Absolute change in EoE-EREFS from baseline to week 52, mean change (SD)[a]	-3.64 (3.342) (N1=14)	-1	-4.77 (3.081) (N1=30)	-6
Absolute change in EoE-HSS stage score from baseline to week 52, mean change (SD)[a]	-0.855 (0.3485) (N1=17)	-0.0893	-0.892 (0.3181) (N1=35)	-0.4286
Absolute change in EoE-HSS grade score from baseline to week 52, mean change (SD)[a]	-0.885 (0.2962) (N1=17)	0.0536	-0.967 (0.3920) (N1=35)	-0.3333

Abbreviations: EoE=eosinophilic esophagitis; EoE-EREFS=EoE-Endoscopic Reference Score; EoE-HSS=EoE Histology Scoring System; eos/hpf=eosinophils per high power field; N1=number of participants with observed data; PESQ-C=Pediatric EoE Sign/Symptom Questionnaire-Caregiver version; SAF=safety analysis set; SD=standard deviation.

[a] For endpoints measured by absolute or percent change, changes were calculated from study baseline (ie, start of Part A).
[b] Values from Part B CSR (Module 5.3.5.1 R668-EE-1877 Part B Table 15 and PTT 6.2.2/1B).
[c] Participant #840023006 in placebo/higher exposure dupilumab group.
[d] Participant #840023007 in higher exposure dupilumab/ higher exposure dupilumab group.
[e] PESQ-C data at week 52 were missing for both participants.

As these updates were considered minor by the sponsor and did not affect the integrity of results or study conclusions presented in the Part B CSR, the summaries of efficacy data were not re-run.

Transcriptome signature data (ie, change in NES) summarized in the Part B CSR have been updated to reflect additional Part B data from analyses conducted after the Part B data cutoff date (17 Jan 2023) until the time of the Part B addendum data cutoff date (15 Jun 2023).

Summaries of change in NES were re-run to include these additional data to ensure that the interpretation of the data did not change from the Part B database lock as presented in the Part B CSR. The updated change in NES data summaries, as well as updated heatmaps of genes included in the EDP and in the T2INF, are presented in Section 3.3.1. These updated summaries were consistent overall with the previous findings and conclusions presented in the Part B CSR.

Part C

The results from Part C show the long-term efficacy of dupilumab in pediatric participants with EoE.

Results from selected clinically relevant endpoints

Table 3 - Summary of Proportion of Patients Achieving Peak Esophageal Intraepithelial Eosinophil Count of ≤6 eos/hpf in All Three Regions During Part C (Part C SAF)

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%)
At Week 100	1/1 (100%)	17/27 (63.0%)	9/10 (90.0%)	2/3 (66.7%)	29/41 (70.7%)
Early EOT Visit [a]	0/0	5/7 (71.4%)	5/6 (83.3%)	0/1	10/14 (71.4%)

[a] Refers to the last assessment available for the participant, either from Week 160 EOT visit or ET visit, including assessments that occurred prior to Week 100 for 7 participants.
Percentage is based on the number of participants with non-missing values at each visit.
Baseline of Part C is based on the week 52 assessment.
Abbreviations: EOT=End of treatment; SAF=Safety analysis set

Table 4 - Summary of Proportion of Participants Achieving Peak Esophageal Intraepithelial Eosinophil Count of <15 eos/hpf in All Three Regions During Part C

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%)
At Week 100	1/1 (100%)	25/27 (92.6%)	10/10 (100%)	2/3 (66.7%)	38/41 (92.7%)
Early EOT Visit [a]	0/0	5/7 (71.4%)	5/6 (83.3%)	1/1 (100%)	11/14 (78.6%)

[a] Refers to the last assessment available for the participant, either from Week 160 EOT visit or ET visit, including assessments that occurred prior to Week 100 for 7 participants.
Percentage is based on the number of participants with non-missing values at each visit.
Baseline of Part C is based on the week 52 assessment.
Abbreviations: EOT=End of treatment; SAF=Safety analysis set

Table 5 - Summary of Percent Change from Part A, Part B, and Part C Baseline in Peak Esophageal Intraepithelial Eosinophil Count (eos/hpf) by Visit During Part C (Part C SAF)

