Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial

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Summary

Background Dupilumab, a fully human anti-interleukin-4 receptor α monoclonal antibody, inhibits interleukin-4 and interleukin-13 signalling, key drivers of type-2-mediated inflammation. Adults with uncontrolled persistent asthma who are receiving medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist require additional treatment options as add-on therapy. We aimed to assess the efficacy and safety of dupilumab as add-on therapy in patients with uncontrolled persistent asthma on medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist, irrespective of baseline eosinophil count.

Methods We did this randomised, double-blind, placebo-controlled, parallel-group, pivotal phase 2b clinical trial at 174 study sites across 16 countries or regions. Adults (aged ≥18 years) with an asthma diagnosis for 12 months or more based on the Global Initiative for Asthma 2009 Guidelines receiving treatment with medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist were eligible for participation. Patients were randomly assigned (1:1:1:1:1) to receive subcutaneous dupilumab 200 mg or 300 mg every 2 weeks or every 4 weeks, or placebo, over a 24-week period. The primary endpoint was change from baseline at week 12 in forced expiratory volume in 1 s (FEV_1 in L) in patients with baseline blood eosinophil counts of at least 300 eosinophils per μL assessed in the intention-to-treat population. Safety outcomes were assessed in all patients that received at least one dose or part of a dose of study drug. This trial is registered at ClinicalTrials.gov, number NCT01854047, and with the EU Clinical Trials Register, EudraCT number 2013-000856-16.

Findings 769 patients (158 in the placebo group and 611 in the dupilumab groups) received at least one dose of study drug. In the subgroup with at least 300 eosinophils per μL, the greatest increases (200 mg every 2 weeks, p=0·0008; 300 mg every 2 weeks, p=0·0063) in FEV_1 compared with placebo were observed at week 12 with doses every 2 weeks in the 300 mg group (mean change 0·39 L [SE 0·05]; mean difference 0·21 [95% CI 0·06–0·36; p=0·0063]) and in the 200 mg group (mean change 0·43 L [SE 0·05]; mean difference 0·26 [0·11–0·40; p=0·0008]) compared with placebo (0·18 L [SE 0·05]). Similar significant increases were observed in the overall population and in the fewer than 300 eosinophils per μL subgroup (overall population: 200 mg every 2 weeks, p<0·0001; 300 mg every 2 weeks, p<0·0001; <300 eosinophils per μL: 200 mg every 2 weeks, p=0·0034; 300 mg every 2 weeks, p=0·0086), and were maintained to week 24. Likewise, dupilumab every 2 weeks produced the greatest reductions in annualised rates of exacerbation in the overall population (70–70·5%), the subgroup with at least 300 eosinophils per μL (71·2–80·7%), and the subgroup with fewer than 300 eosinophils per μL (59·9–67·6%). The most common adverse events with dupilumab compared with placebo were upper respiratory tract infections (33–41% *vs* 35%) and injection-site reactions (13–26% *vs* 13%).

Interpretation Dupilumab increased lung function and reduced severe exacerbations in patients with uncontrolled persistent asthma irrespective of baseline eosinophil count and had a favourable safety profile, and hence in addition to inhaled corticosteroids plus long-acting β_2-agonist therapy could improve the lives of patients with uncontrolled persistent asthma compared with standard therapy alone.

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Introduction

Asthma affects nearly 250 million people worldwide, of whom approximately 20–25% have moderate-to-severe uncontrolled disease.[1] These patients have a higher risk of disease exacerbation, admission to hospital, and death, and have a substantially impaired quality of life.[1–3] Patients with severe uncontrolled persistent asthma are defined as those in whom symptoms remain uncontrolled

Research in context

Evidence before this study

In previous phase 1 and 2a trials, dupilumab showed significant efficacy and a favourable safety profile in patients with atopic dermatitis, symptomatic chronic sinusitis with nasal polyposis, and asthma, with asthma data limited to those with eosinophil counts of at least 300 eosinophils per μL and a weekly dosing regimen. To obtain information about the unmet need of patients with uncontrolled persistent asthma, we searched PubMed on Dec 30, 2015, for randomised, controlled, blinded clinical trials for treatment of uncontrolled persistent asthma, published in English. The following search terms were used: "asthma AND ICS AND LABA AND (medium OR high) AND dose". The search was done from 2013 onwards. Overall, we identified 27 randomised, controlled, blinded studies. The information available confirms that patients receiving medium-to-high-dose inhaled corticosteroids plus long-acting β_2-agonist therapy with uncontrolled persistent asthma require additional treatment options as add-on therapy. This is in line with Global Initiative for Asthma 2015 treatment guidelines.

Added value of this study

Our study provides the first evidence that dupilumab administered every 2 weeks decreases severe asthma exacerbations and improves FEV_1 and patient-reported outcomes in a wide range of patients with uncontrolled persistent asthma irrespective of baseline blood eosinophil count. Unlike other approved drugs, dupilumab appears to have a broad effect on these variables.

Implications of the available evidence

Blocking interleukin-4 receptor α with dupilumab, in addition to inhaled corticosteroids plus long-acting β_2-agonist therapy, could improve the lives of patients with uncontrolled persistent asthma compared with standard therapy with inhaled corticosteroids plus long-acting β_2-agonist alone. Additionally, dupilumab is unique among biologics as it might also ameliorate comorbid conditions that frequently exist in this population such as nasal polyps and, especially, atopic dermatitis.

(manifested by symptoms, exacerbations, and airflow limitation) despite treatment with medium-to-high-dose inhaled corticosteroids and a second controller agent or systemic corticosteroids.[4,5]

Asthma is increasingly recognised as a heterogeneous disorder comprising different clinical and inflammatory characteristics, and type 2 cytokines (specifically interleukin 4, interleukin 5, and interleukin 13) are recognised as playing a substantial pathobiological part in many cases.[4,6–11] These cytokines contribute to a type-2/T-helper-2-cell (Th2)-high molecular asthma phenotype in up to 50% of patients with asthma, across all severities.[10–12] Emerging data suggest that most biologics tested to date, including interleukin-5 and interleukin-13 blockers, are mainly active in patients with type-2/Th2-high asthma, as reflected by baseline eosinophil count or biomarkers such as IgE and periostin, or both.[13,14]

Dupilumab, a fully human monoclonal antibody directed against the interleukin-4 receptor α subunit, inhibits both interleukin-4 and interleukin-13 signalling. In a previous phase 2a, randomised, placebo-controlled, double-blind clinical trial, dupilumab was efficacious in patients with persistent moderate-to-severe asthma with evidence of ongoing type 2/Th2 inflammation at screening, as measured by elevated blood or sputum eosinophils (defined as ≥300 eosinophils per μL).[7] The 300 eosinophils per μL cutoff has been used previously in other interventional studies[7,15] and has been reported to be associated with more severe asthma.[15] Dupilumab has shown significant clinical improvements in other conditions driven by type 2/Th2 inflammation—namely, atopic dermatitis and symptomatic chronic sinusitis with nasal polyposis, both of which often coexist with asthma,[4,16–19] suggesting that several comorbid systemic conditions can be broadly addressed by dupilumab.[14] Given the positive outcomes of the phase 2a trial, this randomised phase 2b dose-ranging clinical trial was designed to assess the efficacy and safety of add-on therapy with dupilumab in patients with uncontrolled persistent asthma on medium-to-high-dose inhaled corticosteroids plus long-acting β_2-agonist therapy with baseline blood eosinophils counts of at least 300 eosinophils per μL and fewer than 300 eosinophils per μL.

See Online for appendix

Methods

Study design and patients

We did this randomised, double-blind, placebo-controlled, parallel-group, pivotal phase 2b clinical trial at 174 study sites in Argentina, Australia, Chile, France, Italy, Japan, the Republic of Korea, Mexico, New Zealand, Poland, Russia, South Africa, Spain, Turkey, Ukraine, and the USA (study sites and investigators are listed in the appendix.

