11 December 2025
EMADOC-1700519818-2798394
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/0000301728

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	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	CHMP Rapporteur AR	17 November 2025	17 November 2025	☐
☐	CHMP comments	1 December 2025	n/a	☐
☐	Updated CHMP Rapporteur AR	4 December 2025	n/a	☐
☒	CHMP outcome	11 December 2025	11 December 2025	☐

Table of contents

1. Introduction

On 18 September 2025, the MAH submitted a completed paediatric substudy 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 substudy in LTS14424/EXCURSION is a stand-alone study.

The MAH stated that substudy in LTS14424 is part of a clinical development program for Japan.

2.2. Information on the pharmaceutical formulation used in the study

A 150 mg/mL dupilumab solution in a pre-filled syringe to deliver 100 mg in 0.67 mL.

A 175 mg/mL dupilumab solution in a pre-filled syringe to deliver 200 mg in 1.14 mL.

A 150 mg/mL dupilumab solution in a pre-filled syringe to deliver 300 mg in 2 mL.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Substudy in LTS14424/EXCURSION

2.3.2. Clinical study

Substudy in LTS14424/EXCURSION: One year study to evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study (Japan substudy)

Description

The LTS14424 Japan substudy was a multicenter, open-label, single arm, 1-year treatment study evaluating dupilumab given subcutaneously (SC) for a period of 52 weeks among pediatric participants with asthma in Japan aged 6 to <12 years. Pediatric participants 6 to <12 years of age, with a physician diagnosis of persistent asthma for ≥12 months prior to screening based on clinical history and examination, and pulmonary function parameters according to GINA 2015 Guidelines were enrolled in the study. Participants with chronic lung diseases that could impair lung function, other than asthma were excluded from the study. The dose regimens were tiered by body weight: 200 mg q2w for participants with body weight >30 kg, and 100 mg q2w or 300 mg q4w (randomized in a 1:1 ratio) for participants with body weight ≥15 kg and ≤30 kg. The total planned duration of participation in LTS14424 Japan substudy was approximately 68 weeks for each participant. The substudy was divided in 3 periods: screening period (4 ± 1 weeks); treatment period (52 weeks); and post-treatment period (12 weeks).

The primary endpoint of substudy was the change from baseline in pre-bronchodilator percent predicted forced expiratory volume in 1 second (FEV1) at Week 12. Participants were randomized to

dupilumab (200 mg q2w, 100 mg q2w or 300 mg q4w [using a 1:1 ratio]), the same weight-tiered dose regimens of dupilumab which have demonstrated efficacy with an acceptable safety profile in EFC14153/VOYAGE study. The 52-week treatment period and 12-week follow-up period allowed adequate assessment of efficacy and safety over time.

Methods

Study participants

Pediatric participants 6 to <12 years of age, with a physician diagnosis of persistent asthma for ≥12 months prior to screening based on clinical history and examination, and pulmonary function parameters according to GINA 2015 Guidelines were enrolled in the study. Participants with chronic lung diseases that could impair lung function, other than asthma were excluded from the Study.

Treatments

The study interventions and study arms are outlined in Table 1.

Table 1. Investigational medicinal product(s) administered

Intervention label	Dupilumab 100 mg	Dupilumab 200 mg	Dupilumab 300 mg
Intervention name	Dupilumab 100 mg	Dupilumab 200 mg	Dupilumab 300 mg
Intervention description	A 150 mg/mL dupilumab solution in a pre-filled syringe to deliver 100 mg in 0.67 mL	A 175 mg/mL dupilumab solution in a pre-filled syringe to deliver 200 mg in 1.14 mL	A 150 mg/mL dupilumab solution in a pre-filled syringe to deliver 300 mg in 2 mL
Type	Biological/Vaccine	Biological/Vaccine	Biological/Vaccine
Dose formulation	Pre-filled syringe	Pre-filled syringe	Pre-filled syringe
Unit dose strength(s)	100 mg	200 mg	300 mg
Dosage level(s)	100 mg every 14±3 days q2w for participants with body weight ≥15 kg and ≤30 kg	200 mg every 14±3 days q2w for participants with body weight > 30 kg	300 mg every 28±3 days q4w for participants with body weight ≥15 kg and ≤30 kg
Route of administration	Subcutaneous	Subcutaneous	Subcutaneous
Use	Experimental	Experimental	Experimental
Packaging and labeling	Dupilumab was supplied as glass prefilled syringes packed in a participant kit box. Each glass prefilled syringe and the participant kit box was labeled as required per country requirements	Dupilumab was supplied as glass prefilled syringes packed in a participant kit box. Each glass prefilled syringe and the participant kit box was labeled as required per country requirements	Dupilumab was supplied as glass prefilled syringes packed in a participant kit box. Each glass prefilled syringe and the participant kit box was labeled as required per country requirements
[Current/Former name(s) or alias(es)]	Dupixent®	Dupixent®	Dupixent®

