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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/P46/009

Note

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

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Abbreviations

ACQ-5: asthma control questionnaire, 5-question version
AD: atopic dermatitis
AESI: adverse event of special interest
AQLQ: asthma quality of life questionnaire
CI: confidence interval
COVID-19: coronavirus disease 2019
CRSwNP: chronic rhinosinusitis with nasal polyposis
CSR: clinical study report
EU: European Union
FeNO: fractional exhaled nitric oxide
FEV1: forced expiratory volume in 1 second
GINA: Global Initiative for Asthma
HR: hazard ratio
ICS: inhaled corticosteroids
IgE: immunoglobulin E
IMP: investigational medicinal product
ITT: intent-to-treat
LABA: long-acting beta2 agonist
LAMA: long-acting muscarinic antagonist
LS: least squares
LTRA: leukotriene receptor antagonist
MAH: Marketing Authorization Holder
OCS: oral corticosetroids
PD: pharmacodynamics
PK: pharmacokinetics
ppb: parts per billion
PT: preferred term
q2w: bi-weekly
SAE: serious adverse event
SC: subcutaneous
TEAE: treatment-emergent adverse event

Introduction

On 09 December 2022, the MAH submitted a clinical study report for Study EFC13995, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. A short critical expert overview has also been provided.

The provided critical expert overview is being submitted to provide the Agency with an outline of the EFC13995 study results in the single adolescent participant exposed to dupilumab.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that study EFC13995, a Phase 3, randomized, double-blind, placebo-controlled, parallel group study designed to investigate the efficacy and safety of dupilumab over 24 weeks in Chinese and Indian patients with persistent asthma in need of an additional treatment added to their standard of care management is a stand-alone study.

Dupilumab was approved by the EC for the asthma indication (as described above) for adults and adolescents 12 years and older on 06 May 2019 and for children 6 to 11 years old on 04 April 2022.

In the European Union (EU), Dupixent is approved for the treatment of the following Type 2 inflammatory diseases:

• Atopic dermatitis:

- *Adults and adolescents 12 years and older:* Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis (AD) in adults and adolescents 12 years and older who are candidates for systemic therapy,

- *Children 6 to 11 years of age*: Dupixent is indicated for the treatment of severe AD in children 6 to 11 years old who are candidates for systemic therapy.

• Asthma:

- *Adults and adolescents 12 years and older:* Dupixent is indicated as add-on maintenance treatment for severe asthma with Type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled fractional exhaled nitric oxide (FeNO), who are inadequately controlled with high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment,

- *Children 6 to 11 years of age*: Dupixent is indicated as add-on maintenance treatment for severe asthma with Type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled FeNO, who are inadequately controlled with medium to high dose ICS plus another medicinal product for maintenance treatment.

• Chronic rhinosinusitis with nasal polyposis (CRSwNP):

- Dupixent is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe chronic rhinosinusitis with nasal polyposis (CRSwNP) for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

In addition, dupilumab is being investigated for the treatment of several other Type 2 inflammatory diseases in adult and pediatric populations.

1.2. Information on the pharmaceutical formulation used in the study

Each prefilled syringe (PFS) contained 2 mL of dupilumab at the concentration of 150 mg/mL to deliver 300 mg or 1.14 mL at a concentration of 175 mg/mL to deliver 200 mg. Matching placebo containing the identical formulation to the active formulation without dupilumab was administered via PFS (see study treatment).

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for:

Study number: EFC13995

Study title: A randomized, double blind, placebo-controlled, parallel-group phase 3 study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma

Study dates: First patient enrolled: 14 March 2019, last patient completed: 21 May 2022

Database lock date: 22 June 2022.

1.3.2. Clinical study

A randomized, double blind, placebo-controlled, parallel-group phase 3 study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma (EFC13995)

Description

Study EFC13995 was a multinational, multicenter, randomized, double-blind, placebo-controlled,

parallel group, Phase 3 study assessing the effect of dupilumab as an add-on therapy in participants with persistent asthma when administered for 24 weeks by bi-weekly (q2w) subcutaneous (SC) injection. Adult and adolescent participants with persistent asthma on a stable dose of ICS in combination with one or two other controller medications with or without OCS were randomized to receive dupilumab (200 mg q2w for participants without OCS maintenance, or 300 mg q2w for participants on OCS maintenance) or matching placebo in a 1:1 ratio.

The total duration of study per participant was up to 41 weeks and included the following 3 periods:

• Screening Period (4 ±1 weeks): determine a participant's eligibility status and establish level of asthma control before randomization.

