16 October 2025
EMADOC-1700519818-2346978
Human Medicines Division

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

Dupixent

Dupilumab

Procedure no: EMA/PAM/0000291086

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**
☐	CHMP Rapporteur AR	22 September 2025	23 September 2025
☐	CHMP comments	6 October 2025	n/a
☐	Updated CHMP Rapporteur AR	9 October 2025	n/a
☒	CHMP outcome	16 October 2025	16 October 2025

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1. Introduction

On 29 July 2025, the MAH submitted a completed paediatric study for Dupixent, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study EFC16724 [A randomized double-blind placebo-controlled parallel group study assessing the efficacy and safety of dupilumab in patients with Allergic Fungal Rhinosinusitis (AFRS)] is a standalone study. Furthermore, it is not part of a paediatric investigation plan.

2.2. Information on the pharmaceutical formulation used in the study

Table 1. Investigational medicinal product(s) administered

Intervention label	Dupilumab	Placebo
Intervention name	Dupilumab	Placebo
Intervention description	200 mg or 300 mg	0 mg
Type	Drug	Other
Dose formulation	Dupilumab 200 mg: A 175 mg/mL dupilumab solution in a pre-filled syringe to deliver 200 mg in 1.14 mL or Dupilumab 300 mg: A 150 mg/mL dupilumab solution in a pre-filled syringe to deliver 300 mg in 2 mL	Placebo matching dupilumab 200 mg, supplied as an identical formulation to the active 200 mg formulation without dupilumab, in a pre-filled syringe to deliver placebo in 1.14 mL or Placebo matching dupilumab 300 mg, supplied as an identical formulation to the active 300 mg formulation without dupilumab, in a pre-filled syringe to deliver placebo in 2 mL
Unit dose strengths	200 mg or 300 mg	0 mg
Dosage levels	One injection of 200 mg q2w for adolescents/children ≥30 kg and <60 kg at screening or One injection of 300 mg q2w for all adults and for adolescents/children weighing ≥60 kg at screening or One injection of 300 mg q4w for adolescents/children ≥15 kg and <30 kg at screening	One injection of placebo matching 200 mg q2w for adolescents/children ≥30 kg and <60 kg at screening or One injection of placebo matching 300 mg q2w for all adult participants and for adolescents/children weighing ≥60 kg at screening or One injection of placebo matching 300 mg q4w for adolescents/children ≥15 kg and <30 kg at screening
Route of administration	Subcutaneous injection	Subcutaneous injection
Use	Experimental	Experimental
Packaging and labeling	Each dose of dupilumab was supplied as 1 glass pre-filled syringe packed in a participant kit box. Both glass pre-filled syringe and box were labeled as required per country requirement	Each dose of placebo was supplied as 1 glass pre-filled syringe packed in a participant kit box. Both glass pre-filled syringe and box were labeled as required per country requirement
Current name	Dupilumab	N/A

Abbreviations: N/A = not applicable; Q2W = every 2 weeks; Q4W = every 4 weeks

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- EFC16724: A randomized double-blind placebo-controlled parallel group study assessing the efficacy and safety of dupilumab in patients with Allergic Fungal Rhinosinusitis (AFRS)

2.3.2. Clinical study

EFC16724: A randomized double-blind placebo-controlled parallel group study assessing the efficacy and safety of dupilumab in patients with Allergic Fungal Rhinosinusitis (AFRS)

Description

Study EFC16724 was a randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of dupilumab in the treatment of Allergic fungal rhinosinusitis (AFRS) in adults, adolescents and children aged 6 years and older.

The study period per participant included a screening period of 2 to 4 weeks, a randomized IMP intervention period of 52 weeks ±3 days, and a post-intervention follow-up period of 12 weeks ±5 days.

AFRS is rare, it is seen most commonly in warm, humid environments where the inciting fungi thrive. AFRS appears to be very rare in Europe as evidenced by the paucity of published literature from Europe. Study EFC16724 was not conducted as part of an approved European Paediatric Investigation Plan (PIP) for the treatment of AFRS with dupilumab. No PIP or PIP waiver application was submitted to EMA as it is not currently the intention of the dupilumab MAH to seek an indication for the treatment of AFRS for patients of any age in the EU.

