10 November 2022
EMA/824354/2022
Committee for Medicinal Products for Human Use (CHMP)

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/P46/007

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	12/09/2022	12/09/2022	☐
☐	CHMP Rapporteur Assessment Report	17/10/2022	12/10/2022	☐
☐	CHMP members comments	28/10/2022	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	03/11/2022	n/a	☐
☒	CHMP adoption of conclusions:	10/11/2022	10/11/2022	☐

Abbreviations

AD:	Atopic dermatitis
AE:	Adverse event
AESI:	Adverse event of special interest
BMI:	Body mass index
CRSwNP:	Chronic rhinosinusitis with nasal polyposis
CSR:	Clinical study report
EC:	European Commission
EMA:	European medicines Agency
EU:	European Union
GCP:	Good Clinical Practice
ICS:	Inhaled corticosteroids
LABA:	Long-acting beta adrenoceptor agonist
LTRA:	Leukotriene receptor antagonist
MAH:	Marketing Authorization Holder
NSAID:	Nonsteroidal anti-inflammatory drug
OCS:	Oral corticosetroids
PIP:	Pediatric investigational plan
PY:	Patient-years
Q2W:	Every 2 weeks
SAE:	Serious adverse event
SC:	Subcutaneous(ly)
SD:	Standard deviation
SOC:	System organ class
TEAE:	Treatment-emergent adverse event

Table of contents

1. Introduction

On 26 August 2022, the MAH submitted a completed paediatric study for study LPS15023, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of a post-authorisation measure (PAM).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study LPS15023, an open-label, interventional, cohort study to evaluate long-term safety of dupilumab in adult and adolescent patients with moderate-to-severe asthma who completed the TRAVERSE-LTS12551 clinical trial, is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Each prefilled syringe contained 2 mL of dupilumab at the concentration of 150 mg/mL to deliver 300 mg.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study number: LPS15023
Study title: Open-label, interventional, cohort study to evaluate long-term safety of dupilumab in patients with moderate-to-severe asthma who completed the TRAVERSE-LTS12551 clinical trial
Study dates: First patient enrolled: 30 August 2018, last patient completed: 18 February 2022

2.3.2. Clinical study

LPS15023 / Open-label, interventional, cohort study to evaluate long-term safety of dupilumab in patients with moderate-to-severe asthma who completed the TRAVERSE-LTS12551 clinical trial

Description

Study LPS15023 was a Phase 3b study, open-label, interventional, prospective, multinational, multicenter, noncomparative, single-arm, safety study in adult and adolescent (12 to <18 years of age) patients with moderate-to-severe asthma who completed the parent study LTS12551 (TRAVERSE). The LTS12551 parent study was part of the PIP, whereas the LPS15023 study was not. The parent study, LTS12551, was a multinational, multicenter, single-arm, open-label study that evaluated the long-term safety and tolerability of dupilumab 300 mg every 2 weeks (Q2W) added on standard of care background controller therapy in adult and adolescent patients with asthma who had participated in previous dupilumab asthma studies (DRI12544, PDY14192, EFC13579, or EFC13691).

Study LPS15023 was conducted from 30 August 2018 (first patient enrolled) through 18 February 2022 (last patient last visit), in 123 centers in Argentina, Belgium, Canada, France, Germany, Israel, Japan, Netherlands, South Africa, and USA. The study enrolled 393 patients.
The LPS15023 study used as a basis for clinical data presented in this dossier was conducted in compliance with GCP, as required by the ICH E6 Guideline for Good Clinical Practice. The study also met the requirements of the Declaration of Helsinki, standard operating procedures for clinical investigations and documentation of the Sponsor, applicable national laws and regulations and the ethical principles of the Directive 2001/20/EC.

Methods

Study participants

The LPS15023 study population consisted of patients with asthma who completed the treatment period in LTS12551. Patients were on background dose of medium or high dose ICS, as maintained during LTS12551, in combination with a second controller and/or oral corticosteroids for those patients from the original parent study EFC13691. Patients requiring a third controller medication (e.g., LABA, LTRA, methylxanthines) were allowed.