• Treatment Period (24 weeks): treat with dupilumab or placebo SC injection.

• Post-treatment Period (12 weeks): monitor a participant's status when off study drug treatment.

A total of 67 sites (China: 54 sites, India: 13 sites) enrolled 486 participants in the study.

Methods

Study participants

This study enrolled adults and adolescent participants (≥12 years of age) with a physician diagnosis of asthma for ≥12 months, based on the GINA 2017 Guidelines.

Main criteria included:

• Existing treatment with medium to high dose ICS (≥250 µg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 µg/day of fluticasone propionate or equivalent) in combination with a second controller (eg, LABA, LTRA, LAMA, or theophylline, etc.) for at least 3 months with a stable dose ≥1 month prior to the screening visit (Visit 1). Participants on budesonide/formoterol combo with budesonide 640 µg/day were considered as medium dose ICS and were eligible.

- Participants requiring a third controller for their asthma were considered eligible for this study, and it was also to be used for at least 3 months with a stable dose ≥1 month prior to the screening visit (Visit 1).

- Participants requiring maintenance OCS with a stable dose ≤10 mg/day prednisone or equivalent were allowed; OCS was to be used for at least 3 months with a stable dose ≥1 month prior to the screening visit (Visit 1).

• Pre-bronchodilator FEV1 ≤80% of predicted normal for adults and ≤90% of predicted normal for adolescents at the screening visit and the randomization visit (Visits 1 and 2), prior to randomization.

• Prior to randomization, reversibility of at least 12% and 200 mL in FEV1 after the administration of 200 to 400 µg albuterol/salbutamol or levalbuterol/levosalbutamol (2 to 4 inhalations of albuterol/salbutamol or levalbuterol/levosalbutamol, or of a nebulized solution of albuterol/salbutamol or levalbuterol/levosalbutamol, if considered as a standard office practice).

• Must have experienced, within 1 year prior to the screening visit (Visit 1), any of the following events:

  - Treatment with a systemic steroid (oral or parenteral) or treatment with systemic steroid at least twice the previous dose (for participants on OCS maintenance) for worsening asthma at least once.

  - Hospitalization or emergency medical care visit for worsening asthma, requiring systemic steroids.

• For participants not requiring maintenance OCS, screening blood eosinophil count ≥0.15 Giga/L or FeNO ≥25 ppb was required; for participants requiring maintenance OCS, there was no minimum requirement for blood eosinophil count or FeNO level.

Main exclusion criteria

• Pregnant or breast-feeding women.

• Weight was less than 30 kg at the screening visit (Visit 1) or the randomization visit (Visit 2).

• Current smoker or cessation of smoking within 6 months prior to the screening visit (Visit 1).

• Previous smoker with a smoking history >10 pack-years.

• Evidence of lung disease(s) other than asthma, either clinical or imaging evidence (eg, chest X-ray, CT, and MRI) within 3 months prior to the screening visit (Visit 1) as per local standard of care.

• Participants with a history of systemic eosinophilic diseases, such as hypereosinophilic syndromes and eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome).

• History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin.

• Drug induced liver injury related criteria:

- Underlying clinically significant/active hepatobiliary disease or

- ALT >3 ULN

• Anti-IgE therapy (omalizumab) within 130 days prior to the screening visit (Visit 1) or any other biologic therapy/immunosuppressant to treat inflammatory disease or autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, and multiple sclerosis) as well as other diseases within 2 months or 5 half-lives prior to the screening visit (Visit 1), whichever was longer.

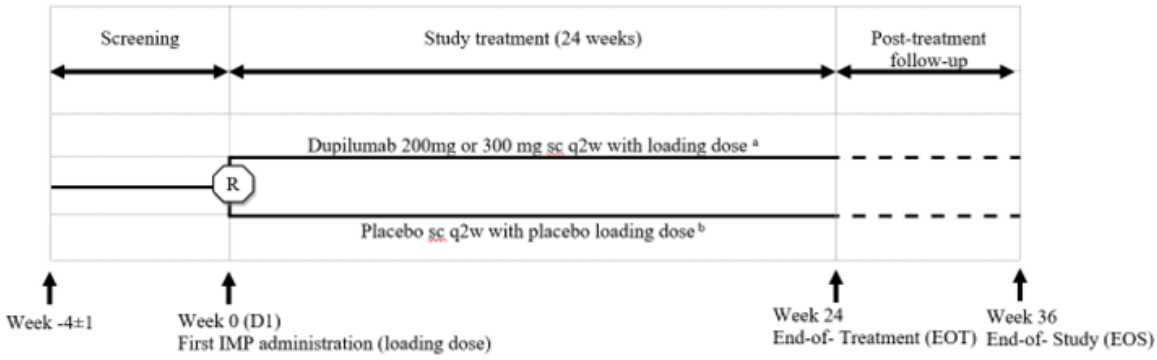
• Participants who had previously been treated in any clinical trial of dupilumab.