Methods

Study participants

Treatments

The IMPs were dupilumab and placebo, both supplied in pre-filled syringes. Dupilumab was administered as an SC injection with a dose regimen tailored to the participant's weight. The placebo was formulated to match the active dupilumab formulation without the active ingredient. Also refer to Section 2.2. above.

Objectives / Endpoints

The primary and secondary objectives and endpoints are shown below.

Table 2. Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of treatment with dupilumab to reduce sinus opacification in a population with allergic fungal rhinosinusitis (AFRS)	• Change from baseline in sinus opacifications assessed by computerized tomography (CT) scans using the Lund Mackay (LMK) score at Week 52
Secondary	
• To evaluate the efficacy of treatment with dupilumab to reduce sinus opacification in a population with allergic fungal rhinosinusitis (AFRS) at Week 24	• Change from baseline in sinus opacifications assessed by CT scans using the LMK score at Week 24
• To assess the efficacy of dupilumab to reduce the need for rescue treatments	• Proportion of participants who receive SCS and/or undergo/plan to undergo surgery for AFRS during the planned study intervention period
• To evaluate the efficacy of treatment with dupilumab in improving symptoms in AFRS	• Change from baseline in monthly average nasal congestion/obstruction score from the Nasal Symptom Diary at Week 24 and Week 52 • Change from baseline in the monthly average anterior/posterior rhinorrhea score from the Nasal Symptom Diary at Week 24 and Week 52
• To evaluate the efficacy of dupilumab to reduce nasal polyp formation in participants with AFRS	• Change from baseline in endoscopic nasal polyp score (NPS) compared with placebo at Week 24 and Week 52
• To evaluate the efficacy of dupilumab in improving overall symptom severity and quality of life in AFRS	• Change from baseline in 22-item sino-nasal outcome test (SNOT-22) total score at Week 24 and Week 52 • Change from baseline in monthly average total symptom score (TSS) derived from the Nasal Symptom Diary at Week 24 and Week 52 • Change from baseline in visual analog scale (VAS) rhinosinusitis at Week 24 and Week 52
• To evaluate the efficacy of dupilumab in improving sense of smell in participants with AFRS	• Change from baseline in University of Pennsylvania smell identification test (UPSIT) at Week 24 and Week 52 • Change from baseline in the score of decreased/loss of smell using the Nasal Symptom Diary at Week 24 and Week 52
• To explore the effect of dupilumab as assessed by three-Dimensional CT volumetric measurement of the paranasal sinuses	• Change from baseline to Week 52 in three-Dimensional CT volumetric measurement of the paranasal sinuses
• To evaluate the safety and tolerability of dupilumab when administered to participants with AFRS	• Incidence of treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs) through Week 52
• To evaluate the PK of dupilumab in participants with AFRS	• Dupilumab concentration in serum over time
• To characterize the effect of dupilumab on total IgE and specific IgE	• Percent change from baseline in total IgE in serum compared with placebo over the 52-week treatment period • Percent change from baseline in fungal-specific IgE in serum compared with placebo over the 52-week treatment period
• To assess immunogenicity to dupilumab in participants with AFRS	• Assessment of incidence of treatment-emergent anti-drug antibodies (ADA) to dupilumab over time

Sample size

Due to severe recruitment challenges attributed to the COVID-19 pandemic, the Sponsor reduced the sample size of the study from 120 participants to 62 participants and updated the primary endpoint from the proportion of subjects who undergo or plan to receive rescue therapy (SCS and/or surgery) to an objective endpoint that was not impacted by the pandemic dynamics and was clinically relevant, namely change from baseline in sinus opacifications assessed by CT scans using the LMK score at Week 52.

Randomisation and blinding (masking)

All participants were centrally assigned to randomized study intervention using an IRT. Randomization was stratified first by age (adults versus adolescents/children [≥6 years old]). In adults, randomization was stratified further by time from last surgery (≤2 years [including surgery naive participants], >2 years), disease pattern (unilateral/bilateral in the endoscopy at screening), and country. In adolescents/children ≥6 years of age, randomization was not stratified further.