Treatments

This study evaluated the long-term safety of dupilumab with a dosing regimen of 300 mg Q2W administered subcutaneously (SC) until its approval for use in asthma and market availability to the patient, or for a maximum of 144 weeks after the start of treatment (Visit 1), whichever came first.

Patients who had discontinued dupilumab for at least 6 weeks after completion of LTS12551 study were to receive a loading dose (2 injections of 300 mg) at the time of the first injection in the LPS15023 study.

Objective(s)

The primary objective of the LPS15023 study was to assess the long-term safety of dupilumab 300 mg Q2W administered SC over a maximum of 144 weeks from the start of the study, in the treatment of patients with moderate-to-severe asthma who completed the parent study.

Outcomes/endpoints

The safety of dupilumab was evaluated based on the assessment of AEs, SAEs, and AESIs.

The primary safety endpoint was the incidence rate of TEAEs (percentage of patients reporting any TEAEs), and the event rate (number of TEAE events per 100 PY).

Secondary endpoints were AESI incidence rates and event rates, SAE and death incidence rates, and incidence rates for TEAEs leading to study discontinuation.

Sample size

No formal sample size determination was conducted. The objective of the study was to continue to evaluate the long-term safety and tolerability of dupilumab in patients with asthma who participated in the previous long-term study TRAVERSE. Therefore, all qualifying patients from participating countries who completed the treatment period in TRAVERSE were offered to enroll in this study.

Randomisation and blinding (masking)

This was an open-label study.

Statistical Methods

Continuous data was summarized using the number of available data (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical and ordinal data was summarized using the number and percentage of patients. For categorical variables, patients with missing data were not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data was presented. For purposes of analysis the following 2 populations are defined:

Enrolled population
The enrolled population was defined as the set of all patients who signed the ICF and had a treatment kit number allocated and recorded in IRT database, regardless of whether the treatment kit was used or not. The enrolled population was be used to summarize demographics and baseline characteristics.

Safety population
The primary analysis population was the safety population, defined as all patients who received at least one dose or part of a dose of dupilumab during this study. The treatment-emergent period was defined as the time from the first dose of dupilumab during LPS15023 until the last dose of dupilumab plus 2 weeks for completers, or plus 12 weeks for prematurely discontinued patients.
The primary and secondary analyses are safety related. All safety analyses were performed on the safety population. The primary focus of adverse event reporting was on TEAEs. Treatment-emergent AE was defined as any AE with onset on or after the first dose of dupilumab, until the last dose of dupilumab plus 14 days for completers, or plus 12 weeks for prematurely discontinued patients.
If an AE date/time of onset (occurrence, worsening, or becoming serious) was incomplete, an imputation algorithm was used to classify the AE as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset was conservative and classified an AE as treatment-emergent unless there was definitive information to determine it was pre-treatment or post-treatment.
Adverse event incidence tables (including TEAEs, treatment-emergent SAEs and TEAEs leading to treatment discontinuation) were presented by System Organ Class (SOC), High-level Group Term (HLGT), and Preferred Term (PT), sorted in alphabetical order, the number and percentage of patients experiencing an AE. Multiple occurrences of the same event in the same patient were counted only once in the tables within a treatment phase. The denominator for computation of percentages was the safety population.

Primary safety analysis
The primary endpoint was analyzed through the incidence rates (defined as the percentage of patients reporting any TEAEs), and event rates (defined as the number of TEAE events per 100 PY).
Incidence rates of TEAEs with corresponding 95% confidence interval (CI, by the Clopper-Pearson method) were calculated as follows:
• Incidence Rate = number of patients with at least one TEAE / number of patients at risk (i.e., safety population) × 100
• Event rate = number of TEAEs/number of patient-years at follow-up
Event rates per 100 person-years of TEAEs with corresponding 95% CI (two-sided exact Poisson CIs) were calculated. All events reported during the study follow-up period were counted, regardless of whether they are reported in the same patient (ie, multiple events per patients), or different patients.
The person-years at follow-up were calculated using the standard on-treatment duration formula:
• Date of last IMP – date of first dose of IMP + 14 days) / 365.25