		Value at Visit								Percentage Change from Baseline							
	Visit	n	Mean	SD	Min	Q1	Median	Q3	Max	n	Mean	SD	Min	Q1	Median	Q3	Max
Change from Part A Baseline																	
Total (N=61)	Part A Baseline	61	75.25	35.460	19.0	48.00	72.00	93.00	178.0								
	Part C Baseline	61	9.56	16.401	0.0	1.00	2.00	12.00	67.0	61	-87.49	20.426	-100.0	-98.86	-96.55	-88.24	3.1
	Week 100	41	4.59	6.241	0.0	1.00	2.00	7.00	25.0	41	-91.50	13.348	-100.0	-98.98	-97.22	-90.24	-45.9
	Early EOT Visit [a]	14	12.07	20.882	0.0	0.00	3.00	7.00	66.0	14	-87.65	19.249	-100.0	-100.00	-95.95	-90.32	-40.5
Change from Part B Baseline																	
Total (N=61)	Part B Baseline	60	29.97	41.960	0.0	2.00	6.00	57.50	132.0								
	Part C Baseline	61	9.56	16.401	0.0	1.00	2.00	12.00	67.0	54	-36.85	75.488	-100.0	-98.72	-65.75	0.00	200.0
	Week 100	41	4.59	6.241	0.0	1.00	2.00	7.00	25.0	35	-54.70	68.503	-100.0	-100.00	-75.00	-37.50	233.3
	Early EOT Visit [a]	14	12.07	20.882	0.0	0.00	3.00	7.00	66.0	13	-39.33	64.540	-100.0	-93.41	-58.33	0.00	100.0
Change from Part C Baseline																	
Total (N=61)	Part C Baseline	61	9.56	16.401	0.0	1.00	2.00	12.00	67.0								
	Week 100	41	4.59	6.241	0.0	1.00	2.00	7.00	25.0	34	142.22	531.802	-100.0	-76.32	-37.50	0.00	2300.0
	Early EOT Visit [a]	14	12.07	20.882	0.0	0.00	3.00	7.00	66.0	12	-26.56	65.754	-100.0	-90.63	-11.61	7.89	100.0

[a] Refers to the last assessment available for the participant; includes both participants with last assessment prior and after week 100.
Baseline of Part C is based on the week 52 assessment.
Abbreviations: EOT=End of treatment; Q1=First quartile; Q3=Third quartile; SAF=Safety analysis set; SD=Standard deviation

The results for the other endpoints (e.g. Absolute Change from Baseline in EoE-HSS Mean Grade Score at Week 100, Absolute Change from Baseline in EoE-HSS Mean Stage Score at Week 100, Change in Total Score from Baseline by Visit as Measured by the PEESSv2.0 Caregiver Version Questionnaire, Absolute Change from Baseline in EoE-EREFS (Central Reading) Total Score) show that improvements observed at Part C baseline were maintained or even slightly improved with with additional dupilumab treatment through week 100.

Furthermore, participants experienced continued increases in Body Weight for Age Percentile with additional dupilumab treatment through week 100. Overall, the mean (SD) Body Weight for Age Percentile at Part A baseline was 37.41 (27.183) points and at Part C baseline (ie, week 52), the mean body weight for age percentile (SD) was 42.26 (28.589) points; n=61. Additionally, 9 out of the 52 participants, who were on at least 1 food elimination diet regimen 9 reported having reintroduced a previously eliminated food.

Overall, the results from Part C show that the improvements in the clinically relevant endpoints observed during Part A and Part B were generally maintained or showed further improvements with longer duration of dupilumab treatment during Part C, including meaningful improvements across symptomatic, histologic, endoscopic, molecular, and observer-reported outcomes of EoE.

Safety results

Part B

Additional SAE and AESI data collected after the date cutoff date for the Part B CSR database lock are presented in the Part B addendum. In addition, new Part B safety data (eg, TEAEs, laboratory PCSVs, and vital sign PCSVs) for the 2 participants who were ongoing in Part B of the study at the time of the Part B database lock are summarized. None of the updates were clinically meaningful or changed the interpretation of the safety data. No data summaries were re-run to include the additional data.

Part C

Exposure

The number of study intervention injections during Part C is summarized below.

Table 6 - Part C – Summary of Study Intervention Administration (Injections) During Part C (Part C SAF)