Dupilumab 300 mg/200 mg and matching placebo matching dupilumab 300 mg/200 mg were provided in identically matched 2 mL/1.14 mL pre-filled syringes that are visually indistinguishable for each dose. With regard to the treatment with either dupilumab or placebo, they were not blinded to weight-based dose levels, due to the different volume size (2 mL versus 1.14 mL). The study was not blinded to dose regimen due to the different frequency of IMP administration (q4w versus q2w).

Statistical Methods

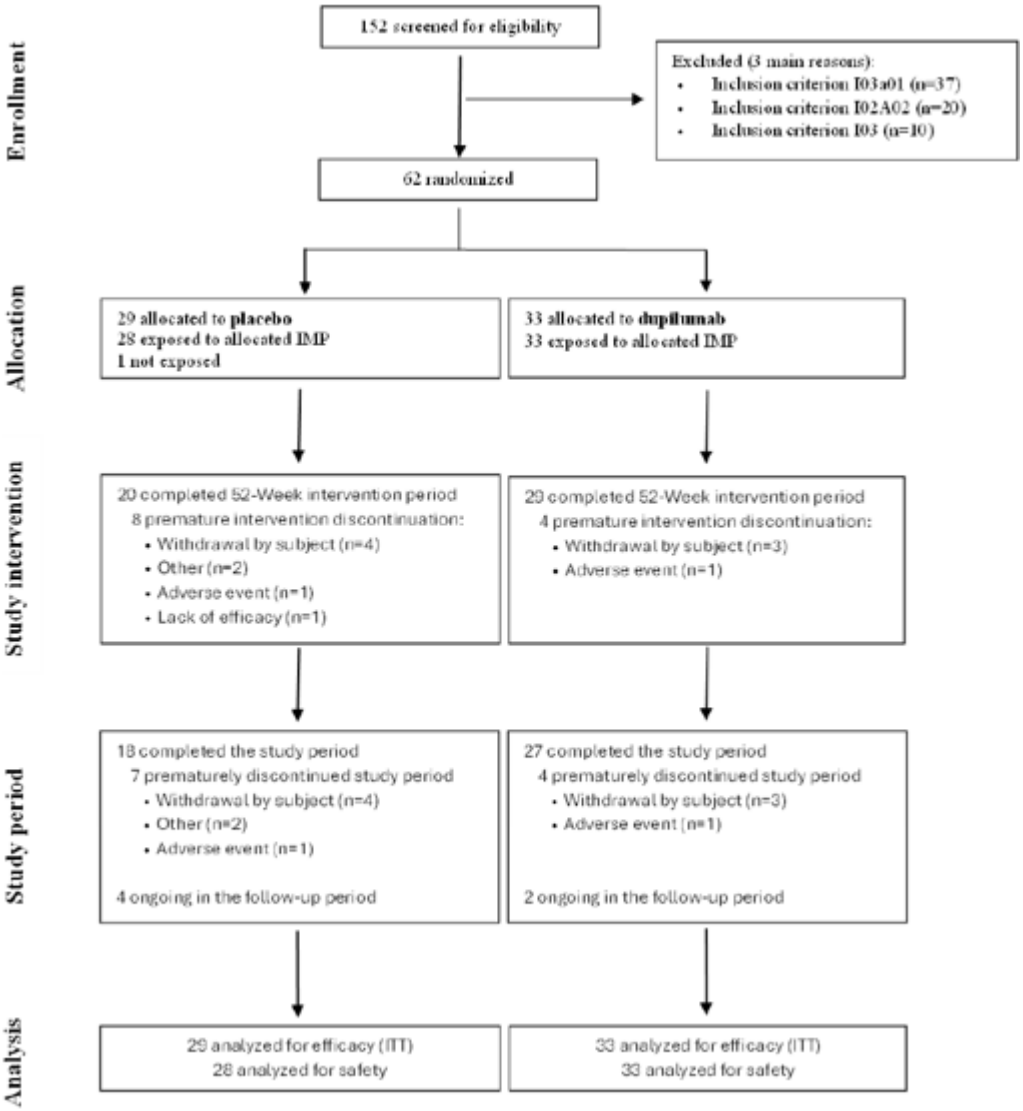
The planned analyses, comparisons, statistical tests, and determination of sample size are described in the final version of the SAP and contained in the study protocol. Given the very low number of patients in the paediatric population, only descriptive analyses can be made for this age group.