Secondary safety analysis

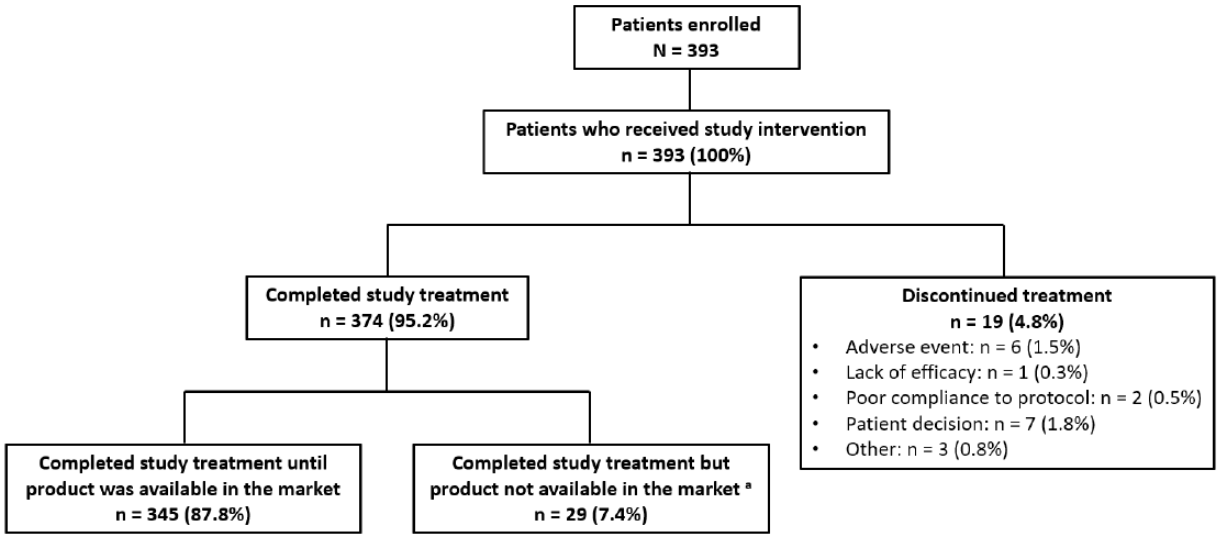
The secondary endpoints were analyzed through incidence rates and event rates per 100 person-years for AESIs over the study, incidence rates for SAEs/death over the study, and incidence rates for AEs leading to study discontinuation over the study. Incidence rates with corresponding 95% CI (Clopper-Pearson method) and event rates with corresponding 95% CI (exact Poisson method) were presented for AESIs, using the same methodology used for the analysis of the primary safety endpoints. Incidence rates with corresponding 95% CI (Clopper-Pearson method) were presented for SAEs/death and for AEs leading to study discontinuation over the study period.

Results

Participant flow

A total of 393 patients with moderate-to-severe asthma were enrolled into the LPS15023 study and treated with dupilumab 300 mg Q2W. Of the 393 enrolled patients, 8/393 (2.0%) were adolescents (aged 12 to <18 years). 374/393 (95.2%) patients completed the study treatment, and 19/393 (4.8%) patients discontinued treatment. All 8 adolescent patients completed the study treatment.

Figure 1 Disposition of Patients in Study According to Study Treatment Category



n = the number of patients meeting the criterion; N = the number of patients in the analysis set

[a] Confirmed by treatment exposure duration ≥ 143 weeks.
Percentages were calculated using the number of patients enrolled as denominator.
Additional information can be seen in Listing 2 and Listing 17.
Source: Table 1.a. Patient Disposition According to Study Treatment Category. Section 14.1.1.

Recruitment

LPS15023 was conducted from 30 August 2018 (first patient first visit) through 18 February 2022 (last patient last visit), at 123 centers in 10 countries (Argentina, Belgium, Canada, France, Germany, Israel, Japan, Netherlands, South Africa, USA).

For all patients, there was a period between completion of LTS12551 and initiation of LPS15023, ranging from 13 days (1.86 weeks) to 1324 days (189.14 weeks). In addition, the duration of the study was variable, and patients were able to discontinue the study at the time of market availability of dupilumab in their respective countries.