Study design

The study design is depicted in Figure 1. Dupilumab was to be added-on to an existing ICS treatment in combination with one or two other controller medications with or without OCS. Participants were randomized using a 1:1 ratio to dupilumab (200 mg q2w or 300 mg q2w) or matching placebo, the approved doses for asthma in the EU and US. The study periods are described above.

The primary population for this study was non-OCS maintenance participants with evidence of Type 2 inflammation (blood eosinophils ≥0.15 Giga/L or FeNO ≥25 ppb), consistent with the dupilumab mechanism of action, which lead to suppression of Type 2 inflammation as demonstrated in the pivotal asthma Phase 3 study EFC13579.

Figure 1 Graphical study design



Background therapy: medium to high dose ICS plus second controller (LABA, LTRA, LAMA, theophylline, etc). Third controller was allowed.

a For participants without OCS maintenance therapy, the dose was 200 mg dupilumab q2w with 400 mg loading dose; for participants on OCS maintenance therapy, the dose was 300 mg dupilumab q2w with 600 mg loading dose.

b For participants without OCS maintenance therapy, the participants took placebo matching to 200 mg dupilumab q2w with loading dose; for participants on OCS maintenance therapy, the participants took placebo matching to 300 mg dupilumab q2w with loading dose.

Treatments

The study interventions are outlined in Table 1 and study arms with associated interventions in Table 2.

Table 1 Overview of study intervention(s) administered

Intervention label	Dupilumab	Placebo
Intervention name	Dupilumab 200 mg or 300 mg	Placebo
Intervention description	Solution for injection, 200 mg q2w after a 400 mg loading dose, or 300 mg q2w after a 600 mg loading dose	Identical formulation to the active formulation without dupilumab
Type	Biological	Other
Dose formulation	Pre-filled syringe	Pre-filled syringe
Unit dose strength(s)	150 mg/mL (2 mL) 175 mg/mL (1.14 mL)	NA
Dosage level(s)	200 mg q2w or 300 mg q2w	NA
Route of administration	Subcutaneous injection	Subcutaneous injection
Use	Experimental	Placebo
IMP or NIMP	IMP	IMP
Packaging and labeling	Study intervention was provided in 2 mL or 1.14 mL pre-filled syringes packed in a participant kit box. Both glass pre-filled syringe and box were labelled as required per country requirements.	Study intervention was provided in Identically matched 2 mL or 1.14 mL pre-filled syringes packed in a participant kit box. Both glass pre-filled syringe and box were labelled as required per country requirements.
Current/Former name(s) or alias(es)	Dupilumab/SAR231893	NA

Table 2 Arms and associated interventions

Arm title	Dupilumab	Placebo
Arm type	Experimental	Placebo
Arm description	Received dupilumab 200 mg q2w or 300 mg q2w	Receive matching placebo
Associated intervention labels	• Dupilumab • ICS in combination with LABA/LTRA/LAMA/theophylline with or without OCS • Albuterol/salbutamol or levalbuterol/levosalbutamol as needed	• Placebo • ICS in combination with LABA/LTRA/LAMA/theophylline with or without OCS • Albuterol/salbutamol or levalbuterol/levosalbutamol as needed

Objective(s)

Primary objective:

• To evaluate the efficacy of dupilumab in patients with persistent asthma

Secondary objectives:

• To evaluate the safety and tolerability of dupilumab

• To evaluate the effect of dupilumab on improving patient reported outcomes including health-related quality of life

• To evaluate dupilumab systemic exposure and immunogenicity

Outcomes/endpoints

Primary endpoint

Absolute change from baseline in pre-bronchodilator FEV1 at Week 12

Secondary endpoints

Secondary efficacy endpoints

• Percent change from baseline in pre-bronchodilator FEV1 at Week 12

• Annualized rate of severe exacerbation events during the 24-week placebo-controlled treatment period

• Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 24-week placebo-controlled treatment period