Results

Participant flow

The patient disposition for the total study population including adults and children is shown below.

Figure 1. Participant disposition



Of the paediatric participants 4 out of 6 completed the study. One adolescent on placebo terminated the study 11 weeks and 2 days after randomization due to the participant moving far from the location of the study site. In addition, 1 child on placebo permanently discontinued study intervention at Week 38 due to issues with IMP supply logistics, and did not complete the post-intervention follow-up period. There were no safety concerns driving premature end of study in either of these participants.

Recruitment

The study was conducted in the United States, Canada, China, Turkey, India, Japan, Saudi Arabia, Israel as well as in Argentina from 21 May 2021 (first participant first visit) to 07 March 2025 (last participant last visit).

Baseline data

Demographics

The mean (SD) age of the randomized population was 39.8 (16.0) years. One (1.6%) child aged 6 to 11 years and 5 (8.1%) adolescents aged 12 to 17 years were randomized while the majority of patients (56; 90.3%) were adults. A total of 45 (72.6%) male and 17 (27.4%) female participants were included in the study, most of them were White (27 [43.5%]) or Asian (25 [40.3%]); 8 (12.9%) were Black or African American. There were no paediatric participants with body weight <30 kg, so no dosing regimen of 300 mg q4w was administered.

Baseline characteristics for paediatric patients are shown below.

Table 3. Demographics and participant characteristics at baseline in children and adolescents - Randomized population

	Placebo (N=3)	Dupilumab (N=3)	All (N=6)
Age (years)			
Number	3	3	6
Mean (SD)	12.7 (3.5)	15.3 (0.6)	14.0 (2.7)
Median	13.0	15.0	15.0
Q1 ; Q3	9.0 ; 16.0	15.0 ; 16.0	13.0 ; 16.0
Min ; Max	9 ; 16	15 ; 16	9 ; 16
Age group [n (%)]			
Number	3	3	6
Children (6-11 years)	1 (33.3)	0	1 (16.7)
Adolescents (12-17 years)	2 (66.7)	3 (100)	5 (83.3)
Sex [n (%)]			
Number	3	3	6
Male	3 (100)	3 (100)	6 (100)
Female	0	0	0
Race [n (%)]			
Number	3	3	6
White	1 (33.3)	1 (33.3)	2 (33.3)
Black or African American	1 (33.3)	1 (33.3)	2 (33.3)
Asian	1 (33.3)	1 (33.3)	2 (33.3)
Japanese	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	0	0	0
Not reported	0	0	0
Unknown	0	0	0

	Placebo (N=3)	Dupilumab (N=3)	All (N=6)
Ethnicity [n (%)]			
Number	3	3	6
Hispanic or Latino	0	1 (33.3)	1 (16.7)
Not Hispanic or Latino	3 (100)	2 (66.7)	5 (83.3)
Not reported	0	0	0
Unknown	0	0	0
Region [n (%)]			
Number	3	3	6
Americas[a]	2 (66.7)	3 (100)	5 (83.3)
Asia[b]	1 (33.3)	0	1 (16.7)
Baseline Weight (kg)			
Number	3	3	6
Mean (SD)	61.53 (30.75)	67.17 (15.00)	64.35 (21.86)
Median	58.00	64.00	61.00
Q1 ; Q3	32.70 ; 93.90	54.00 ; 83.50	54.00 ; 83.50
Min ; Max	32.7 ; 93.9	54.0 ; 83.5	32.7 ; 93.9
Baseline Weight by category (kg) [n (%)]			
Number	3	3	6
<70	2 (66.7)	2 (66.7)	4 (66.7)
70 to <90	0	1 (33.3)	1 (16.7)
≥90	1 (33.3)	0	1 (16.7)
Baseline Weight by category (kg) [n (%)]			
Number	3	3	6
≥60	1 (33.3)	2 (66.7)	3 (50.0)
≥30 to <60	2 (66.7)	1 (33.3)	3 (50.0)
≥15 to <30	0	0	0
Baseline BMI (kg/m^2)			
Number	3	3	6
Mean (SD)	23.21 (9.93)	21.17 (5.06)	22.19 (7.14)
Median	19.38	20.20	19.79
Q1 ; Q3	15.77 ; 34.49	16.67 ; 26.65	16.67 ; 26.65
Min ; Max	15.8 ; 34.5	16.7 ; 26.7	15.8 ; 34.5
Baseline BMI by category (kg/m^2) [n (%)]			
Number	3	3	6
<27	2 (66.7)	3 (100)	5 (83.3)
≥27	1 (33.3)	0	1 (16.7)

BMI: Body mass index

[a] Americas: Argentina, USA, Canada [b] Asia: China, Japan, India, Turkey, Saudi Arabia

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Number analysed

The number of paediatric patients enrolled was very small with 3 patients in placebo and 3 patients in active arm.