Baseline data

All patients were diagnosed by a physician with asthma that was present for ≥12 months, based on the Global Initiative for Asthma (GINA) guidelines in effect at the time of the parent study initiation. Patients enrolled from Studies DRI12544, EFC13579, and PDY14192 had moderate-to-severe asthma, while those from Study EFC13691 were severe OCS-dependent asthma patients.

Demographic characteristics

Demographic characteristics for all patients in the enrolled population are summarized in Table 1. Among the 393 patients enrolled, 8/393 (2.0%) were adolescent patients (aged 12 to <18 years). The mean age was 52.1 years. More females than males were included (58.8% and 42.2%). The mean (SD) weight at baseline was 78.82 (19.59) kg.

Overall, 136/393 (38.5%) patients had a body mass index ≥30 (kg/m2) at baseline and 45/393 (12.5%) patients weighed ≥100 kg. 54/393 (13.7%) patients enrolled within 4 weeks after ending the parent study.

Table 1 Patient Demographics and Other Baseline Characteristics (Enrolled Population)

	Total (N = 393) n (%)
Age (years)	
Number	393
Mean (SD)	52.1 (14.19)
Median	54.0
Q1; Q3	43.0; 62.0
Min; Max	14; 81
Age group, n (%)	
Number	393
<18 years	8 (2.0)
≥18 to <65 years	306 (77.9)
≥65 to <75 years	64 (16.3)
≥75 to <85years	15 (3.8)
≥85 years	0

Gender, n (%)	
Number	393
Male	162 (41.2)
Female	231 (58.8)
Baseline weight (kg)	
Number	360
Mean (SD)	78.82 (19.593)
Median	76.25
Q1; Q3	64.1; 90.0
Min; Max	39.5; 165.0
Baseline weight by category, n (%)	
Number	360
<50 kg	10 (2.8)
≥50 to <100 kg	305 (84.7)
≥100 kg	45 (12.5)
Baseline BMI (kg/m^2)	
Number	353
Mean (SD)	29.09 (6.359)
Median	28.70
Q1; Q3	24.7; 32.3
Min; Max	15.0; 49.8
Baseline BMI by category, n (%)	
Number	353
<18.5 (kg/m^2)	6 (1.7)
≥18 to <25 (kg/m^2)	93 (26.3)
≥25 to <30 (kg/m^2)	118 (33.4)
≥30 (kg/m^2)	136 (38.5)
Patients enrolled within 4 weeks after ending parent study, n (%)	
Number	393
Yes	54 (13.7)
No	339 (86.3)
Pregnancy test results, n (%)	
Number	69
Positive	0
Negative	69 (100)

BMI = body mass index; max = maximum; min = minimum; n = the number of patients meeting the criterion; N = the number of patients in the analysis set; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.
Source: Table 2. Demographics and patient characteristics at baseline - Enrolled population. Section 14.1.2.

Treatment Compliance

Overall, 392 patients complied with study treatment, of which 391/393 (99.7%) patients complied with ≥80% of study treatment. Most patients had no under-planned doses during study treatment. An under-planned dose happened when the actual dose administered was smaller than the intended dose, or when there was no dose administration.

Table 2 Summary of Study Intervention Compliance (Safety Population)

	Total (N = 393)
Overall compliance, n (%)	
Number	392
Patients with <40%	0
Patients with ≥40 to <60%	0
Patients with ≥60 to <80%	1 (0.3)
Patients with >80%	391 (99.7)
Patients with <80%	1 (0.3)
Number of patients with at least 1 above-planned dosing, n (%)	1 (0.3)
Under-planned dosing, n (%)	
Number	392
Patients with no under-planned dosing	290 (74.0)
Patients with >0 to <20%	100 (25.5)
Patients with ≥20%	2 (0.5)

n = the number of patients meeting the criterion; N = the number of patients in the analysis set
Note: Percentage of compliance for a patient was defined as 100 x (the number of administrations the patient was compliar with, divided by the total number of administrations the patient was to take during the treatment period).
Source: Table 7. Treatment compliance - Safety population. Section 14.2.1.