• Time to first severe exacerbation event during the 24-week placebo-controlled treatment period

• Annualized rate of LOAC event during the 24-week placebo-controlled treatment period

• Time to first LOAC event during the 24-week placebo-controlled treatment period

• Change from baseline at Week 24 in:

- Morning/evening asthma symptom score and nocturnal awakenings (e-diary)

- Use of daily puffs of rescue medication

• Change from baseline in AQLQ with Standardized Activities (≥12 years) (AQLQ+12) at

Week 24

• Change from baseline in EQ-5D-5L at Week 24

Sample size

The sample size of the study was determined based on power calculations for the primary endpoint in patients with evidence of type 2 inflammation not on OCS maintenance. Assuming a common standard deviation of 0.44 L and a drop-out rate of approximately 5% prior to the Week 12, with 384 randomized patients with evidence of type 2 inflammation (randomization ratio of 1:1, 192 in dupilumab 200 mg q2w group, and 192 in the matching placebo group) the study was considered to have 90% power to detect a 0.15 L difference in terms of absolute change from baseline in pre-bronchodilator FEV1 at Week 12 at the 2 tailed significance level of $\alpha = 0.05$. The study also enrolled OCS-maintenance patients treated with 300 mg q2w regimen with a cap of 48 patients (approximately 10% of the total population). The overall study recruitment continued until at least 384 non-OCS-maintenance type 2 inflammatory patients have been randomized. In addition, a maximum of 48 OCS-maintenance patients were planned to be enrolled. Considering that non-OCS-maintenance non-type 2

inflammatory patients were enrolled in this study prior to implementation of the amended protocol 02, the study includes approximately 54 non-OCS-maintenance non-type 2 inflammatory patients.

Randomisation and blinding (masking)

Participants were randomized in an automated manner to either dupilumab or matching placebo treatment, following specific stratification rules in order to avoid treatment assignment bias and confounding effects of age, eosinophil count, country, and baseline OCS maintenance.

Randomization was stratified by age (<18 years, ≥18 years), central lab blood eosinophil count at screening (<150 cells/μL, 150-299 /cells/μL, and ≥300 cells/μL), baseline OCS maintenance (yes or no), and region (China versus non-China).

Dupilumab and placebo were provided in identically matched 2 mL or 1.14 mL pre-filled syringes. Both the patient and Investigator were blinded to assigned active drug or placebo, but not to the dose levels due to different volume sizes. Study patients, Investigators, and study site personnel did not have access to the treatment codes except for emergency unblinding.

Statistical Methods

Analysis population

The efficacy endpoints were primarily based on the type 2 inflammatory population not on OCS maintenance defined as all randomized non-OCS maintenance patients with central lab blood eosinophils count at screening ≥150 cells/μL or FENO level at screening ≥25 ppb. The Sponsor performed additional analysis on the population with blood eosinophils count ≥150 cells/μL at screening and on the combination of type 2 inflammatory population not on OCS maintenance and OCS maintenance population. The efficacy analyses were conducted according to the treatment group allocated by randomization. The analysis population for the safety endpoints were the safety population, defined as all randomized patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses were conducted according to the treatment that patients actually received.

Analysis of the primary efficacy endpoint

The absolute change from baseline in FEV1 at Week 12 were analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model included change from baseline FEV1 values up to Week 12 as response variables, and factors for treatment, age, sex, height, screening blood eosinophil level (<300 cells/μL or ≥300 cells/μL), screening FENO level (<25 ppb or ≥25 ppb), baseline OCS maintenance (yes or no, if applicable), region (China versus non-China), baseline ICS dose level (medium or high), visit, treatment by-visit interaction, baseline FEV1 value, and baseline-by-visit interaction as covariates. An unstructured correlation matrix was used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method using the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change from baseline in FEV1 at Week 12 were derived from the mixed-effect model. For patients discontinuing the treatment before Week 12, off study-treatment FEV1 values measured up to Week 12 were included in the primary analysis.

Multiplicity considerations

The hypothesis on the primary efficacy endpoint of absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in type 2 inflammatory population not on OCS maintenance were controlled with a two-sided type I error of 0.05. If the primary endpoint is significant at the 0.05 level,

the secondary endpoints in the hierarchy was tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about successive secondary endpoints require statistical significance at the 0.05 significance level of the prior one (see SAP).