Adults (aged ≥18 years) with an asthma diagnosis for 12 months or more based on the Global Initiative for Asthma 2009 Guidelines were eligible for participation.[20] Patients were required to provide written informed consent and to have existing treatment with medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist (fluticasone propionate ≥250 μg, or equivalent inhaled corticosteroids, twice daily) with a stable dose of inhaled corticosteroids plus a long-acting β_2 agonist for at least 1 month before screening; a pre-bronchodilator forced expiratory volume in 1 s (FEV_1) of 40–80% predicted at screening and at baseline; a 5-item Asthma Control Questionnaire (ACQ-5) score of 1·5 or higher at screening and at baseline;[21] and reversibility of at least

12% and 200 mL in FEV_1 after 200–400 μg of salbutamol at screening. Patients were also required for study inclusion to have had any of the following within 1 year before screening: at least one systemic (oral or parenteral) corticosteroid burst therapy, or a hospital admission or an emergency or urgent medical care visit that required treatment with systemic steroids for worsening asthma.

Exclusion criteria included a diagnosis of chronic obstructive pulmonary disease or other diseases that impair pulmonary function tests; use of β-adrenergic receptor blockers for any reason; and use of systemic corticosteroids within 28 days of, or during, the screening period. Current smokers or smokers who had stopped within 6 months before screening or had a previous history of more than 10 pack-years were also excluded. Additional and detailed exclusion criteria are listed in the appendix. Central laboratory baseline blood eosinophil count (count at time of randomisation or 14–21 days after screening) was neither an inclusion nor an exclusion criterion.

The study consisted of three periods: a 14–21-day screening period, a 24-week randomised treatment period, and a 16-week post-treatment follow-up period. Patient eligibility was confirmed, and the level of asthma control achieved with medium-to-high-dose inhaled corticosteroids plus long-acting β_2-agonist treatment (inhaled corticosteroids ≥250 μg twice daily) was established during the screening period. Three combinations of inhaled corticosteroids plus a long-acting β_2-agonist were permitted during the treatment period: mometasone furoate plus formoterol, budesonide plus formoterol, or fluticasone propionate plus salmeterol; details of their dose, strength, and schedules are listed in the appendix. Any patient receiving an alternative combination was switched to an equivalent dose of one of these combinations and dose stabilised for at least 30 days before being randomly assigned to a study drug.

This study was done in accordance with the principles established in the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. All study documents and procedures were approved by the appropriate institutional review board or ethics committee at each study site. All patients provided written informed consent before participation in the study.

Randomisation and masking

Patients were randomised (1:1:1:1:1) by a centralised treatment allocation system to receive subcutaneous dupilumab 200 mg every 4 weeks (n=154), 300 mg every 4 weeks (n=157), 200 mg every 2 weeks (n=150), 300 mg every 2 weeks (n=157), or placebo (n=158). Dupilumab and placebo were provided in 5 mL identical vials containing a deliverable volume of 2 mL, with either 150 mg/mL solution (300 mg dose/2 mL) or 100 mg/mL solution (200 mg dose/2 mL). Patients were randomly allocated according to a central randomisation scheme provided by an interactive voice response system or an interactive web response system. Study patients, investigators, and site personnel remained masked to study treatment.

To ensure a balanced distribution of blood eosinophil counts in patients across treatment regimens, randomisation was stratified by central laboratory blood eosinophil count at screening (≥300 eosinophils per μL, 200–299 eosinophils per μL, and <200 eosinophils per μL) and by country. Randomisation continued until at least 300 patients with eosinophil counts of at least 300 eosinophils per μL were included. To achieve this goal, and based on an expected recruitment rate of 40% of patients with eosinophil counts of at least 300 eosinophils per μL, approximately 750 patients were anticipated to be recruited.

Procedures

Patients received masked subcutaneous administrations of dupilumab or matching placebo every 2 weeks or every 4 weeks on their first day of treatment until week 24 as follows: dupilumab 200 mg (every 2 weeks and every 4 weeks), loading dose of 400 mg; dupilumab 300 mg (every 2 weeks and every 4 weeks), loading dose of 600 mg; or placebo; followed by a 16-week post-treatment follow-up period to monitor patients after treatment. Patients continued background therapy with inhaled corticosteroids plus a long-acting β_2-agonist at a stable dose throughout the randomised treatment period and during follow-up. Throughout the study, and as needed, patients were allowed to administer a short-acting β_2-adrenergic receptor agonist (either salbutamol or levosalbutamol) as relief medication for asthma symptoms. Concomitant medications were permitted during the study; exceptions are listed in the appendix. Study assessments were done every 2 weeks from baseline to week 12, followed by every 4 weeks until week 24, and every 4 weeks during the 16-week follow-up period.

Outcomes

The primary efficacy endpoint was change from baseline at week 12 in FEV_1 (L) in patients with baseline blood eosinophil counts of at least 300 eosinophils per μL. Secondary endpoints were prespecified at week 12 and week 24 for both the overall population and for the subgroup with eosinophil counts of at least 300 eosinophils per μL. These included percentage change from baseline in FEV_1; annualised severe asthma exacerbation rate (severe exacerbation event defined as deterioration of asthma that required use of systemic corticosteroids for at least 3 days, or hospital admission or emergency department visit because of asthma treated with systemic corticosteroids) during treatment and overall study periods (which included follow-up); time to severe exacerbation events during treatment and overall study periods; and change from baseline at week 12 and week 24 in morning