Number analysed

Safety data from the 393 patients exposed to dupilumab 300 mg Q2W in the LPS15023 study are presented in the dossier. The safety population considered for safety analyses was the population who actually received at least one dose or part of a dose of dupilumab in the LPS15023 study.

Pharmacokinetic / Pharmacodynamic results

PK/PD was not evaluated in the LPS15023 study.

Efficacy results

Efficacy was not evaluated in the LPS15023 study.

Safety results

Extent of Exposure

All 393 patients who entered the study received 300 mg dupilumab Q2W. The overall cumulative exposure to dupilumab was 431.7 PY. The median study treatment duration in the safety population

was of 309 days (range: 25 to 1047 days). Overall exposure to dupilumab in the safety population is presented in Table 3.

Table 3 Exposure to Study Intervention (Safety Population)

	Overall (N = 393)
Cumulative exposure (PY) [a]	431.7
Duration of study treatment (days)	
Number	392
Mean (SD)	402.3 (309.33)
Median	309.0
Q1; Q3	112.0; 672.0
Min; Max	25; 1047
Duration of study treatment by category, n (%)	
Missing duration	1 (0.3)
>0-4 days	0
>4-12 days	0
>12-24 days	0
>24-48 days	8 (2.0)
>48-72 days	19 (4.8)
>72-96 days	17 (4.3)
>96-120 days	62 (15.8)
>120-142 days	47 (12.0)
>142-190 days	38 (9.7)
>190-238 days	3 (0.8)
>238-286 days	1 (0.3)
>286-382 days	5 (1.3)
>382-478 days	13 (3.3)
>478-574 days	22 (5.6)
>574-670 days	36 (9.2)
>670-766 days	90 (22.9)
>766-862 days	2 (0.5)
>862-958 days	0
>958 days	29 (7.4)
Cumulative duration of study treatment by category, n (%)	
Number	392 (99.7)
>0 days	392 (99.7)
>4 days	392 (99.7)
>12 days	392 (99.7)
>24 days	392 (99.7)

	Overall (N = 393)
>48 days	384 (97.7)
>72 days	365 (92.9)
>96 days	348 (88.5)
>120 days	286 (72.8)
>142 days	239 (60.8)
>190 days	201 (51.1)
>238 days	198 (50.4)
>286 days	197 (50.1)
>382 days	192 (48.9)
>478 days	179 (45.5)
>574 days	157 (39.9)
>670 days	121 (30.8)
>766 days	31 (7.9)
>862 days	29 (7.4)
>958 days	29 (7.4)
Number of doses, n (%) [b]	
1-4	8 (2.0)
5-8	83 (21.1)
9-14	101 (25.7)
15-26	8 (2.0)
27-38	31 (7.9)
39-50	111 (28.2)
51-62	21 (5.3)
63-74	29 (7.4)

Max = maximum; Min = minimum; N = the number of patients in the analysis set PY = person-year; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.
[a] Sum of all patients' exposure in person-years.
[b] Loading dose was counted as 2 doses for patients who discontinued treatment ≥6 weeks after the parent study TRAVERSE.
Source: Table 6. Extent of exposure to investigational medicinal product - Safety population. Section 14.2.1.

Adverse Events

Adolescent population

Of the 8 adolescents who participated in the study, 2/8 (25.0%) experienced at least 1 TEAE, none of which was serious or led to permanent treatment discontinuation (Table 4). No AESIs were reported in the adolescent population.

The reported TEAEs in the adolescent population were erythema (reported as "redness of the ear") in one patient and 2 events of injection site induration in another patient (Table 5); all 3 events were assessed as related to the IMP by the investigator. All events were mild and resolved without corrective treatment.