Analysis of secondary endpoints

The annualized rate of severe exacerbation events was analyzed using a negative binomial regression model. The model will include the total number of events occurring during the 24 week treatment period as the response variable, with the treatment group, age, screening blood eosinophil level (<300 cells/μL or ≥300 cells/μL), screening FENO level (<25 ppb or ≥25 ppb), baseline OCS maintenance (yes or no, if applicable), region (China versus non-China), baseline ICS dose level (medium or high), and number of severe exacerbation events within 1 year prior to the study as covariates. Log transformed treatment duration will be the offset variable. The annualized rate of exacerbation events, including severe exacerbation events resulting in hospitalization or emergency room visit and LOAC events, will be analyzed with a similar methodology as for the severe exacerbation events.

Time to first event (eg, severe exacerbation, LOAC) will be analyzed using a Cox regression model with time to event as the dependent variable, and treatment, age, region, screening blood eosinophil level (<300 cells/μL or ≥300 cells/μL), screening FENO level (<25 ppb or ≥25 ppb), baseline OCS maintenance (yes or no, if applicable), baseline ICS dose level (medium or high), and number of severe exacerbation events within 1 year prior to the study as covariates. The Kaplan-Meier method will be used to derive the proportion of patients with a severe asthma exacerbation event at Weeks 12 and 24, specific to each treatment group. The change from baseline for continuous endpoints will be analyzed using a MMRM in the same fashion as for the endpoint of FEV1. Sex and height will be included as covariates only in the models for spirometry parameters. The safety variables, including AEs, laboratory parameters, vital signs, ECG, and physical examinations will be summarized using descriptive statistics.

Results

A total of 1022 participants were screened for study eligibility and 486 were enrolled, with a screen failure rate of 52.4%. The most common reason for screen failure was failure to meet inclusion criterion I01B (16.0%): pre-bronchodilator FEV1 ≤ 80% of predicted normal for adults and ≤90% of predicted normal for adolescents at the screening visit and the randomization visit (Visits 1 and 2), prior to randomization. A total of 486 participants (ITT population) were randomized to study intervention: 242 in the overall dupilumab group and 244 in the overall placebo group (Table 3). The primary analysis population of the study was the type 2 inflammatory asthma population without OCS maintenance (referred to as the type 2 non-OCS maintenance population hereafter) and was comprised of 414 participants (85.2% of the ITT population), including 205 participants in the dupilumab 200 mg q2w group and 209 participants in the matching placebo group. The OCS maintenance population was comprised of 35 participants, with 17 in the dupilumab 300 mg q2w group and 18 in the matching placebo group. There were 37 participants without type 2 inflammation or OCS maintenance, with 20 in the dupilumab 200 mg q2w group and 17 in the matching placebo group.

Participant flow

A total of 236 (97.5%) participants in the overall dupilumab group and 230 (94.3%) participants in the overall placebo group completed the study period. Participants who permanently discontinued the study intervention were encouraged to return to the clinic for all remaining study visits.

Table 3 Participant disposition – Type 2 inflammatory asthma phenotype without OCS maintenance, OCS maintenance and randomized populations