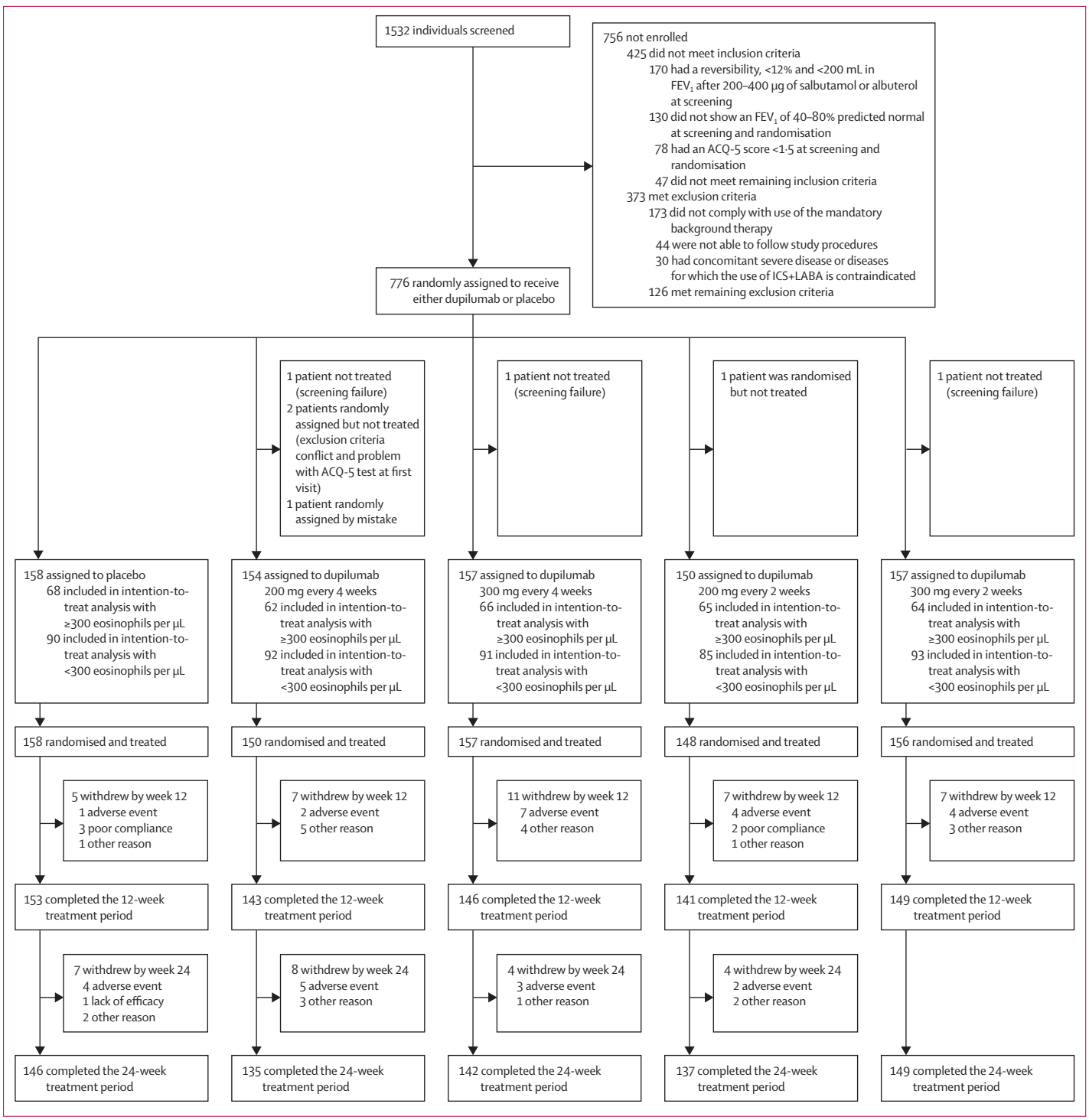

Figure 1: **Trial profile**

The intention-to-treat population was defined as all randomised population analysed according to treatment group allocated by randomisation, irrespective of whether or not treatment kit was used. Screened patients (n=1532) might have been counted twice if they were rescreened. If patients did not meet more than one inclusion criterion or met more than one exclusion criterion, the number might also include some patients more than once. Not all randomised patients were treated. ACQ-5=5-item Asthma Control Questionnaire. FEV_1=forced expiratory volume in 1 s. ICS=inhaled corticosteroids. LABA=long-acting β_2 agonist.

	Overall population (n=776)	≥300 eosinophils per µL (n=325)	<300 eosinophils per µL (n=451)
Mean age (years)	48·6 (13·0)	48·0 (12·8)	49·1 (13·0)
Male	286 (37%)	128 (39%)	158 (35%)
Race			
White	607 (78%)	247 (76%)	360 (80%)
Black or African American	42 (5%)	14 (4%)	28 (6%)
Asian	115 (15%)	60 (18%)	55 (12%)
American Indian or Alaska Native	1 (<1%)	0	1 (<1%)
Native Hawaiian or Pacific Islander	1 (<1%)	1 (<1%)	0
Other	10 (1%)	3 (1%)	7 (2%)
Mean body-mass index (kg/m^2)	29·45 (6·34)	28·97 (6·21)	29·79 (6·42)
Body-mass index ≥30 (kg/m^2)	312 (40%)	117 (36%)	195 (43%)
Mean baseline eosinophil count (eosinophils per µL)	347·46 (427·59)	590·09 (572·92)	172·02 (69·90)
Mean baseline total IgE (IU/mL)	435·05 (753·88); 775	558·93 (931·65); 325	345·58 (578·14); 450
Mean time since first asthma diagnosis (years)	22·03 (15·42); 773	20·22 (14·46); 323	23·33 (15·96); 450
Mean FEV_1 (L)	1·84 (0·54)	1·82 (0·56)	1·86 (0·53)
Mean FEV_1 predicted (%)	60·77% (10·72)	59·16% (11·08)	61·94% (10·31)
Mean number of asthma exacerbations in past year	2·17 (2·14); 775	2·37 (2·34); 324	2·02 (1·98); 451
High-dose inhaled corticosteroid plus long-acting β_2-agonist* use	384/755 (51%)	174/317 (55%)	210/438 (48%)
Mean ACQ-5 score†	2·74 (0·81); 775	2·73 (0·85); 324	2·75 (0·79); 451
Mean AQLQ global score‡	4·02 (1·09); 766	3·98 (1·16); 321	4·04 (1·04); 445
Mean AM asthma symptom score§	1·25 (0·80)	1·26 (0·80)	1·25 (0·79)
Mean PM asthma symptom score§	1·44 (0·81)	1·48 (0·82)	1·40 (0·80)
Salbutamol use for symptom relief,¶ mean puffs per 24 h	3·06 (3·00)	2·95 (2·95)	3·15 (3·03)
Mean FeNO (parts per billion)	39·10 (35·09); 699	51·70 (42·40); 298	29·73 (24·66); 401
Comorbid medical history	590/763 (77%)	258/322 (80%)	332/441 (75%)
Atopic dermatitis	79/763 (10%)	37/322 (11%)	42/441 (10%)
Allergic rhinitis	494/763 (65%)	209/322 (65%)	285/441 (65%)
Nasal polyposis‖	125/763 (16%)	85/322 (26%)	40/441 (9%)
Former smoker	174/775 (22%)	75/324 (23%)	99/451 (22%)
Mean number of packs per year	4·37 (3·09); 173	4·15 (3·09); 74	4·53 (3·10); 99

Data are mean (SD), n (%), mean (SD); N, or n/N (%). ACQ-5=5-item Asthma Control Questionnaire. AQLQ=Asthma Quality of Life Questionnaire. FeNO=fractional exhaled nitric oxide. FEV_1=forced expiratory volume in 1 s. *Use of inhaled corticosteroids plus long-acting β_2 agonists was recorded in an electronic diary. †ACQ-5 is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment; higher scores indicate less control; a global score is calculated ranging from 0–6. ‡AQLQ is a patient-reported measure of the effect of asthma on quality of life; higher scores indicate better quality of life; a global score is calculated ranging from 0–7. §Asthma symptom scores are patient-reported measures of asthma symptoms, taken on waking and in the evening, and their effects on activities (PM) and sleep (AM); higher scores indicate greater disruption; symptom scores range from 0–4. ¶Includes the use of levosalbutamol for symptom relief; the number of salbutamol or levosalbutamol inhalations was recorded daily by the patients; alternatively salbutamol and levosalbutamol nebulisers were used and converted to number of puffs. ‖Nasal polyposis was assessed by clinical history.

Table 1: **Baseline characteristics in the overall population and by baseline blood eosinophil count**

and evening asthma symptom scores (appendix), ACQ-5 score, Asthma Quality of Life Questionnaire (AQLQ) score,[22,23] and number of inhalations per day of salbutamol or levosalbutamol for symptom relief. Changes from baseline in fractional exhaled nitric oxide (FeNO) concentrations at weeks 12 and 24 were also assessed. The full list of secondary efficacy endpoints is presented in the appendix. Safety outcomes, including treatment-emergent adverse events, serious treatment-emergent adverse events, vital signs, clinical laboratory values, and electrocardiogram results, were reported from baseline through to week 40. Blood eosinophils were measured as part of a standard five-part white blood cell differential count on a haematology autoanalyser.

Statistical analysis

For the primary endpoint, enrolment of 60 patients per group with eosinophil counts of at least 300 eosinophils per µL provided 83% power to detect a difference in FEV_1 change of 0·2 L between the highest dupilumab dose and placebo, assuming the common SD was 0·35, with a two-sided test at a 0·05 significance level and an expected dropout rate of 10% by week 12. The values used in this sample size estimation were based on a comparison between dupilumab doses versus placebo with regard to the primary endpoint in patients with eosinophils counts of at least 300 eosinophils per µL in the previous phase 2a study (NCT01312961).[7]