Efficacy results

In the paediatric population at Week 52, the mean (SD) change from baseline in LMK scores was -8.67 (4.04) in the dupilumab group and 1.50 (7.78) in the placebo group.

In 2 adolescents from the dupilumab group, the individual change from baseline in NPS at Week 52 was -4 and -1, and in 1 adolescent from the dupilumab group the individual change from baseline in NPS at Week 36 was -5 (the last available measurement during treatment period). These results were, overall, comparable to the data obtained during the 52-week treatment period. In 2 adolescents from the placebo group with available Week 52 data, the change from baseline in NPS was 0 and -3.

At Week 52, change from baseline in nasal congestion/obstruction score was -1.26, -2.93 and 0 in the 3 adolescents from the dupilumab group. In the placebo group, a single adolescent participant had Week 52 data available showing the change from baseline in nasal congestion/obstruction score of -0.24.

At Week 52, change from baseline in TSS was -4.42, -0.07, and -8.62 in the 3 adolescents from the dupilumab group. In the placebo group, a single adolescent participant had Week 52 data available showing the change from baseline in TSS of 1.31.

Safety results

In the dupilumab group, 32 out of 33 participants received dupilumab 300 mg q2w, including 2 adolescents (with body weight ≥60 kg at screening). In addition, 1 adolescent with body weight <60 kg at screening received dupilumab 200 mg q2w. There were no paediatric participants with body weight <30 kg, so no dosing regimen of 300 mg q4w was administered.

Table 4. Overview of adverse event profile: Treatment emergent adverse events – Safety population

n (%)	Placebo (N=28)	Dupilumab (N=33)
Participants with any TEAE	22 (78.6)	23 (69.7)
Participants with any severe TEAE	1 (3.6)	1 (3.0)
Participants with any treatment emergent SAE	2 (7.1)	0
Participants with any TEAE leading to death	0	0
Participants with any TEAE leading to permanent intervention discontinuation	1 (3.6)	1 (3.0)
Participants with any treatment emergent AESI	0	0
Participants with any treatment emergent other selected AE	2 (7.1)	4 (12.1)
Participants with any treatment-related TEAE	3 (10.7)	9 (27.3)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event, AESI: Adverse event of special interest
n (%) = number and percentage of participants with at least one TEAE
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Overall, 2 out of 3 paediatric participants in the dupilumab group and 1 out of 3 paediatric participants in the placebo group experienced at least 1 TEAE. All the TEAEs were mild or moderate.

TEAEs by primary SOC and PT for the paediatric participants by the cut-off date for the main CSR are shown in the Table 5 below. Until the cut-off 07 March 2025, there were no new TEAEs reported in paediatric participants in either treatment group. Overall, the number of paediatric participants with reported TEAEs was low across treatment groups with no patterns or trends identified.

- One adolescent participant in the dupilumab group had moderate Allergic fungal rhinosinusitis (worsening) during the treatment-emergent period. The study intervention was not discontinued. The participant recovered from the event without corrective treatment. This event was assessed as not related to the IMP by the Investigator.
- One adolescent participant in the dupilumab group had moderate Influenza during the treatment-emergent period. The study intervention was not discontinued. The participant received corrective treatment and recovered from the event. This participant also had mild post-treatment AEs of Accident and Joint dislocation. None of the AEs were assessed as related to the IMP by the Investigator.
- One adolescent participant in the placebo group had mild TEAEs of COVID-19, Cough, and Allergic fungal rhinosinusitis (worsening) during the treatment-emergent period. The study intervention was not discontinued. The participant received corrective treatments and recovered from the events. None of the AEs were assessed as related to the IMP by the Investigator.