n (%)	Type 2 inflammatory asthma phenotype without OCS maintenance		OCS maintenance		All[a]	
	Placebo 1.14mL q2w (N=209)	Dupilumab 200mg q2w (N=205)	Placebo 2mL q2w (N=18)	Dupilumab 300mg q2w (N=17)	Placebo (N=244)	Dupilumab (N=242)
Exposed but not randomized	0	0	0	0	0	0
Randomized and not exposed	1 (0.5)	1 (0.5)	0	0	1 (0.4)	1 (0.4)
Randomized and exposed	208 (99.5)	204 (99.5)	18 (100)	17 (100)	243 (99.6)	241 (99.6)
Completed the study intervention period	193 (92.3)	190 (92.7)	14 (77.8)	15 (88.2)	222 (91.0)	225 (93.0)
Did not complete the study intervention period	15 (7.2)	14 (6.8)	4 (22.2)	2 (11.8)	21 (8.6)	16 (6.6)
Reason for permanent study intervention discontinuation						
Adverse event	2 (1.0)	4 (2.0)	0	0	2 (0.8)	4 (1.7)
Related to COVID-19	0	0	0	0	0	0
Not related to COVID-19	2 (1.0)	4 (2.0)	0	0	2 (0.8)	4 (1.7)
Lack of efficacy	1 (0.5)	0	0	0	1 (0.4)	0
Poor compliance to protocol	0	2 (1.0)	0	1 (5.9)	0	3 (1.2)
Withdrawal by subject	10 (4.8)	2 (1.0)	2 (11.1)	0	12 (4.9)	2 (0.8)
Other[b]	2 (1.0)	6 (2.9)	2 (11.1)	1 (5.9)	6 (2.5)	7 (2.9)
Related to COVID-19	1 (0.5)	5 (2.4)	2 (11.1)	1 (5.9)	5 (2.0)	6 (2.5)
Not related to COVID-19	1 (0.5)	1 (0.5)	0	0	1 (0.4)	1 (0.4)
Reason for study intervention withdrawal by subject						
Adverse event	5 (2.4)	1 (0.5)	0	0	5 (2.0)	1 (0.4)
Related to COVID-19	0	0	0	0	0	0
Not related to COVID-19	5 (2.4)	1 (0.5)	0	0	5 (2.0)	1 (0.4)
Study procedure	1 (0.5)	0	0	0	1 (0.4)	0
Inconvenience of device use	0	0	0	0	0	0
Other[b]	4 (1.9)	1 (0.5)	2 (11.1)	0	6 (2.5)	1 (0.4)
Related to COVID-19	4 (1.9)	0	2 (11.1)	0	6 (2.5)	0
Not related to COVID-19	0	1 (0.5)	0	0	0	1 (0.4)
Completed the study period	196 (93.8)	199 (97.1)	17 (94.4)	17 (100)	230 (94.3)	236 (97.5)
Did not complete the study period	13 (6.2)	6 (2.9)	1 (5.6)	0	14 (5.7)	6 (2.5)
Reason for study discontinuation						
Adverse event	2 (1.0)	0	0	0	2 (0.8)	0
Poor compliance to protocol	0	1 (0.5)	0	0	0	1 (0.4)
Study terminated by sponsor	0	0	0	0	0	0
Withdrawal by subject	7 (3.3)	4 (2.0)	1 (5.6)	0	8 (3.3)	4 (1.7)
Other[b]	4 (1.9)	1 (0.5)	0	0	4 (1.6)	1 (0.4)
Related to COVID-19	1 (0.5)	0	0	0	1 (0.4)	0
Not related to COVID-19	3 (1.4)	1 (0.5)	0	0	3 (1.2)	1 (0.4)
Status at last contact						
Alive	209 (100)	205 (100)	18 (100)	17 (100)	244 (100)	242 (100)
Dead	0	0	0	0	0	0

a Participants without Type 2 inflammatory asthma phenotype in placebo 1.14mL/dupilumab 200mg q2w intervention groups are included.
b Verbatim terms for these discontinuations are provided in the listing of participants with intervention/study discontinuation.
PGM=PRODOPS/SAR231893/EFC13995/CSR/REPORT/PGM/dis_dispo_r_t.sas OUT=REPORT/OUTPUT/dis_dispo_r_t_i.rtf (15JUL2022 10:05)

Recruitment

This study was conducted from 14 March 2019 (first participant enrollment) through 21 May 2022 (last participant last visit), in 67 centers in China and India. This study included a single adolescent participant aged 12-17 years. This study was conducted to support registration of the dupilumab asthma indication in China and is not part of the agreed European Paediatric Investigational Plan (PIP) of dupilumab in the treatment of asthma (EMEA-001501-PIP02-13-M07).

Baseline data

A total of 486 participants (intent-to-treat [ITT] population) were randomized to study intervention: 242 in the overall dupilumab group and 244 in the overall placebo group.

The primary analysis population of the study was the Type 2 inflammatory asthma population without OCS maintenance (referred to as the Type 2 non-OCS maintenance population hereafter) and was comprised of 414 participants (85.2% of the ITT population), including 205 participants in the dupilumab 200 mg q2w group and 209 participants in the matching placebo group. The OCS maintenance population was comprised of 35 participants, with 17 in the dupilumab 300 mg q2w group and 18 in the matching placebo group. There were 37 participants without Type 2 inflammation or OCS maintenance, with 20 in the dupilumab 200 mg q2w group and 17 in the matching placebo group.

The median age of the randomized population was 52.0 years with a range of 15 to 80 years. A total of 209 (43.0%) male and 277 (57.0%) female participants were included in the study. Most of the participants were Asian (99.8%). A total of 84.8% of the participants were from China and 15.2% of the participants were from India. The median body mass index of the randomized population was 24.45 kg/m2.