	Placebo	Dupilumab			
		200 mg every 4 weeks	300 mg every 4 weeks	200 mg every 2 weeks	300 mg every 2 weeks
Overall population (n=776)					
Total number of participants	158	154	157	150	157
LS mean change in FEV_1 from baseline at week 12* (L)	0·12 (0·03); 129	0·21 (0·03); 134	0·24 (0·03); 134	0·31 (0·03); 136	0·28 (0·03); 146
LS mean difference *vs* placebo	..	0·10 (0·01–0·18); 134	0·12 (0·04–0·21); 134	0·20 (0·11–0·28); 136	0·16 (0·08–0·25); 146
p value *vs* placebo	..	0·0304	0·0048	<0·0001	0·0002
LS mean change in FEV_1 from baseline at week 12 (%)	6·06% (1·89); 129	13·53% (1·90); 134	14·03% (1·86); 134	18·00% (1·89); 136	17·75% (1·84); 146
LS mean difference *vs* placebo	..	7·47 (2·29–12·65); 134	7·97 (2·85–13·09); 134	11·94 (6·77–17·11); 136	11·69 (6·59–16·80); 146
p value *vs* placebo	..	0·0047	0·0023	<0·0001	<0·0001
LS mean change in FEV_1 from baseline at week 24 (L)	0·13 (0·03); 125	0·23 (0·03); 126	0·26 (0·03); 132	0·29 (0·03); 135	0·28 (0·03); 143
LS mean difference *vs* placebo	..	0·10 (0·01–0·19)	0·13 (0·04–0·21)	0·16 (0·07–0·24)	0·16 (0·07–0·24)
p value *vs* placebo	..	0·0218	0·0037	0·0005	0·0004
LS mean change in FEV_1 from baseline at week 24 (%)	7·01% (1·87); 125	14·52% (1·90); 126	15·68% (1·86); 132	16·62% (1·88); 135	17·34% (1·83); 143
LS mean difference *vs* placebo	..	7·51 (2·35–12·67)	8·67 (3·58–13·77)	9·60 (4·47–14·74)	10·33 (5·26–15·40)
p value *vs* placebo	..	0·0044	0·0009	0·0003	<0·0001
≥1 severe exacerbation event in the 24-week treatment period	41/158 (26%)	23/150 (15%)	29/157 (18%)	13/148 (9%)	17/156 (11%)
Adjusted annualised severe exacerbation event rate estimate	0·897 (0·619–1·300)	0·415 (0·260–0·664)	0·599 (0·396–0·907)	0·269 (0·157–0·461)	0·265 (0·157–0·445)
Risk reduction *vs* placebo (%)	..	53·7% (17·3–74·1)	33·2% (–13·8 to 74·1)	70·0% (43·5–84·1)	70·5% (45·4–84·1)
p value *vs* placebo	..	0·0093	0·1380	0·0002	0·0001
≥300 eosinophils per µL (n=325)					
Total number of participants	68	62	66	65	64
LS mean change in FEV_1 from baseline at week 12* (L)	0·18 (0·05); 58	0·26 (0·06); 53	0·35 (0·05); 55	0·43 (0·05); 57	0·39 (0·05); 59
LS mean difference *vs* placebo	..	0·08 (–0·07 to 0·23)	0·17 (0·03–0·32)	0·26 (0·11–0·40)	0·21 (0·06–0·36)
p value *vs* placebo	..	0·2774	0·0212	0·0008	0·0063
LS mean change in FEV_1 from baseline at week 12 (%)	10·17% (3·32); 58	17·93% (3·43); 53	21·57% (3·32); 55	25·91% (3·32); 57	25·80% (3·35); 59
LS mean difference *vs* placebo	..	7·76 (–1·55 to 17·07)	11·40 (2·28–20·52)	15·74 (6·61–24·87)	15·63 (6·47–24·80)
p value *vs* placebo	..	0·1018	0·0145	0·0008	0·0009
LS mean change in FEV_1 from baseline at week 24 (L)	0·22 (0·05); 52	0·28 (0·06); 50	0·37 (0·05); 57	0·38 (0·05); 59	0·38 (0·05); 58
LS mean difference *vs* placebo	..	0·06 (–0·09 to 0·21)	0·15 (0·01–0·30)	0·16 (0·02–0·31)	0·16 (0·01–0·30)
p value *vs* placebo	..	0·4349	0·0401	0·0264	0·0345
LS mean change in FEV_1 from baseline at week 24 (%)	12·83% (3·22); 52	18·87% (3·36); 50	23·31% (3·20); 57	22·89% (3·21); 59	24·92% (3·25); 58
LS mean difference *vs* placebo	..	6·04 (–3·04 to 15·12)	10·48 (1·66–19·31)	10·07 (1·23–18·90)	12·09 (3·20–20·97)
p value *vs* placebo	..	0·1913	0·02	0·0257	0·0078
≥1 severe exacerbation event in the 24-week treatment period	19/68 (28%)	7/59 (12%)	11/66 (17%)	5/64 (8%)	7/64 (11%)
Adjusted annualised severe exacerbation event rate estimate	1·044 (0·572–1·904)	0·358 (0·158–0·809)	0·678 (0·356–1·290)	0·300 (0·133–0·678)	0·201 (0·078–0·517)
Risk reduction *vs* placebo (%)	..	65·7% (8·3–87·2)	35·1% (–49·9 to 71·9)	71·2% (24·3–89·1)	80·7% (44·1–93·3)
p value *vs* placebo	..	0·0329	0·3119	0·0116	0·0024
<300 eosinophils per µL (n=451)					
Total number of participants	90	92	91	85	93
LS mean change in FEV_1 from baseline at week 12* (L)	0·10 (0·04); 71	0·19 (0·04); 81	0·18 (0·04); 79	0·25 (0·04); 79	0·22 (0·04); 87
LS mean difference *vs* placebo	..	0·09 (–0·01 to 0·20)	0·08 (–0·02 to 0·18)	0·15 (0·04–0·25)	0·12 (0·01–0·22)
p value *vs* placebo	..	0·0795	0·1231	0·0057	0·0262
LS mean change in FEV_1 from baseline at week 12 (%)	4·82% (2·16); 71	11·03% (2·14); 81	10·02% (2·08); 79	13·63% (2·14); 79	12·56% (2·06); 87
LS mean difference *vs* placebo	..	6·20 (0·37–12·04)	5·20 (–0·61 to 11·01)	8·81 (2·93–14·69)	7·74 (1·98–13·50)
p value *vs* placebo	..	0·0371	0·0791	0·0034	0·0086
LS mean change in FEV_1 from baseline at week 24 (L)	0·09 (0·04); 73	0·21 (0·04); 76	0·20 (0·04); 75	0·23 (0·04); 76	0·23 (0·04); 85
LS mean difference *vs* placebo	..	0·12 (0·01–0·22)	0·10 (–0·00 to 0·21)	0·14 (0·03–0·25)	0·14 (0·03–0·24)
p value *vs* placebo	..	0·0306	0·0536	0·0104	0·0109

(Table 2 continues on next page)

	Placebo	Dupilumab			
		200 mg every 4 weeks	300 mg every 4 weeks	200 mg every 2 weeks	300 mg every 2 weeks
(Continued from previous page)					
LS mean change in FEV_1 from baseline at week 24 (%)	4·65% (2·21); 73	12·04% (2·21); 76	11·62% (2·16); 75	13·41% (2·22); 76	12·55% (2·12); 85
LS mean difference *vs* placebo	..	7·39 (1·38–13·40)	6·97 (0·98–12·95)	8·75 (2·70–14·81)	7·90 (1·98–13·81)
p value *vs* placebo	..	0·016	0·0228	0·0047	0·009
≥1 severe exacerbation event in the 24-week treatment period	22/90 (24%)	16/91 (18%)	18/91 (20%)	8/84 (10%)	10/92 (11%)
Adjusted annualised severe exacerbation event rate estimate	0·779 (0·493–1·231)	0·445 (0·252–0·786)	0·489 (0·286–0·837)	0·253 (0·124–0·516)	0·313 (0·170–0·576)
Risk reduction *vs* placebo (%)	..	42·9% (–15·9 to 71·9)	37·2% (–24·3 to 68·3)	67·6% (24·4–85·9)	59·9% (16·1–80·8)
p value *vs* placebo	..	0·1209	0·1819	0·0081	0·0152

Data are mean change (SE); N, mean difference (95% CI); N, or n/N (%), unless otherwise stated. FEV_1=forced expiratory volume in 1 s. LS=least squares. *Primary efficacy endpoint was change from baseline in FEV_1 (L) at 12 weeks in patients with an eosinophil count of at least 300 eosinophils per µL. A severe exacerbation event during the study was defined as deterioration of asthma requiring use of systemic corticosteroids for at least 3 days or hospital admission or emergency department visit because of asthma treated with systemic corticosteroids; adjusted annualised severe exacerbation rates were derived from the 24-week treatment period.

Table 2: **Lung function and asthma exacerbations in the overall population and by baseline blood eosinophil count**

The primary efficacy endpoint and continuous secondary endpoint variables were analysed with a mixed-effects model with a repeated-measures approach. The model included change from baseline to week 12 as response variables, factors (fixed effects) for treatment, baseline blood eosinophil strata, pooled countries or regions, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction. Missing data-points were not imputed. FEV_1 measurements collected from systemic corticosteroid start date to systemic corticosteroid end date plus 30 days for each exacerbation episode were excluded from the primary analysis to reduce the confounding effect of systemic corticosteroids. For patients discontinuing treatment before week 12, off-treatment FEV_1 values were excluded in the primary analysis.