Table 4 Overview of adverse event profile: Treatment emergent adverse events – Safety population – Adolescents (12-17 years)

	Overall (N=8) n(%)	Number of Events	Exposure Adjusted Event Rate (per 100 person- years)[a]
Patients with at least 1 TEAE	2(25.0)	3	35.0
Patients with at least 1 AESI	0	0	0
Patients with at least 1 treatment emergent SAE	0	0	0
Patients with at least 1 TEAE leading to death	0	0	0
Patients with at least 1 AE or SAE (regardless of treatment emergent status) leading to death	0	0	0
Patients with at least 1 TEAE leading to definitive treatment discontinuation	0	0	0
Patients with at least 1 TEAE leading to study discontinuation	0	0	0
Patients with at least 1 treatment-related TEAE	2(25.0)	3	35.0

TEAE: Treatment emergent adverse event, AESI: Adverse events of special interest, SAE: Serious adverse event.
n (%) = number and percentage of patients with at least one adverse event.
Note: Table contained 8 adolescent patients in safety population and 8.58 person-years of exposure.
[a]Event rate (ER) = 100*((number of respective AEs) / number of person−years at follow up). All events reported during the study follow-up period are counted, regardless of whether they are reported in the same subject (ie, multiple events per subjects), or different subjects. The person-years at follow-up will be calculated using the standard on-treatment duration formula: (the date of last IMP – date of first dose of IMP + 14 days)/365.25.
Note: Total exposure defined as sum of each person's exposure on treatment period (in days)/365.25.
Data cutoff date: 28MAR2022
PROGRAM: T8_1.SAS (27JUN2022 03:27)

Table 5 Incidence rates and event rates of patients with TEAE(s) by Primary SOC, HLGT and PT – Safety population – Adolescents (12-17 years)

High Level Group Term Preferred Term	n of patients, n of events	Incidence Rate(%)	95% CI of Incidence Rate	Event Rate (per 100-py)	95% CI of Event Rate
Any class	2,3	25.0	3.03,90.31	35.0	11.66,81.59
Skin and subcutaneous tissue disorders	1,1	12.5	0.32,69.65	11.7	0.00,46.62
Epidermal and dermal conditions	1,1	12.5	0.32,69.65	11.7	0.00,46.62
Erythema	1,1	12.5	0.32,69.65	11.7	0.00,46.62
General disorders and administration site conditions	1,2	12.5	0.32,69.65	23.3	5.83,64.10
Administration site reactions	1,2	12.5	0.32,69.65	23.3	5.83,64.10
Injection site induration	1,2	12.5	0.32,69.65	23.3	5.83,64.10

TEAE: Treatment emergent adverse event, SOC: System organ class, HLGT: High level group term, PT: Preferred term.
MedDRA 24.1.
Note: Table contained 8 adolescent patients in safety population and 8.58 person-years of exposure.
Note: Table sorted by SOC internationally agreed order and HLGT, PT by alphabetic order.
Note: Incidence rate (IR) with corresponding 95% CI (by the Clopper-Pearson method) are calculated as follows: IR = number patients with one or more TEAEs / number of subjects at risk (ie, safety population) × 100.
Note: Event rate (ER) per 100 person-years with corresponding 95% CI (two-sided exact Poisson CIs) are calculated as follows: Event rate (ER) = number of TEAEs / number of 100 person-years at follow up. All events reported during the study follow-up period are counted, regardless of whether they are reported in the same subject (ie, multiple events per subjects), or different subjects. The person-years at follow-up was calculated using the standard on-treatment duration formula: (the date of last IMP – date of first dose of IMP + 14 days)/365.25.
Data cutoff date: 28MAR2022
PROGRAM: T9_1_1.SAS (27JUN2022 03:27)

Overall population

Table 6 summarises the treatment-emergent adverse events reported in the overall safety population.

Overall, 214/393 (54.5%) patients experienced at least 1 TEAE during the LPS15023 study, 22/393 (5.6%) patients experienced at least 1 treatment-emergent SAE, including 5/393 (1.3%) patients who had TEAEs leading to death (COVID-19 pneumonia for 3 patients, pulmonary embolism, and pancreatitis), none of which being assessed as related to dupilumab. 6/393 (1.5%) patients had TEAEs leading to permanent treatment discontinuation. In addition, 24/393 (6.1%) patients experienced AESIs, and the exposure-adjusted event rate of AESIs was 6.0 per 100 PY.
The exposure-adjusted incidence rate of patients with at least 1 TEAE observed in the LPS15023 study was lower (49.6 per 100 PY) compared to that observed in the parent LTS12551study (137.4 and 129.9 per 100 PY for non-OCS dependent patients and OCS-dependent patients, respectively).
The Infections and infestations SOC had the highest proportion of patients with TEAEs (33.1%).