Exposure Characteristics	≥5kg to <15kg (N=2)	≥15kg to <30kg (N=38)	≥30kg to <40kg (N=17)	≥40kg (N=4)	Total (N=61)
Number of study drug administered during the Part C study					
n	2	38	17	4	61
Mean (SD)	12.5 (13.44)	25.7 (4.79)	27.5 (9.53)	56.5 (9.29)	27.8 (10.55)
Median	12.5	27.5	28.0	55.0	28.0
Q1 : Q3	3.0 : 22.0	24.0 : 29.0	24.0 : 30.0	49.0 : 64.0	24.0 : 30.0
Min : Max	3 : 22	13 : 34	10 : 52	48 : 68	3 : 68
Summary of treatment duration (Days) in Part C [1]					
n	2	38	17	4	61
Mean (SD)	231.5 (238.29)	374.4 (58.02)	327.9 (87.58)	397.8 (62.47)	358.3 (79.55)
Median	231.5	392.0	336.0	386.0	374.0
Q1 : Q3	63.0 : 400.0	349.0 : 423.0	273.0 : 406.0	347.5 : 448.0	336.0 : 414.0
Min : Max	63 : 400	189 : 481	117 : 427	343 : 476	63 : 481

[1] Treatment Duration in Part C is defined as: if weight tier at the last injection is ≥5 kg to <15 kg then treatment duration = date of last study drug injection in Part C - date of first study drug injection in Part C + 21; if weight tier at the last injection is ≥15 kg to <30 kg OR ≥30 kg to <40 kg then treatment duration = date of last study drug injection in Part C - date of first study drug injection in Part C + 14; if weight tier at the last injection is ≥40 kg then treatment duration = date of last study drug injection in Part C - date of first study drug injection in Part C + 7.

The weight tiers are the initial weight tiers at the entry of Part C. If a participant gains weight during Part C, the weight tier and the corresponding dosing regimen will be adjusted, but the participant will still be summarized in the initial weight tier group at the entry of Part C.

Abbreviations: Max=maximum; Min=minimum; Q1=First quartile; Q3=Third quartile; SAF=Safety analysis set; SD=Standard deviation

Adverse events

Overview

An overview of all TEAEs reported during Part C is shown below.

Table 7 - Part C – Overall Summary of Number of Participants with Treatment-Emergent Adverse Events (TEAE) During Part C Treatment Period (Part C SAF)

	≥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%)	4 (100%)	53 (86.9%)
Any study drug related TEAE, n (%)	1 (50.0%)	7 (18.4%)	2 (11.8%)	0	10 (16.4%)
Any TEAE leading to discontinuation of study drug permanently, n (%)	0	0	0	0	0
Maximum intensity for any TEAE, n (%)					
Mild	2 (100%)	16 (42.1%)	12 (70.6%)	1 (25.0%)	31 (50.8%)
Moderate	0	17 (44.7%)	2 (11.8%)	3 (75.0%)	22 (36.1%)
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	5 (13.2%)	1 (5.9%)	0	6 (9.8%)

Abbreviations: AESI=adverse event of special interest; SAF=safety analysis set; SAE=serious adverse event; TEAE= Treatment-Emergent Adverse Events

During Part C of the study, a total of 357 TEAEs were reported in 53/61 (86.9%) participants.

The SOCs in which TEAEs were experienced by ≥20% participants overall were:

- Infections and infestations: Overall, the Infections and infestations SOC had the highest proportion of participants with TEAEs (33/61, 54.1%). The PTs with the highest incidence overall were Pharyngitis streptococcal (13/61, 21.3%) and Upper respiratory tract infection (8/61, 13.1%). Infection-related TEAEs are discussed in more detail in Section 5.2.1.7.2
- Gastrointestinal disorders (36.1%; 22/61)
- General disorders and administration site conditions (34.4%; 21/61)
- Respiratory, thoracic, and mediastinal disorders (34.4%; 21/61)
- Skin and subcutaneous tissue disorders (31.1%; 19/61)

By PT, the most frequently reported TEAEs overall (in ≥10% of the 61 participants) during Part C were Pharyngitis streptococcal (13/61, 21.3%), Upper respiratory tract infection (8/61 13.1%), Vomiting (11/61, 18.0%), Pyrexia (10/61, 16.4%), and Cough (8/61, 13.1%). All these most frequent events were assessed as nonserious and mild or moderate in severity by the investigator.

Treatment-Related Adverse Events

Overall, 10/61 (16.4%) participants had at least 1 TEAE assessed as treatment-related (causal relationship to the study intervention assessed as related by the investigator) in Part C. The most commonly reported treatment-related TEAE by PT overall was Injection site reaction (2/61 [3.3%] participants).

Treatment-Emergent Adverse Events by Severity

There were no severe TEAEs during Part C of this study.

Deaths

There were no TEAEs leading to death reported during Part C of the study.

Serious Adverse Events

A total of 4 treatment-emergent SAEs were reported in 3/61 (4.9%) participants during Part C, all were assessed as not related to dupilumab by the investigator. All SAEs resolved and none led to dupilumab discontinuation.