The annualised rate of severe asthma exacerbation events during the treatment period only was analysed with a negative binomial regression model, including the total number of events occurring during the double-blind treatment period as the response variable; treatment group, baseline blood eosinophil strata, pooled countries or regions, and number of asthma events in the year before the study as covariates; and log-transformed treatment duration as the offset variable. For patients who prematurely discontinued the study drug, events occurring during the treatment period were included and the analysis adjusted for the treatment duration.

Time to severe exacerbation was analysed using a Cox regression model with time to exacerbation event as the dependent variable and treatment group, baseline blood eosinophil strata, number of asthma events in the year before the study, and pooled countries or regions as covariates. The Kaplan-Meier method was used to derive the proportion of patients with an event at weeks 12 and 24 specific to each treatment group. If a patient had no exacerbation event before treatment discontinuation or completion, they were considered free of event until the end of the treatment period (last dose date plus 14 days). Safety variables, including adverse events, laboratory variables, vital signs, electrocardiograms, and physical examinations, were summarised with descriptive statistics.

The intention-to-treat population included all patients randomly assigned to treatment. The safety population included all randomly assigned patients who received at least one dose or part of a dose of study treatment. Analyses for both primary and secondary efficacy endpoints and safety were prespecified for the subgroup of patients with an eosinophil count of at least 300 eosinophils per µL and the overall intention-to-treat safety population (both intention to treat and safety). Outcomes in patients with an eosinophil count of fewer than 300 eosinophils per µL were also assessed. For the primary endpoint and within each secondary endpoint, a step-down procedure was used to control the overall type I error rate for testing multiple doses against placebo. The hierarchy was dupilumab 300 mg every 2 weeks, 200 mg every 2 weeks, 300 mg every 4 weeks, and 200 mg every 4 weeks.

An independent data monitoring committee reviewed safety data throughout the trial. Acting in an advisory capacity, their role was to communicate any recommendations regarding the trial conduct to the sponsors, who were obliged to react promptly. SAS version 9.2 was used for all analyses. This trial is registered at ClinicalTrials.gov, number NCT01854047, and with the EU Clinical Trials Register, EudraCT number 2013-000856-16.

Role of the funding source

The external authors and study sponsors participated in the study design, data analysis and interpretation, and development of the report, and gave approval to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

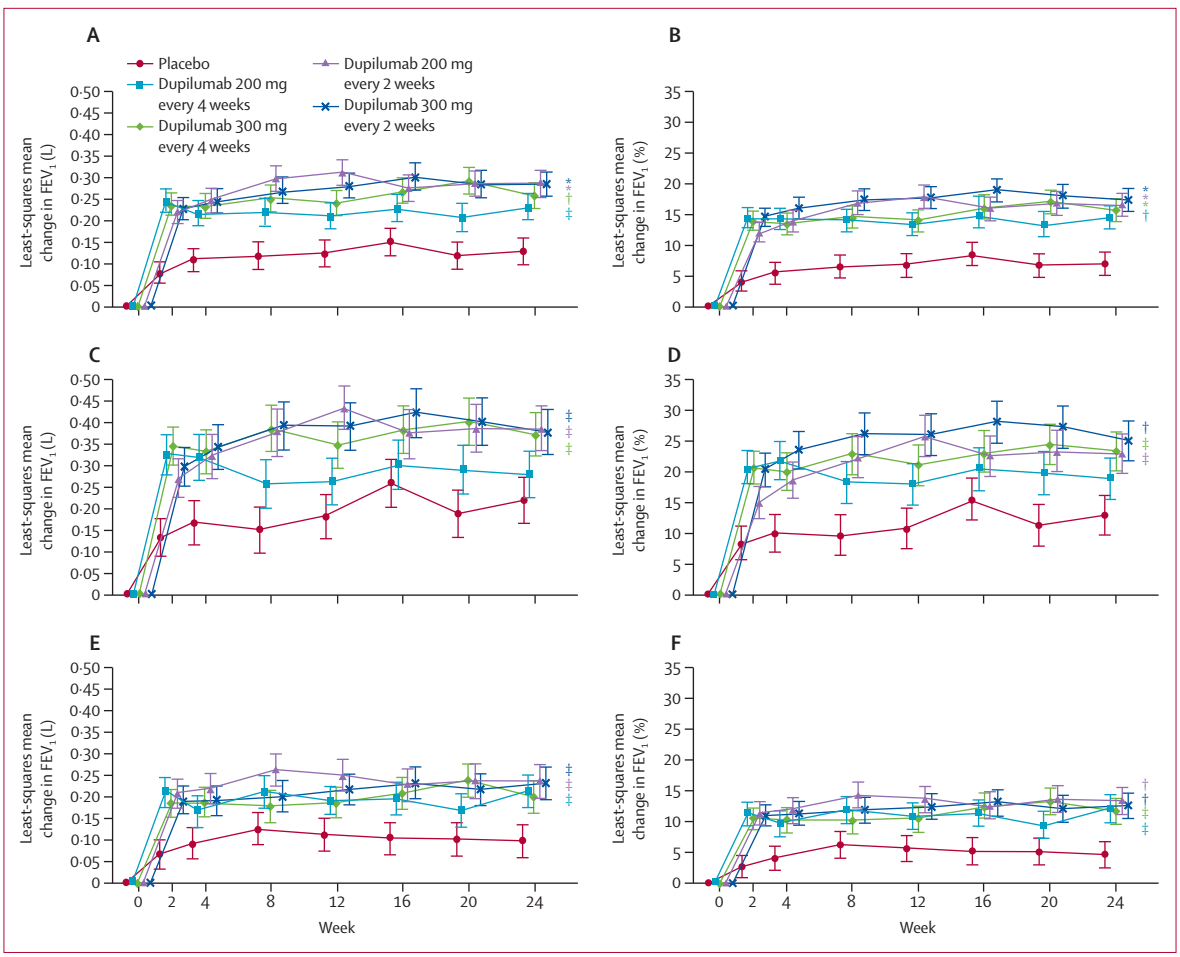

Figure 2: **Improvement in FEV_1 in L (A, C, E) and percentage change (B, D, F) from baseline to week 24**
Data are in the overall population (A, B), patients with baseline blood eosinophil counts of at least 300 eosinophils per μL (C, D), and patients with counts lower than 300 eosinophils per μL (E, F). FEV_1=forced expiratory volume in 1 s. *p<0·001. †p<0·01. ‡p<0·05. Error bars indicate SE.

Results

Between June 10, 2013, and June 16, 2014, 1532 patients were screened for study eligibility and 776 were subsequently randomly assigned. 158 were assigned to the placebo group and 618 were assigned to the dupilumab groups. Of these, 769 patients (158 in the placebo group and 611 in the dupilumab groups) received at least one dose of study medication and, of these, 732 completed the 12-week study treatment period (primary endpoint); 709 completed the 24-week treatment period (135–149 patients per treatment group); and 689 completed both the 24-week treatment and the 16-week post-treatment follow-up periods. Overall, 325 patients (42%) had a baseline blood eosinophil count of at least 300 eosinophils per μL and were included in the primary analysis population (62–68 patients per treatment group; figure 1). Baseline patient characteristics were generally similar between the treatment groups (table 1). Mean baseline FeNO concentrations and percentage of patients with nasal polyposis were higher in the subgroup with eosinophil counts of at least 300 eosinophils per μL than in the subgroup with fewer than 300 eosinophils per μL (table 1, appendix).

For the primary endpoint, in the subgroup with eosinophil counts of at least 300 eosinophils per μL, all dupilumab dose regimens, except for the 200 mg every 4 weeks dose regimen, showed significant (300 mg every 4 weeks, p=0·0212; 200 mg every 2 weeks, p=0·0008; 300 mg every 2 weeks, p=0·0063) increases in FEV_1 from baseline at week 12 that ranged from 0·35 L (SE 0·05) to 0·43 L (0·05) and ranged from 0·17 L (95% CI 0·03–0·32) to 0·26 L (0·11–0·40) versus placebo (table 2). Increases were sustained through the 24-week treatment period (figure 2), ranging from 0·37 L (0·05) to 0·38 L (0·05) from baseline and ranging from 0·15 L (0·01–0·30) to 0·16 L (0·01–0·30) versus placebo at week 24, and were significant (300 mg every 4 weeks, p=0·0401; 200 mg every 2 weeks, p=0·0264; 300 mg every 2 weeks, p=0·0345) for all dose regimens except 200 mg dupilumab every 4 weeks (table 2).