Objective(s)

The objectives and endpoints are included in Table 2.

Table 2. Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of dupilumab in children of 6 to <12 years of age with uncontrolled persistent asthma in the Japan substudy	• Change from baseline in pre-bronchodilator percentage (%) predicted FEV_1 at Week 12
Secondary	
• To evaluate the safety and tolerability of dupilumab in pediatric participants with asthma in the Japan substudy	• Safety: - The number (n) and percentage (%) of participants experiencing any treatment-emergent adverse events (TEAEs). • Efficacy: - Annualized rate of severe asthma exacerbation events, during the treatment period. - Change from baseline in pre-bronchodilator % predicted FEV_1 at Weeks 2, 4, 8, 24, 52, and 64. - Change from baseline in other lung function measurements (absolute FEV_1, FVC, FEF 25-75%) at Weeks 2, 4, 8, 12, 24, 52, and 64. - Change from baseline at Week 2, 4, 8, 12, 24, 36, 52, and 64 in ACQ-IA.
• To evaluate dupilumab in pediatric participants with asthma in the Japan substudy with regard to: - Systemic exposure, - Anti-drug antibodies (ADAs) - Biomarkers	• Dupilumab systemic exposure and immunogenicity - Serum dupilumab concentration - ADAs • Biomarkers - Serum: Total immunoglobulin E (IgE) - FeNO

Outcomes/endpoints

See Table 2 above.

Sample size

The primary objective of this substudy is to evaluate the efficacy of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma. Assuming the change from baseline in pre-bronchodilator % predicted FEV1 at Week 12 among the study participants follows a normal distribution with mean of 10.74% and standard deviation of 14.12%, a sample size of 16 will lead to a half-width of the 95% confidence interval being 7.5%. A minimum of 3 participants assigned to treatment in each of the 3 dose regimens is targeted.

Randomisation and blinding (masking)

N/A

Statistical Methods

The planned analyses and determination of sample size are described in the final version of the SAP There were no changes in the planned analyses for LTS14424 Japan substudy and contained in the protocol.

Results

Participant disposition

A total of 13 participants (3 in the dupilumab 100 mg q2w group, 3 in the dupilumab 300 mg q4w group, and 7 in the dupilumab 200 mg q2w group) were enrolled in this study and received open-label study treatment with dupilumab. All 13 (100%) participants had completed the study treatment period. At the cutoff date (07 January 2025) of this report, in total, 8 (61.5%) participants (2 [66.7%] in the dupilumab 100 mg q2w group, 3 [100%] in the dupilumab 300 mg q4w group, and 3 [42.9%] in the dupilumab 200 mg q2w group) have completed the study period, and 1 (7.7%) participant in the dupilumab 200 mg q2w group did not complete the study period (but completed the study treatment period) due to being started on dupilumab as treatment by the investigator. The remaining 4 participants were ongoing in the follow-up period at time of cutoff. No participant discontinued the study intervention.

Recruitment

This substudy was conducted from 25 July 2022 (first participant enrollment) through 01 April 2025 (last participant last visit), in 7 centers in Japan.