Table 8 - Listing of Serious TEAEs During Part C Treatment Period (Part C SAF)

Participant ID	Age/ Gender	Weight Category	System Organ Class/ Preferred Term/ Verbatim Term	(Study Day Start)/ (Study Day Stop) [a]	Relation-ship to Study Drug	Action Taken with Study Drug	Outcome	Severity	Treatment for AE	AESI
		≥15 kg to <30 kg	Infections and infestations / Perirectal abscess / Hospitalization due to perirectal abscess on left buttock	(610/247/245)/ (613/250/248)	Not related	Dose Not Changed	Recovered/ Resolved	Moderate	Drug therapy/ medication	No
			Investigations / Endoscopy gastrointestinal / Hospitalization for bowel prep for EGD, colonoscopy, and EUA tomorrow	(648/285/283)/ (649/286/284)	Not related	Dose Not Changed	Recovered/ Resolved	Mild	Drug therapy/ medication	No
		≥15 kg to <30 kg	Gastrointestinal disorders / Oesophageal food impaction / Hospitalization due to suspected food impaction	(800/428/332)/ (801/429/333)	Not related	Dose Not Changed	Recovered/ Resolved	Moderate	Drug therapy/ medication, Other	No
		≥15 kg to <30 kg	Cardiac disorders / Cardiac arrest / Cardiac asystole, requiring hospitalization for evaluation	(550/178/64)/ (554/182/68)	Not related	Dose Not Changed	Recovered/ Resolved	Moderate	Drug therapy/ medication, Other	No

Discontinuations Due to Adverse Events

There were no participants who experienced a TEAE leading to permanent withdrawal of study intervention during Part C of the study.

Adverse Events of Special Interest

Prespecified 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

Overall, 6 participants (6/61, 9.8%) reported an event that was captured by the AESI search criteria during Part C of the stud. All AESIs were non-serious and did not result in dupilumab discontinuation. 3 AESIs (2 events of Arthralgia in 1 participant and 1 event of Helminthic infection in 1 participant) were considered to be related to dupilumab by the investigator, while the remainder were considered not related. There were no reports of Keratitis. An AE of Astigmatism was identified by the Sponsor as per the AESI search criteria for Keratitis (which is based on the Narrow SMQ for 'Corneal disorders'); this event of Astigmatism was not reported as an AESI of Keratitis by the investigator.

Other Significant Adverse Events

Injection Site Reactions

Overall, 11/61 (18.0%) participants had injection site reactions (per HLT) during Part C. None of the injection site reactions were judged to be serious or led to permanent discontinuation of study intervention. All injection site reactions were assessed as mild in intensity, with no severe events reported, and all resolved. Within the HLT Injection site reaction, the most commonly reported PT overall during Part C was Injection site reaction (in 8.2% overall) followed by Injection site pain (in 4.9% overall).

Infections, Including Adverse Events Related to COVID-19

In the SOC of Infections and infestations, the incidence of TEAEs was 33/61 (54.1%) participants overall.

All infection-related TEAEs were assessed as mild or moderate in intensity; none were assessed as severe . None led to permanent discontinuation of study intervention. There was 1 SAE reported in the SOC of Infections and infestations: Perirectal abscess (verbatim term “hospitalization due to perirectal abscess on left buttock”). The event was considered not related to dupilumab by the investigator, was reported as resolved, and resulted in no change to the dupilumab dose.

The most frequently reported HLTs (≥10%) were Upper respiratory tract infections in 16/61 (26.2%) participants, Streptococcal infections in 13/61 (21.3%) participants, Viral infections NEC in 11/61 (18.0%) participants, and Ear infections in 7/61 (11.5%) participants.

The most commonly reported PTs in the SOC of Infections and infestations overall were pharyngitis streptococcal in 13/61 (21.3%) participants; Upper respiratory tract infection in 8/61 (13.1%) participants; and Gastroenteritis viral, Ear infection, and COVID-19 in 5/61 (8.2%) participants each.

Five participants (5/61; 8.2%) reported a TEAE of COVID-19, none of which were serious and which were all mild or moderate in intensity. None of the COVID-19 TEAEs led to study drug discontinuation. All COVID-19 TEAEs resolved and apart from 1 participant with helminthic infection (1/61; 1.6%), all other TEAEs were assessed as not related to study intervention by the investigator. See narrative in Section 8 for more information on the participant with helminthic infection.

Immunogenicity

Anti-Dupilumab Antibody Analysis in Part C

All samples collected in Study R668-EE-1877 Part C were negative for ADA. One participant with pre-existing immunoreactivity at baseline in Part A was negative for ADA at the week 100 visit.