Table 6 Overview of Adverse Event Profile: Treatment-Emergent Adverse Events (Safety population)

	Total (N = 393) n (%)	Number of events
Patients with at least 1 TEAE	214 (54.5)	740
Patients with at least 1 AESI	24 (6.1)	26
Patients with at least 1 treatment-related TEAE	37 (9.4)	125
Patients with at least 1 treatment-emergent SAE	22 (5.6)	30
Patients with at least 1 TEAE leading to death	5 (1.3)	5
Patients with at least 1 TEAE leading to definitive treatment discontinuation [a]	5 (1.3) [a]	5 [a]
Patients with at least 1 TEAE leading to study discontinuation [a]	5 (1.3) [a]	5 [a]

AE = adverse event; AESI = adverse event of special interest; n = the number of patients meeting the criterion; N = the number of patients in the analysis set; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a] Patient 710007132, who experienced a fatal AE of pulmonary embolism, is not included in the categories of TEAEs leading to definitive treatment discontinuation or study discontinuation. This patient had not discontinued treatment at the time of the event (ie, the categorization of 'drug withdrawn' did not apply at the time of the event; this categorization was required to generate the number of patients with treatment or study discontinuation for the source table), thereby resulting in this AE not having been recorded as a TEAE that led to treatment or study discontinuation. However, due to this fatal AE, there was no further treatment or study participation for this patient.
Source: LPS15023 CSR Table 8. Overview of adverse event profile: Treatment-emergent adverse events - Safety population.

The most frequently reported TEAEs at PT level (at least 5% of patients) were asthma (13.7%), nasopharyngitis (8.4%), and COVID-19 (6.4%).

Deaths

Adolescent population
In the adolescent population, no TEAEs leading to death were reported.

Overall population
5/393 (1.3%) patients experienced TEAEs leading to death; none of them were assessed as related to the IMP.
- 3 patients had fatal TEAEs of **COVID-19 pneumonia**.
- 1 patient had a fatal TEAE of **pancreatitis**.
- and 1 patient had a fatal TEAE of **pulmonary embolism**.

Serious adverse events

Adolescent population
In the adolescent population, no treatment-emergent SAEs were reported including no cases of COVID-19.

Overall population
Overall, 22/393 (5.6%) patients experienced at least 1 treatment-emergent SAE during the study. None of them were assessed as related to the IMP by the Investigator.
The most frequently reported treatment-emergent SAEs (PT), that occurred in at least 2 (0.5%) patients, were asthma (1.0%), and COVID-19 and COVID-19 pneumonia (0.8% each).
The exposure-adjusted incidence rate of patients with at least 1 treatment-emergent SAE observed in the LPS15023 study was lower (5.1 per 100 PY) compared to that observed in the parent LTS12551

study (6.5 and 9.0 per 100 PY for non-OCS dependent patients and OCS-dependent patients, respectively).

Adverse events leading to discontinuation of the study drug

Adolescent population
In the adolescent population, no TEAE leading to permanent treatment discontinuation were reported.

Overall population
A total of 6/393 (1.5%) patients had TEAE leading to permanent treatment discontinuation, including the 5 patients mentioned in Table 11 and one additional patient who had his study treatment discontinued due to a fatal TEAE of pulmonary embolism but had not discontinued treatment at the time of the event, thereby resulting in this AE not having been recorded as a TEAE that led to treatment or study discontinuation. TEAEs leading to permanent treatment discontinuation consisted of fatal COVID-19 pneumonia (3 patients), fatal pancreatitis (1 patient), fatal pulmonary embolism (1 patient), and pregnancy (1 patient).
The exposure-adjusted incidence of TEAEs leading to permanent treatment discontinuation was low (1.2 per 100 PY) (Table 9) and consistent with that observed in the parent LTS12551 study (1.9 and 3.5 per 100 PY for non-OCS dependent patients and OCS-dependent patients, respectively).

Adverse events of special interest

Adolescent population
In the adolescent population, no AESIs were reported.