Baseline data

Demographics

Demographics and participant characteristics at baseline for participants enrolled in this study are provided in Table 3. The mean (SD) age of the enrolled population was 9.69 (1.11) years (range: 8.0 to 11.0 years), with 2 (15.4%) participants in 6 to 8 years age group and 11 (84.6%) participants in 9 to 11 years age group. Nine (69.2%) participants were males, and 4 (30.8%) participants were females. The median body weight was 31.40 kg (range: 24.9 to 54.7 kg), with 6 (46.2%) participants in the ≥15 to ≤30 kg weight group, and 7 (53.8%) participants in the >30 kg weight group.

Table 3. Demographics and participant characteristics at baseline – Enrolled population

	Dupilumab 100mg q2w (N=3)	Dupilumab 300mg q4w (N=3)	Dupilumab 200mg q2w (N=7)	All (N=13)
Age (years)				
Number	3	3	7	13
Mean (SD)	8.67 (0.58)	9.33 (1.53)	10.29 (0.76)	9.69 (1.11)
Median	9.00	9.00	10.00	10.00
Q1 ; Q3	8.00 ; 9.00	8.00 ; 11.00	10.00 ; 11.00	9.00 ; 11.00
Min ; Max	8.0 ; 9.0	8.0 ; 11.0	9.0 ; 11.0	8.0 ; 11.0
Age group [n (%)]				
Number	3	3	7	13
From 6 - 8 years	1 (33.3)	1 (33.3)	0	2 (15.4)
From 9 - 11 years	2 (66.7)	2 (66.7)	7 (100)	11 (84.6)
Sex [n (%)]				
Number	3	3	7	13
Male	3 (100)	3 (100)	3 (42.9)	9 (69.2)
Female	0	0	4 (57.1)	4 (30.8)
Baseline height (cm)				
Number	3	3	7	13
Mean (SD)	129.67 (5.86)	128.33 (6.66)	144.71 (5.44)	137.46 (9.73)
Median	132.00	130.00	143.00	138.00
Q1 ; Q3	123.00 ; 134.00	121.00 ; 134.00	142.00 ; 150.00	132.00 ; 143.00
Min ; Max	123.0 ; 134.0	121.0 ; 134.0	138.0 ; 154.0	121.0 ; 154.0
Baseline weight (kg)				
Number	3	3	7	13
Mean (SD)	27.57 (2.41)	26.83 (1.45)	39.87 (7.97)	34.02 (8.74)
Median	28.20	26.10	37.30	31.40
Q1 ; Q3	24.90 ; 29.60	25.90 ; 28.50	35.40 ; 46.50	28.20 ; 37.30
Min ; Max	24.9 ; 29.6	25.9 ; 28.5	31.4 ; 54.7	24.9 ; 54.7 ¶
Baseline weight by category (kg) [n (%)]				
Number	3	3	7	13
≥15 to ≤30	3 (100)	3 (100)	0	6 (46.2)
>30	0	0	7 (100)	7 (53.8)
Baseline BMI (kg/m^2)				
Number	3	3	7	13
Mean (SD)	16.47 (2.17)	16.44 (2.67)	18.91 (2.51)	17.78 (2.59)
Median	16.48	15.44	18.75	17.56
Q1 ; Q3	14.29 ; 18.64	14.42 ; 19.47	17.36 ; 20.67	15.44 ; 19.47
Min ; Max	14.3 ; 18.6	14.4 ; 19.5	15.4 ; 23.1	14.3 ; 23.1
Baseline BMI by category (kg/m^2) [n (%)]				
Number	3	3	7	13
<20	3 (100)	3 (100)	5 (71.4)	11 (84.6)
≥20	0	0	2 (28.6)	2 (15.4)

BMI: Body mass index
PGM=PRODOPS/SAR231893/LTS14424/CSR_JP2/REPORT/PGM/dem_demo_r_t.sas OUT=REPORT/OUTPUT/dem_demo_r_t_i.rtf (25MAR2025 9:59)

Number analysed

The number of paediatric patients enrolled was low with overall 13 study participants. 3 participants each were assigned to the dupilumab 100mg Q2W and the dupilumab 3300 mg Q4W groups, and 7 participants were included in the dupilumab 200 mg Q2W treatment group.