For the secondary endpoints assessed in the overall population and the subgroup with eosinophil counts of

fewer than 300 eosinophils per µL, dupilumab every 2 weeks resulted in significant (overall population: 200 mg every 2 weeks, p<0·0001; 300 mg every 2 weeks, p=0·0002; fewer than 300 eosinophils per µL: 200 mg every 2 weeks, p=0·0057; 300 mg every 2 weeks, p=0·0262) increases in FEV_1 (L) compared with placebo at week 12 that were sustained through to week 24 (table 2, figure 2). Both doses of dupilumab every 2 weeks also resulted in significant (table 2) increases in percentage change in FEV_1 compared with placebo through to week 24 in the overall population and in the two subgroups. After treatment withdrawal, the FEV_1 change from baseline declined in all three subgroups (data not shown). For the overall population, FEV_1 percentage change from baseline at week 24 ranged from 16·6% (SE 1·88) to 17·3% (1·83) in the overall population, from 22·9% (3·21) to 24·9% (3·25) for the subgroup with at least 300 eosinophils per µL, and for those with fewer than 300 eosinophils per µL from 12·6% (2·12) to 13·4 % (2·22; figure 2, table 2).

During the 24-week treatment period, dupilumab every 2 weeks significantly (table 2) reduced the annualised rates of severe asthma exacerbations compared with placebo (table 2, figure 3). In the overall population, significant reductions in annualised severe asthma exacerbations were observed in patients receiving doses every 2 weeks (table 2). Dupilumab every 2 weeks also resulted in reductions in annualised severe asthma exacerbations in both eosinophil-count-based subgroups. In the overall population and in both subgroups, dupilumab every 2 weeks significantly delayed time to first severe exacerbation versus placebo (overall population: 200 mg every 2 weeks, p<0·0001; 300 mg every 2 weeks, p=0·0002; ≥300 eosinophils per µL: 200 mg every 2 weeks, p=0·0008; 300 mg every 2 weeks, p=0·0048; <300 eosinophils per µL: 200 mg every 2 weeks, p=0·0092; 300 mg every 2 weeks, p=0·0130; appendix). Less consistent improvements were observed for dupilumab every 4 weeks with both doses in the eosinophil-count-based subgroups. Data for the overall study period (including follow-up) are provided in the appendix.

In the overall population and in the subgroup with eosinophil counts of at least 300 eosinophils per µL, improvements in ACQ-5 total scores at week 24 relative to baseline were significantly greater in patients receiving dupilumab every 2 weeks (table 3) than in those receiving placebo. In the subgroup with eosinophil counts of fewer

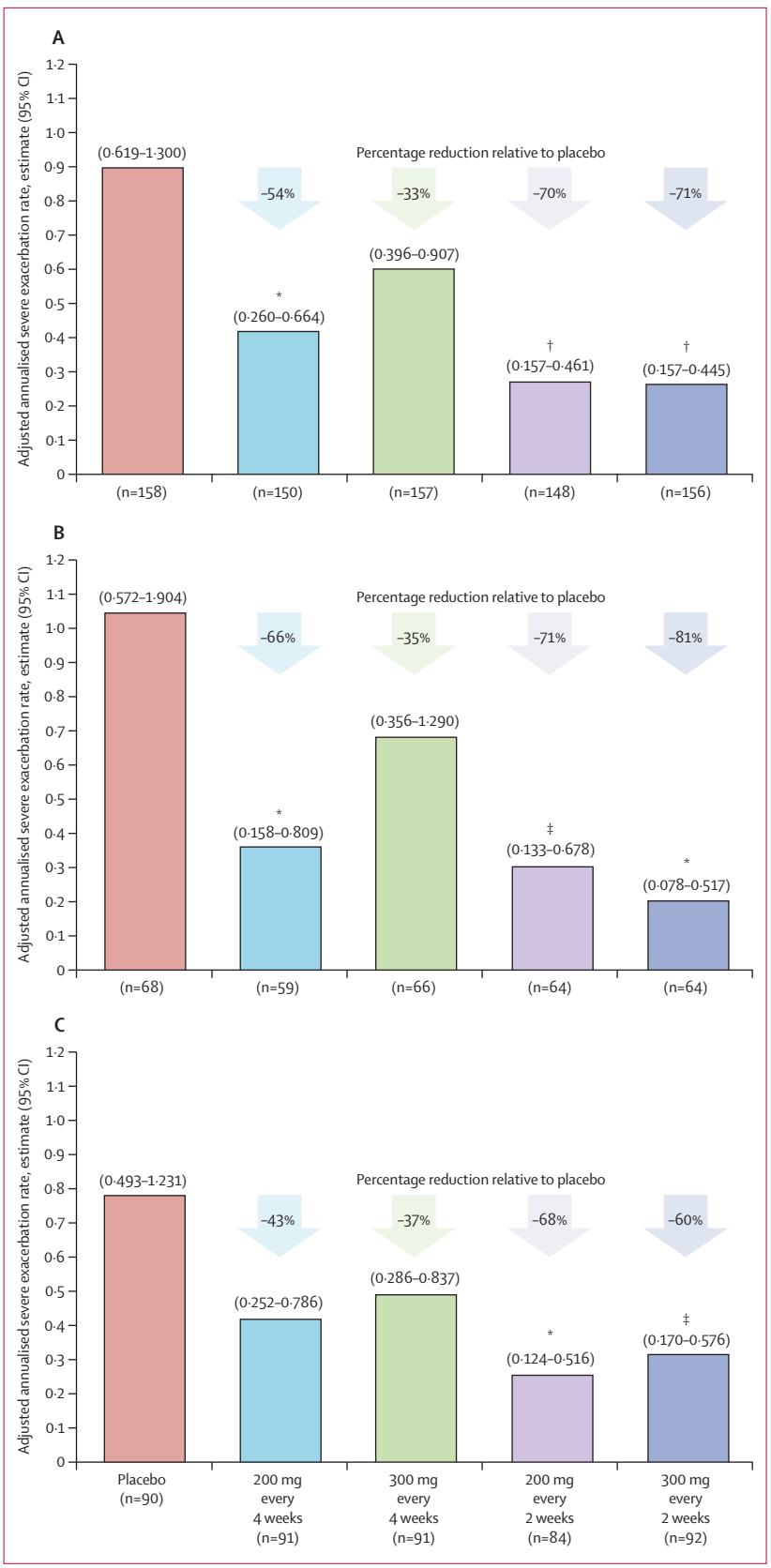

Figure 3: **Adjusted annualised severe exacerbation event rates estimated from the 24-week treatment period in the overall population (A) and in patients with baseline blood eosinophil counts of at least 300 eosinophils per µL (B) and fewer than 300 eosinophils per µL (C)**
Error bars indicate point estimate from adjusted annualised severe exacerbation event rates in 24-week treatment period. A severe exacerbation event during the study was defined as a deterioration of asthma requiring use of systemic corticosteroids for 3 days or more or hospital admission or emergency department visit because of asthma, requiring systemic corticosteroids. *p<0·01. †p<0·001. ‡p<0·05 *vs* placebo.