Table 5. Number (%) of participants with TEAE(s) by primary SOC and PT - Paediatric Safety population

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Placebo (N=3)	Dupilumab (N=3)
Any event	1 (33.3)	2 (66.7)
INFECTIONS AND INFESTATIONS	1 (33.3)	1 (33.3)
Influenza	0	1 (33.3)
COVID-19	1 (33.3)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (33.3)	1 (33.3)
Allergic fungal rhinosinusitis	1 (33.3)	1 (33.3)
Cough	1 (33.3)	0

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term
MedDRA 27.1
n (%) = number and percentage of participants with at least one TEAE
Note: Table sorted by SOC internationally agreed order and by decreasing frequency of PT in dupilumab group
PGM=PRODOPS/SAR231893/EFC16724/CSR/REPORT/PGM/ae_socpt_s_t.sas OUT=REPORT/OUTPUT/ae_socpt_ps_t_i.rtf (20FEB2025 7:15)

Immunogenicity

Positive ADA responses were observed during the on-treatment period in 2 (9.1%) participants in the dupilumab group and 0 (0%) participants in the placebo group.

2.3.3. Discussion on clinical aspects

The applicant submitted efficacy and safety data from study EFC16724, a randomized, double-blind, placebo-controlled, phase 3 study to evaluate the efficacy and safety of dupilumab in the treatment of Allergic fungal rhinosinusitis (AFRS). The study included adults, adolescents and children ≥ 6 years. Participants were treated for 52 weeks with dupilumab or placebo followed-up for 12 weeks.

The primary endpoint was the change from baseline in sinus opacifications assessed by CT scans using the LMK score at Week 52. Secondary endpoints included changes from baseline in sinus opacifications at Week 24, improvement in symptoms, nasal polyp presence and characteristics, overall symptom severity, quality of life, sense of smell, and three-dimensional CT volumetric measurement of the paranasal sinuses. Safety, tolerability, pharmacokinetics, pharmacodynamics, immunogenicity of dupilumab were also evaluated.

The study mainly enrolled adult participants (90.3%) while a total of 6 participants in the age range of 6 to 17 years included were included of whom 3 received dupilumab. Two adolescents with body weight ≥60 kg received dupilumab 300 mg q2w; one adolescent with body weight <60 kg at screening received dupilumab 200 mg q2w. There were no paediatric participants with body weight <30 kg, so no dosing regimen of 300 mg q4w was administered. Of the paediatric participants 4 out of 6 completed the study. The limited number of paediatric patients only allows a descriptive evaluation of efficacy and safety data.

The study met the primary endpoint (evaluated for the total study population) as seen by a reduction in sinus opacification as measured by the LMK score at Week 52 (difference versus placebo in change from baseline in LMK score of -7.36). Similar results were seen for the small paediatric population included (change from baseline in LMK: dupilumab -8.67; placebo: 1.50) with similar trends of efficacy also for the secondary endpoints.

In the total study population, 69.7% participants in the dupilumab group and 78.6% participants in the placebo group experienced at least one TEAE. There was one severe TEAE in the dupilumab group and one in the placebo group, respectively. All three SAE reported occurred in the placebo group. There were no AESIs during the study. In the paediatric population, 2 out of 3 participants in the dupilumab group and 1 out of 3 paediatric participants in the placebo group experienced at least 1 TEAE. These events included 2 events of worsening of AFRS disease and one event of influenza. These events were all mild or moderate. No paediatric participants discontinued treatment for safety-related reasons.

The safety results obtained in study EFC16724 are consistent with the known safety profile of dupilumab. No new safety findings were identified in this study. No amendments of the product information were introduced by the applicant which is supported.

3. Rapporteur's overall conclusion and recommendation

The applicant submitted efficacy and safety data from study EFC16724, a phase 3 clinical study designed and conducted to investigate the efficacy and safety profile of dupilumab in adults, adolescents and children ≥6 years with AFRS. A total of 6 paediatric participants were enrolled. The study met its primary endpoint with similar results seen for patients 6 to 17 years included. The collected safety data are consistent with the known safety profile of dupilumab. It is agreed with the MAH that no amendment of the product information is warranted.

☒ **Fulfilled:**

No regulatory action required.