Efficacy results

Dupilumab led to improvement in lung function compared to baseline. Overall, there was a mean improvement from baseline of +7.08% in pre-bronchodilator percent predicted FEV1 at Week 12. Improvement in pre-bronchodilator percent predicted FEV1 from baseline was rapid, noted as early as Week 2 and then sustained up to 52 weeks (+6.73%), and upon discontinuation of the study drug, showed a loss of response in the improvement in pre-bronchodilator percent predicted FEV1 from baseline to Week 64 (+1.17%) in the ITT populations.

- Pre-bronchodilator percent predicted FEV1: the mean pre-bronchodilator percent predicted FEV1 was 87.00% at the baseline, improved to 94.08% at Week 12, with a mean change from baseline of +7.08% at Week 12. Improvement in mean pre-bronchodilator percent predicted

FEV1 was observed in all treatment groups, and the mean changes from baseline at Week 12 were +7.33%, +6.00%, and +7.43% in the dupilumab 100 mg q2w group (N=3), the dupilumab 300 mg q4w group (N=3), and the dupilumab 200 mg q2w group (N=7), respectively.

- Subgroup analyses: in the ITT population,
    - Based on the ICS dose, a consistent improvement in pre-bronchodilator percent predicted FEV1 at Week 12 was observed (the mean [SD] change in the medium ICS dose subgroup was 7.20% [7.58] and in the high ICS dose subgroup was 6.67% [4.04], respectively).
    - Based on participants with baseline FeNO, improvement in pre-bronchodilator percent predicted FEV1 at Week 12 was also observed in participants with baseline FeNO≥20 ppb (N=8) and participants with baseline FeNO <20 ppb (N=5). The mean (SD) change in participants with baseline FeNO ≥20 ppb was 9.38% (7.29) and 3.40% (4.16) for participants with baseline FeNO <20 ppb.
- Severe asthma exacerbation rate: at baseline, the mean (SD) number of asthma exacerbations in previous year prior to Visit 1 was 1.54 (0.88) (median: 1.00, range: 1.0 to 4.0). Treatment with dupilumab resulted in a low unadjusted annualized rate of severe asthma exacerbations of 0.462 during the 52-week study treatment period. Ten (76.9%) participants had no severe asthma exacerbations (over a cumulative exposure of 13.0 participant-years to dupilumab treatment). Three (23.1%) participants with at least 1 event of severe asthma exacerbation. Two (15.4%) participants had events that required hospitalization or emergency room visit (unadjusted annualized severe exacerbation event rate was 0.308).
- FEV1 (L): There was a rapid improvement in pre-bronchodilator FEV1 from baseline to Week 2 (mean [SD] change of 0.13 [0.15] L) and showed improvement over time up to 52 weeks. There was a slight loss in pre-bronchodilator FEV1 improvement from 0.34 (0.21)◦L observed at Week 52 to 0.25 (0.14) L at the end of study follow-up period at Week 64.
    - There was also improvement across other measures of lung function including FVC and FEF 25-75%. A rapid increase in pre-bronchodilator FVC (L) and FEF 25-75% (L/s) was observed from baseline to Week 2. An improvement was observed over time for percent predicted FVC up to Week 64 and for percent predicted FEF 25-75% up to Week 52 with a slight decrease at Week 64.
- ACQ-IA:
    - The mean (SD) ACQ-5-IA score was 2.08 (0.65) at baseline. The improvement in mean ACQ-5-IA score was observed over time, the mean (SD) change from baseline was -1.20 (0.84) at Week 12 and -1.49 (0.54) at Week 52, and -1.28 (0.59) at the end of study follow-up period at Week 64.
    - mean (SD) ACQ-7-IA score was 1.85 (0.48) at baseline. The mean (SD) change from baseline was -1.03 (0.66) at Week 12 and -1.21 (0.37) at Week 52, and -0.99 (0.52) at the end of study follow-up period at Week 64.

Overall, dupilumab led to improvement in lung function compared to baseline.