	Placebo	Dupilumab			
		200 mg every 4 weeks	300 mg every 4 weeks	200 mg every 2 weeks	300 mg every 2 weeks
Overall population (n=776)					
Total number of participants	158	154	157	150	157
LS mean change in ACQ-5 score* from baseline to week 24	−1·14 (0·08); 127	−1·32 (0·08); 126	−1·34 (0·08); 132	−1·49 (0·08); 134	−1·45 (0·08); 145
LS mean difference *vs* placebo	..	−0·18 (−0·40 to 0·03)	−0·20 (−0·41 to 0·02)	−0·35 (−0·57 to −0·14)	−0·31 (−0·52 to −0·09)
p value *vs* placebo	..	0·0992	0·0724	0·0015	0·0049
LS mean change in AQLQ global score† from baseline to week 24	0·88 (0·09); 127	1·12 (0·09); 127	1·18 (0·08); 132	1·20 (0·09); 132	1·24 (0·08); 141
LS mean difference *vs* placebo	..	0·23 (−0·00 to 0·47)	0·30 (0·07–0·53)	0·31 (0·08–0·55)	0·36 (0·12–0·59)
p value *vs* placebo	..	0·0530	0·0120	0·0090	0·0027
LS mean change in AM asthma symptom score‡ from baseline to week 24	−0·36 (0·05); 132	−0·53 (0·05); 134	−0·54 (0·05); 135	−0·57 (0·05); 136	−0·56 (0·05); 145
LS mean difference *vs* placebo	..	−0·17 (−0·31 to −0·04)	−0·18 (−0·31 to −0·04)	−0·22 (−0·35 to −0·08)	−0·20 (−0·33 to −0·07)
p value *vs* placebo	..	0·0128	0·0093	0·0018	0·0030
LS mean change in PM asthma symptom score‡ from baseline to week 24	−0·39 (0·06); 132	−0·52 (0·06); 135	−0·59 (0·06); 136	−0·60 (0·06); 136	−0·61 (0·06); 145
LS mean difference *vs* placebo	..	−0·14 (−0·29 to 0·02)	−0·20 (−0·36 to −0·05)	−0·21 (−0·37 to −0·06)	−0·23 (−0·38 to −0·07)
p value *vs* placebo	..	0·0832	0·0107	0·0077	0·0040
≥300 eosinophils per µL (n=325)					
Total number of participants	68	62	66	65	64
LS mean change in ACQ-5 score* from baseline to week 24	−1·17 (0·13); 52	−1·48 (0·13); 50	−1·38 (0·12); 57	−1·59 (0·12); 59	−1·72 (0·13); 58
LS mean difference *vs* placebo	..	−0·31 (−0·66 to 0·05)	−0·21 (−0·55 to 0·14)	−0·42 (−0·76 to −0·07)	−0·55 (−0·90 to −0·20)
p value *vs* placebo	..	0·0878	0·2371	0·0171	0·0021
LS mean change in AQLQ global score† from baseline to week 24	0·79 (0·13); 53	1·32 (0·14); 50	1·22 (0·13); 57	1·46 (0·13); 58	1·57 (0·13); 56
LS mean difference *vs* placebo	..	0·53 (0·16–0·90)	0·43 (0·07–0·79)	0·67 (0·31–1·03)	0·78 (0·42–1·15)
p value *vs* placebo	..	0·0054	0·0184	0·0003	<0·0001
LS mean change in AM asthma symptom score‡ from baseline to week 24	−0·45 (0·07); 55	0·61 (0·08); 53	−0·72 (0·07); 58	−0·69 (0·07); 59	−0·68 (0·08); 58
LS mean difference *vs* placebo	..	−0·16 (−0·37 to 0·04)	−0·27 (−0·47 to −0·07)	−0·24 (−0·44 to −0·04)	−0·23 (−0·44 to −0·02)
p value *vs* placebo	..	0·1208	0·0094	0·0212	0·0285
LS mean change in PM asthma symptom score‡ from baseline to week 24	−0·45 (0·08); 56	−0·72 (0·09); 53	−0·76 (0·09); 58	−0·72 (0·09); 59	−0·84 (0·09); 58
LS mean difference *vs* placebo	..	−0·28 (−0·52 to −0·04)	−0·31 (−0·55 to −0·08)	−0·28 (−0·51 to −0·04)	−0·39 (−0·63 to −0·15)
p value *vs* placebo	..	0·0237	0·0089	0·0209	0·0014

(Table 3 continues on next page)

than 300 eosinophils per µL, a significant improvement in ACQ-5 score was achieved only for the 200 mg dupilumab every 2 weeks regimen compared with placebo (table 3). Week 12 results are shown in the appendix.

In the overall population, the global AQLQ scores at week 24 relative to baseline were significantly higher in patients receiving dupilumab dose regimens every 2 and 4 weeks than in those receiving placebo, except for those receiving 200 mg dupilumab every 4 weeks (table 3). In the subgroup with counts of at least 300 eosinophils per µL, the global AQLQ scores relative to baseline were significantly higher across all dose regimens of dupilumab compared with placebo (table 3). Only numerical improvements in global AQLQ scores were observed for the subgroup with counts of fewer than 300 eosinophils per µL (table 3).

In the overall population and in the subgroup with counts of at least 300 eosinophils per µL, morning and evening asthma symptom scores at week 24 relative to baseline significantly improved for both doses given every 2 weeks and for 300 mg dupilumab every 4 weeks (table 3). For the subgroup with fewer than 300 eosinophils per µL, morning symptom scores were significantly improved for both doses given every 2 weeks (table 3).

In the overall population, all dupilumab dose regimens resulted in significant (overall population: 200 mg every 4 weeks, p=0·0365; 300 mg every 4 weeks, p=0·0004; 200 mg every 2 weeks, p<0·0001; 300 mg every 2 weeks, p<0·0001) dose-dependent reductions in FeNO (differences ranging from −16·39% to −40·31% *vs* placebo) at week 24 (appendix), with near-maximum decreases observed at week 2 (appendix). Decreases in

	Placebo	Dupilumab			
		200 mg every 4 weeks	300 mg every 4 weeks	200 mg every 2 weeks	300 mg every 2 weeks
(Continued from previous page)					
<300 eosinophils per µL (n=451)					
Total number of participants	90	92	91	85	93
LS mean change in ACQ-5 score* from baseline to week 24	−1·13 (0·10); 75	−1·26 (0·10); 76	−1·34 (0·10); 75	−1·46 (0·10); 75	−1·29 (0·10); 87
LS mean difference *vs* placebo	..	−0·13 (−0·41 to 0·14)	−0·21 (−0·49 to 0·06)	−0·33 (−0·61 to −0·05)	−0·17 (−0·44 to 0·10)
p value *vs* placebo	..	0·3505	0·1328	0·0201	0·2259
LS mean change in AQLQ global score† from baseline to week 24	1·01 (0·11); 74	1·05 (0·11); 77	1·20 (0·11); 75	1·06 (0·11); 74	1·07 (0·11); 85
LS mean difference *vs* placebo	..	0·04 (−0·26 to 0·35)	0·19 (−0·11 to 0·49)	0·05 (−0·26 to 0·36)	0·06 (−0·24 to 0·36)
p value *vs* placebo	..	0·7703	0·2176	0·7400	0·6899
LS mean change in AM asthma symptom score‡ from baseline to week 24	−0·30 (0·07); 77	−0·48 (0·06); 81	−0·42 (0·06); 77	−0·50 (0·07); 77	−0·48 (0·06); 87
LS mean difference *vs* placebo	..	−0·18 (−0·35 to 0·00)	−0·12 (−0·30 to 0·06)	−0·20 (−0·38 to −0·02)	−0·18 (−0·35 to −0·00)
p value *vs* placebo	..	0·0517	0·1964	0·0305	0·0444
LS mean change in PM asthma symptom score‡ from baseline to week 24	−0·35 (0·08); 76	−0·40 (0·07); 82	−0·48 (0·07); 78	−0·52 (0·08); 77	−0·46 (0·07); 87
LS mean difference *vs* placebo	..	−0·05 (−0·26 to 0·15)	−0·14 (−0·34 to 0·07)	−0·17 (−0·38 to 0·04)	−0·11 (−0·32 to 0·09)
p value *vs* placebo	..	0·6147	0·1987	0·1040	0·2733

Data are mean change (SE); N or mean difference (95% CI); N, unless otherwise stated. ACQ-5=5-item Asthma Control Questionnaire. AQLQ=Asthma Quality of Life Questionnaire. LS=least squares. *ACQ-5 is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment; higher scores indicate less control; a global score is calculated ranging from 0–6. †AQLQ is a patient-reported measure of the impact of asthma on quality of life; higher scores indicate better quality of life; a global score is calculated ranging from 0–7. ‡Asthma symptom scores are patient-reported measures, taken on waking and in the evening, of asthma symptoms and their effects on activities (PM) and sleep (AM); higher scores indicate greater disruption; symptoms are scored on a range from 0–4.