In the randomized population, most participants had moderate to severe impairment of lung function at enrollment, as demonstrated by a mean percent predicted pre-bronchodilator FEV1 at baseline of 55.27% and a mean baseline FEV1 reversibility of 31.46%. Participants had poorly controlled asthma with a mean asthma control questionnaire, 5-question version (ACQ-5) score at baseline of 2.32 and impairment in quality of life with a mean asthma quality of life questionnaire (AQLQ) score of 4.51. Participants had a history of a mean of 1.5 severe asthma exacerbations in the year prior to screening visit. In addition, 47.5% of enrolled participants had experienced at least 1 severe asthma exacerbation that required hospitalization or an emergency room visit in the prior year. A high proportion of participants had an ongoing atopic medical condition (69.8%).

The single adolescent participant was enrolled in the dupilumab 200 mg q2w group; this participant neither had evidence of Type 2 inflammation nor was receiving OCS maintenance. This participant completed the treatment period and the study. This participant was 12-17 years old, male, with a body weight of 61 kg. In the previous 1 year prior to Visit 1, this participant experienced 1 severe asthma exacerbation that required hospitalization or emergency room visit.

Number analysed

A total of 486 participants (intent-to-treat [ITT] population) were randomized to study intervention: 242 in the overall dupilumab group and 244 in the overall placebo group. This study included a single adolescent participant aged 12-17 years.

A total of 486 participants (ITT population) were randomized to study intervention: 242 in the overall dupilumab group and 244 in the overall placebo group.

The primary analysis population of the study was the type 2 inflammatory asthma population without OCS maintenance (referred to as the type 2 non-OCS maintenance population hereafter) and was comprised of 414 participants (85.2% of the ITT population), including 205 participants in the dupilumab 200 mg q2w group and 209 participants in the matching placebo group.

The OCS maintenance population was comprised of 35 participants, with 17 in the dupilumab 300 mg q2w group and 18 in the matching placebo group.

There were 37 participants without type 2 inflammation or OCS maintenance, with 20 in the dupilumab 200 mg q2w group and 17 in the matching placebo Group.

Efficacy results

Overall population

The efficacy of dupilumab in this study was primarily evaluated in the Type 2 non-OCS maintenance population. Efficacy was also evaluated in the population on OCS maintenance. Dupilumab treatment added to standard of care background therapy of medium to high dose ICS plus 1 or 2 additional controllers improved lung function (pre-bronchodilator FEV1) and asthma control (ACQ-5 score); and both of these improvements were statistically significant and clinically meaningful in a multiplicity-controlled analysis conducted in the Type 2 non-OCS maintenance population.

• **Pre-bronchodilator FEV1:** compared to the matching placebo group, the dupilumab 200 mg q2w group showed a statistically significant and clinically meaningful improvement in pre-bronchodilator FEV1 at Week 12 in the Type 2 non-OCS maintenance population. At 12 weeks, the least squares (LS) mean difference in pre-bronchodilator FEV1 change from baseline with dupilumab 200 mg q2w compared with placebo was 0.31 L, with a 95% CI of 0.23 to 0.39 ($p<0.0001$) in the Type 2 non-OCS maintenance population. The robustness of the primary endpoint finding was confirmed by multiple

sensitivity analyses and supplementary analyses.

• **ACQ-5:** dupilumab 200 mg q2w improved asthma control, as demonstrated by a statistically significant and clinically meaningful greater reduction (improvement) from baseline in ACQ-5 score at Week 24 compared with placebo, with a LS mean difference versus placebo of -0.20 (95% CI: -0.35 to -0.05, p=0.0097) in the Type 2 non-OCS maintenance population.

• **Severe exacerbation rate:** dupilumab 200 mg q2w reduced the risk of severe asthma exacerbations compared to placebo by 62.0% (nominal p=0.0020) and delayed the time to

first severe exacerbation event (hazard ratio [HR]=0.359 [95% CI: 0.195 to 0.658], nominal p=0.0009) compared to placebo. The risk of severe exacerbation events resulting in hospitalization or emergency room visit was also numerically reduced by 57.7% (nominal p=0.0748) compared to placebo. The onset of action of dupilumab 200 mg q2w was rapid across multiple efficacy endpoints, with a substantial difference versus placebo observed in many cases as early as 2 weeks after initiation

of treatment and a continued improvement sustained through Week 24. For the OCS maintenance population treated with dupilumab 300 mg q2w, similar trends of improvement in lung function, improved asthma control, and consistent reduced asthma exacerbations were observed compared to placebo.