2.3.3. Discussion on clinical aspects

The applicant submitted the final CSR for Part C of study R668-EE-1877, a randomized, double-Blind, placebo-controlled study to investigate the efficacy and safety of dupilumab in pediatric patients with active eosinophilic esophagitis (EoE) together with a CSR addendum for Part B of the study.

The study population consisted 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 at the start of Part A. Of the 102 participants who were randomized into Part A of the study, 98 participants entered Part B. Of those, 61 participants (2 weighing ≥5 to <15 kg, 38 weighing ≥15 to <30 kg, 17 weighing ≥30 to <40 kg, and 4 weighing ≥40 kg at entry in Part C) entered Part C.

Efficacy and Safety data for Part A, B and C have been recently submitted and reviewed as part of the approved variation procedure EMEA/H/C/004390/II/0081 to add children from 1-12 years with a body weight of at least 15 kg to the EoE indication. Data included in the final report for Part C are based on the final database lock on 10 July 2024 (17 January 2024 during II-81). Additional efficacy and safety data from 2 participants who were ongoing in Part B at the time of the II-81 procedure are included in the Part B addendum.

Efficacy

With the Part B Addendum additional week 52 efficacy data for 2 participants were submitted. These updates were considered minor by the sponsor. It can be agreed that these data did not affect the integrity of results or study conclusions presented in the Part B CSR.

The results from Part C submitted show that the improvements in the clinically relevant endpoints (e.g. the proportion of participants achieving a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf, the proportion of participants achieving a peak esophageal intraepithelial eosinophil count <15 eos/hpf, percent reduction in peak esophageal intraepithelial eosinophil count, EoE-HSS Mean Grade Score, EoE-HSS Mean Stage Score, Absolute Change from Baseline in EoE-HSS Mean Grade Score at Week 100, Absolute Change from Baseline in EoE-HSS Mean Stage Score at Week 100, Change in Total Score from Baseline by Visit as Measured by the PEESSv2.0 Caregiver Version Questionnaire, Absolute Change from Baseline in EoE-EREFS (Central Reading) Total Score etc.) observed during Part A and Part B were generally maintained or showed further improvements with longer duration of dupilumab treatment during Part C, including meaningful improvements across histologic, endoscopic, symptomatic, molecular, and observer-reported outcomes of EoE.

Safety

The updated safety data for Part B (eg. TEAEs, laboratory PCSVs, and vital sign PCSVs) for 2 participants do not change the interpretation of the safety data as previously evaluated (see II-81 procedure).

During Part C, most participants (53/61; 86.9%) reported at least 1 TEAE. All TEAEs were of mild or moderate intensity. No participants experienced severe TEAEs, TEAEs leading to dupilumab discontinuation, or leading to death. A total of 4 treatment-emergent SAEs were reported in 3/61 (4.9%) participants (Cardiac arrest, Oesophageal food impaction, Perirectal abscess, and Endoscopy gastrointestinal). All SAEs were assessed by the investigator as not related to dupilumab which is agreed and in line with the previous assessment within the II-81 procedure.

The Infections and infestations SOC had the highest proportion of participants with TEAEs (33/61, 54.1%); no severe events or events leading to discontinuation of study intervention were reported in this SOC. The most frequently reported TEAEs (by PT) (in =10% of participants overall) were Pharyngitis streptococcal (13/61, 21.3%), Upper respiratory tract infection (8/61, 13.1%), Vomiting (11/61, 18.0%), Pyrexia (10/61, 16.4%), and Cough (8/61, 13.1%). Five participants (5/61; 8.2%) reported a TEAE of COVID-19, none of which were serious and which were all mild or moderate in intensity. None of the COVID-19 TEAEs led to study drug discontinuation.

Overall, 11/61 (18.0%) participants had injection site reactions (per HLT) during Part C. None of the injection site reactions were judged to be serious or led to permanent discontinuation of study intervention. All injection site reactions were assessed as mild in intensity, with no severe events reported, and all resolved. All samples collected in Part C were negative for ADAs.

Overall, the updated safety data of Part C as now provided based on the final data base lock 10 July 2024 do not change the interpretation of the safety data for paediatric participants with EoE as previously concluded during EMEA/H/C/004390/II/0081.

3. Rapporteur’s overall conclusion and recommendation

The submitted updated efficacy and safety data for paediatric participants with EoE are consistent with data reviewed as part of the recent variation procedure EMEA/H/C/004390/II/0081. No amendment of the product information is warranted.

☒ Fulfilled:

No regulatory action required.