Overall population
Overall, 24/393 (6.1%) patients experienced at least 1 AESI during the study. The exposure-adjusted event rate of AESIs was 6.0 per 100 PY.
One patient experienced anaphylactic reaction (angioedema of the lips and diffuse bronchospasm), reported by the Investigator as 'anaphylaxis secondary to brufen' (known hypersensitivity), that occurred on Day 704 and that resolved on the same day.

A total of 22/393 (5.6%) patients reported infections considered as AESIs (ie, any serious infection, any bacterial infection requiring treatment with parenteral antibiotics for longer than 2 weeks, any parasitic infection, any systemic opportunistic infection, any viral infection requiring antiviral treatment, or any uncommon, atypical, or unusually frequent or persistent infection and TB that required anti-TB medication). The most frequently reported infections were viral infectious disorders, reported in a total of 19 patients, and included influenza (7 patients), COVID-19 (2 patients), COVID-19 pneumonia (3 patients), herpes zoster and oral herpes (3 patients each), and viral upper respiratory tract infection (1 patient).
A 35-year-old female patient had a positive pregnancy test on Day 27. Study treatment was permanently discontinued as a result of the pregnancy.
No injection site reactions that were severe and lasted longer than 24 hours were reported during the study. No symptomatic overdoses were reported during the study.

Clinical laboratory data
Clinical laboratory data were limited to hematology parameters and only clinically significant abnormal values were reported. None of these abnormal values were reported in the adolescent population.

OVERDOSE
There were no symptomatic overdoses reported during the LPS15023 study.

2.3.3. Discussion on clinical aspects

The MAH submitted paediatric safety data that were collected in the completed phase 3b study LPS15023. This study included 8 adolescent and 385 adult patients who had previously participated in the 'TRAVERSE' study (LTS12551), an open-label extension study investigating the long-term safety and efficacy of 300 mg dupilumab Q2W added on standard of care background controller therapy in patients with moderate-to-severe or oral-corticosteroid-dependent severe asthma up to 96 weeks.

Study LPS15023 was an open-label, single-arm study that further investigated the safety and tolerability of dupilumab 300 mg Q2W SC of patients with moderate-to-severe asthma who completed the previous asthma clinical trial for a maximum of 144 weeks or until market availability in the respective country. The safety analysis is based on the reported TEAEs and clinical laboratory data of the safety population defined as all patients who received at least one dose or part of a dose of dupilumab during this study.
The primary endpoint was the incidence rates, defined as the percentage of patients reporting any treatment-emergent adverse events (TEAEs), and event rates, i.e. number of events per 100 patient-years (PY). As secondary endpoints, incidence rates for AESI as well as incidence rates for SAEs/death and for TEAEs leading to study discontinuation were evaluated.
The applied statistical methods are considered adequate. The overall treatment adherence was very good as all adolescent patients completed the study treatment. As the study was conducted across ten countries, the different local approval dates are likely to have caused a highly variable duration of study treatment; however, the cumulative treatment duration was >96 days for 88.5% and >670 days for 31% of the participants, with an overall exposure of 432 PY, thus providing a sufficient extent of exposure to assess the safety of long-term use in the overall study population. However, the minority of study participants were adolescent patients, their cumulative exposure is only 8.6 PY. The assessment of their safety data has therefore descriptive character.

Of the enrolled and treated adolescent patients, 2 (25%) experienced 3 mild treatment-emergent adverse events (erythema and injection-site reaction), no further adverse events were reported; adolescents had a more favourable outcome compared with the adult population participating in this study and results are consistent with the hitherto known safety profile in the paediatric population; however, numbers are very limited to draw conclusions on the safety profile of the paediatric patients included in this study.

No new information related to pharmacokinetics, pharmacodynamics, immunogenicity or efficacy of dupilumab are available from the LPS15023 study.

The overall AE profile was consistent with that observed in the LTS12551 study.

3. CHMP overall conclusion and recommendation

The study results suggest that the safety profile of dupilumab 300 mg Q2W administered for up to 144 weeks was consistent with the safety profile observed in the parent studies and no additional ADRs were identified.

☒ Fulfilled:

No regulatory action required.