Adolescent

For the single adolescent participant, the absolute change in pre-bronchodilator FEV1 from baseline (2.76 L) to Week 12 (3.42 L) was 0.66 L; the reduction (improvement) in ACQ-5 score from baseline (2.80) to Week 24 (0.20) was 2.60; and no severe asthma exacerbation events were reported for the single adolescent participant during the study.

Safety results

EXPOSURE

Overall population

The majority of participants (74.3% and 72.0% in the overall dupilumab group and the overall placebo group, respectively) received a total of 13 injections, corresponding to the planned treatment duration of 24 weeks.

Adolescent

The single adolescent participant received 9 injections of dupilumab 200 mg q2w and missed injections on Week 4, Week 6, Week 8 (reasons unknown for these 3 missing injections), and Week 22 (due to COVID-19).

Overall population

In EFC13995, dupilumab was well tolerated across both studied doses (dupilumab 200 mg q2w and 300 mg q2w) in participants with asthma and demonstrated an acceptable safety profile consistent with the known dupilumab safety profile. No new safety concerns were identified. The percentages of participants with any treatment emergent adverse events (TEAEs) were similar between intervention groups (203 [84.2%] participants in the combined dupilumab group versus 190 [78.2%] participants in the combined placebo group).

The highest overall incidence of TEAEs reported by SOC was Infections and Infestations, with a similar incidence between the combined dupilumab group and the combined placebo group (129 [53.5%] versus 127 [52.3%]). Under this SOC, the 3 most common TEAEs by preferred term (PT) were Upper respiratory tract infection (62 [25.7%] versus 62 [25.5%]) and Nasopharyngitis (14 [5.8%] versus 13 [5.3%]), both with balanced rates between the combined dupilumab and the combined placebo groups, and Pneumonia (3 [1.2%] versus 13 [5.3%]) with lower incident rate in the combined dupilumab group compared to the combined placebo group. The percentages of participants with any treatment-emergent serious adverse events (SAEs) were similar between intervention groups (21 [8.7%] participants in the combined dupilumab group versus 23 [9.5%] participants in the combined placebo group). The incidence of TEAEs leading to permanent study intervention discontinuation as per the Investigator was low in both intervention groups, including 4 [1.7%] participants in the combined

dupilumab group with PTs: Pneumonia, Arthralgia, Thyroiditis, and Cor pulmonale chronic and 2 [0.8%] participants in the combined placebo group with PTs: Rash and Thrombocytopenia. The incidence of adverse events of special interest (AESIs) was similar in the combined dupilumab group (10 [4.1%]) and the combined placebo group (9 [3.7%]), including hypersensitivity reactions (medically reviewed) (6 [2.5%] versus 4 [1.6%]) and severe or serious infections (4 [1.7%] versus 6 [2.5%]).

Eosinophilia (PT) was reported in 6 (2.5%) participants in the combined dupilumab group and none in the combined placebo group. Eosinophil count increased (PT) was reported in 1 (0.4%) participant in the combined dupilumab group and 4 (1.6%) participants in the combined placebo group. All these events were asymptomatic. None of the events were serious or led to permanent study intervention discontinuation.

Adolescent

In the single adolescent participant in the dupilumab 200 mg q2w group, 2 mild, non-serious AEs (Epistaxis and Rhinitis allergic) were reported. Neither of the events were assessed as related to dupilumab by the Investigator.

1.3.3. Discussion on clinical aspects

According to Article 46 requirements, the MAH submitted paediatric study data of a single adolescent participant that had been included in study EFC13995, a multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase 3 study which assessed the effect of dupilumab as an add-on therapy in participants with persistent asthma over a treatment period of 24 weeks by bi-weekly subcutaneous injections. This study was conducted to support the registration of the dupilumab

asthma indication in China and was conducted in 67 centers in China and India. Overall, 486 participants were enrolled.
The primary analysis population of the study was the type 2 inflammatory asthma population without OCS maintenance. The single adolescent participant, however, was enrolled in the dupilumab 200 mg q2w group and belonged to the subgroup of 37 patients who neither had evidence of Type 2 inflammation nor were receiving OCS maintenance.
As this is an individual case, very sparse data is available and no meaningful conclusion on efficacy and safety is to be drawn. The provided efficacy and safety results of this single patient, who received 9/13 injections, indicate an adequate efficacy and acceptable safety.

2. CHMP overall conclusion and recommendation

Data from one single patient was provided that do not raise specific concerns. However, the provided case report is not more than of informative character.

☒ Fulfilled:

No regulatory action required.