Safety results

EXPOSURE

Overall, the cumulative exposure to study intervention was 13.0 participant-years. The mean (SD) duration of treatment was 364.8 (1.1) days. All (100%) participants received dupilumab at their respective doses for >48 weeks and 9 (69.2%) participants received continued treatment for >52 weeks.

In LTS14424 Japan substudy, dupilumab was well tolerated with no new safety concerns identified in 6 to <12 years old Japanese participants with uncontrolled moderate to severe asthma. Overall, a total of 13 participants (100%) experienced at least 1 TEAE during the study. Treatment-emergent AEs considered as related to the study intervention were reported in 4 (30.8%) participants. The majority of TEAEs in the study were mild to moderate in intensity. No participants had a TEAE that led to permanent study treatment discontinuation or death. Treatment-emergent AEs by PT of COVID-19, which were not considered as related to the study intervention by the Investigator were reported in 2 (15.4%) participants. These TEAEs were of mild intensity and resolved. The most frequently reported TEAE by primary SOC was infections and infestations (13 [100%] participants). The most frequently reported TEAEs by overall PT were influenza (6 [46.2%] participants) and pyrexia (6 [46.2%] participants). The most frequently reported TEAE considered as related to the study intervention by the Investigator at PT level was pyrexia (2 [15.4%] participants).

Treatment-emergent SAEs were reported in 4 (30.8%) participants which were not considered as related to the study intervention (PTs: asthma [2 participants], bronchitis, influenza [1 participant, each]). All treatment-emergent SAEs were resolved. Treatment-emergent AESIs were reported in 2 (15.4%) participants which were not considered as related to the study intervention by the Investigator (PTs: bronchitis, influenza [1 participant, each]). All treatment-emergent AESIs were resolved. Injection site reaction AE grouping was reported in 2 (15.4%) participants (PT: injection site erythema and injection site induration [1 participant, each]). All reported injection site reactions were of mild intensity and resolved. Eosinophilia was reported in 1 (7.7%) participant, the event was transient and with no associated clinical symptoms.

2.3.3. Discussion on clinical aspects

The MAH submitted data collected in a Japan substudy conducted over one year to evaluate the long-term safety and tolerability of dupilumab in paediatric patients with asthma who participated in a previous dupilumab asthma clinical study. In the study, 13 paediatric participants were enrolled and treated from 25 July 2022 until 7 January 2025. Study LTS14424 was originally designed without participation of Japanese patients, therefore a substudy was added later. The dossier includes results from until end-of-treatment visit at week 52; the remaining data collected until end-of-study at week 68 will be presented in an addendum to the clinical overview at a later time point. Due to difficult enrolment, it was prematurely terminated in January 2024.

Paediatric participants were 6 to <12 years of age, with a physician diagnosis of persistent asthma for ≥12 months prior to screening based on clinical history and examination, and pulmonary function parameters according to GINA 2015 Guidelines. Participants were treated according to the label. In addition, second controller medication for combined use with ICS included LABA, LTRA, LAMA, or methyxanthines.

A total of 13 participants (3 in the dupilumab 100 mg q2w group, 3 in the dupilumab 300 mg q4w group, and 7 in the dupilumab 200 mg q2w group) were enrolled in this study and received open-label treatment with dupilumab. All participants had completed the study treatment period. The primary

objective of the substudy was to evaluate efficacy of dupilumab in this population and the primary endpoint of substudy was the change from baseline in pre-bronchodilator percent predicted FEV1 at week 12. Dupilumab led to improvement of lung function compared to baseline up to week 52 in all three treatment groups.

The safety results obtained in study LTS14424 are also 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.

The study population is very limited. As far as assessable, the substudy results seem to be consistent with those observed in the paediatric population with uncontrolled severe asthma.

3. Rapporteur's overall conclusion and recommendation

The applicant submitted efficacy and safety data from substudy LTS14424, a phase 3 clinical open-label study designed and conducted to investigate the long-term safety and tolerability of dupilumab in Japanese paediatric patients with asthma. A total of 13 paediatric participants were enrolled. The collected safety data are consistent with the known safety profile of dupilumab. No amendment of the product information is warranted.

☒ **Fulfilled:**

No regulatory action required.