Table 3: **Asthma control, quality of life, and symptoms in the overall population and by baseline blood eosinophil count**

FeNO were greater for dupilumab given every 2 weeks, and sustained throughout treatment (data not shown). In the subgroup with at least 300 eosinophils per µL, significant decreases (≥300 eosinophils per µL: 200 mg every 4 weeks, p=0·0404, 300 mg every 4 weeks, p=0·0196, 200 mg every 2 weeks, p<0·0001, 300 mg every 2 weeks, p<0·0001) in FeNO were observed at week 24, with differences ranging from −23·40% to −46·96% compared with placebo (appendix). Similar significant decreases (<300 eosinophils per µL: 200 mg every 2 weeks, p<0·0028; 300 mg every 2 weeks, p<0·0015; appendix) in FeNO were observed for the fewer than 300 eosinophils per µL subgroup receiving dupilumab every 2 weeks, with differences versus placebo ranging from −31·27% to −32·49% (appendix). Of the two doses of dupilumab given every 4 weeks, only dupilumab 300 mg showed a significant decrease in FeNO compared with placebo (p=0·004) in the fewer than 300 eosinophils per µL subgroup (appendix).

Overall, rates of treatment-emergent adverse events were similar across treatment groups (75–83% with dupilumab *vs* 75% with placebo) in the safety population (table 4). Treatment-emergent adverse events (defined by the Medical Dictionary for Regulatory Activities [MedDRA] preferred term) occurring in 10% or more dupilumab-treated patients in all dose regimens combined were upper respiratory tract infection (14% *vs* 18% for placebo), injection-site erythema (13% *vs* 8% for placebo), and headache (10% *vs* 13% for placebo; table 4). Injection-site reactions (MedDRA high-level term) were reported in 18% (mild 15%, moderate 3%, and severe <1%) of all dupilumab-treated patients combined *vs* 13% (mild 13%, moderate 1%) of placebo-treated patients. A clear dose–response association in injection-site reaction rates was apparent, with observed rates with dupilumab 200 mg and 300 mg every 4 weeks (both 13%) similar to that of placebo (13%) but rates with 200 mg every 2 weeks (20%) and 300 mg every 2 weeks (26%) higher than placebo. The rates of discontinuation of dupilumab because of injection-site reactions were 1% for 300 mg every 2 weeks and <1% for 200 mg every 2 weeks compared with <1% for 300 mg every 4 weeks and <1% for 200 mg every 4 weeks, and zero for placebo (data not shown). Dupilumab did not increase the incidence of bacterial or opportunistic herpes viral infections, as rates across all dose regimens were similar to those observed in the placebo group (table 4).

Serious treatment-emergent adverse events were reported in 45 (7%) dupilumab recipients (all dose regimens combined) and nine (6%) patients in the placebo group (table 4). Two patients in the 300 mg every 4 weeks regimen died during the study due to causes considered by the investigator and sponsor to be unrelated to study medication: one because of acute cardiac failure and one because of metastatic gastric cancer, organising pneumonia, and cor pulmonale. Overall, safety data for both eosinophil-count-based subgroups were similar compared with the overall safety population (appendix).

	Placebo (n=158)	Dupilumab				
		200 mg every 4 weeks (n=150)	300 mg every 4 weeks (n=157)	200 mg every 2 weeks (n=148)	300 mg every 2 weeks (n=156)	Dupilumab regimens combined (n=611)
Any treatment-emergent adverse event	118 (75%)	113 (75%)	130 (83%)	119 (80%)	121 (78%)	483 (79%)
Any serious treatment-emergent adverse event	9 (6%)	6 (4%)	16 (10%)	10 (7%)	13 (8%)	45 (7%)
Treatment discontinuation because of treatment-emergent adverse event	5 (3%)	7 (5%)	10 (6%)	6 (4%)	4 (3%)	27 (4%)
Any treatment-emergent adverse event leading to death	0	0	2 (1%)	0	0	2 (<1%)
Treatment-emergent adverse event (preferred term) occurring in ≥5% of patients*						
Upper respiratory tract infection	28 (18%)	22 (15%)	19 (12%)	22 (15%)	20 (13%)	83 (14%)
Injection-site erythema	12 (8%)	13 (9%)	12 (8%)	21 (14%)	33 (21%)	79 (13%)
Headache	20 (13%)	9 (6%)	19 (12%)	17 (11%)	17 (11%)	62 (10%)
Nasopharyngitis	15 (9%)	9 (6%)	19 (12%)	15 (10%)	16 (10%)	59 (10%)
Bronchitis	16 (10%)	10 (7%)	11 (7%)	11 (7%)	19 (12%)	51 (8%)
Influenza	5 (3%)	10 (7%)	13 (8%)	6 (4%)	9 (6%)	38 (6%)
Sinusitis	11 (7%)	12 (8%)	13 (8%)	5 (3%)	6 (4%)	36 (6%)
Treatment-emergent adverse event (high-level term) occurring in ≥10% of patients†						
Upper respiratory tract infection	56 (35%)	49 (33%)	64 (41%)	49 (33%)	54 (35%)	216 (35%)
Injection-site reactions	21 (13%)	19 (13%)	21 (13%)	29 (20%)	41 (26%)	110 (18%)
Bacterial infections (high-level term)	3 (2%)	0	2 (1%)	1 (1%)	2 (1%)	5 (1%)
Herpes viral infections (high-level term)	1 (1%)	1 (1%)	0	0	2 (1%)	3 (<1%)

MedDRA=Medical Dictionary for Regulatory Activities. *Adverse events occurring in ≥5% of patients in all regimens combined by MedDRA preferred term. †Adverse events occurring in 10% or more patients in all regimens combined by MedDRA high-level term. Injection-site reactions due to non-investigational medicinal product were excluded.

Table 4: **Overview of treatment-emergent adverse events (MedDRA preferred terms) and injection-site reactions (MeDRA high-level terms) in the safety population**

Transient elevation of blood eosinophils was observed in those with higher baseline eosinophil counts (appendix). A post-hoc analysis showed significant differences in change from baseline eosinophils between dupilumab groups and placebo from week 4 until week 16 in the safety population, but no significant difference was observed after week 16. Blood eosinophil elevations were driven mainly by differences in the subgroup with counts of at least 300 eosinophils per µL from week 4 (appendix). About 7 weeks after investigational drug administration (300 mg every 2 weeks dose regimen), one patient with a past medical history of high eosinophils (particularly when not taking corticosteroids) had an adverse event of hypereosinophilic syndrome. The patient was started on methylprednisolone, which rapidly decreased the eosinophil count. As a result of hypereosinophilic syndrome, the patient discontinued the study treatment. In the patient population with baseline eosinophil counts lower than 300 eosinophils per µL, no significant differences between dupilumab and placebo were observed. Vital signs and electrocardiogram assessment outcomes were balanced across the treatment regimens (data not shown).

Discussion

This study showed that dupilumab added to medium-to-high-dose inhaled corticosteroids plus long-acting β_2-agonist therapy in adults with uncontrolled persistent asthma irrespective of baseline eosinophil count significantly improved lung function, reduced the rate of severe exacerbations, and decreased FeNO in all dupilumab-treated groups compared with placebo-treated patients. The efficacy of dupilumab observed in adults with uncontrolled persistent asthma despite the use of medium-to-high-dose inhaled corticosteroids plus long-acting β_2-agonist therapy is consistent with the outcomes of clinical studies of dupilumab in two other comorbid systemic conditions: atopic dermatitis[17,18] and symptomatic chronic sinusitis with nasal polyposis.[19] Taken together, the results of these studies support the hypothesis that inhibition of both interleukin 4 and interleukin 13 might be an effective treatment strategy in conditions driven by type 2 inflammation. Additionally, multiple related comorbidities often exist in the same patient, presumably reflecting a systemic condition, and blocking interleukin 4 or interleukin 13, or both, might allow for a systemic solution.

By contrast with the previous phase 2a study, which included a background treatment withdrawal phase in patients with eosinophil counts of at least 300 eosinophils per µL,[7] controller therapy remained stable throughout the treatment phase of this study. Furthermore, this dose-ranging study was done in a larger population of patients with uncontrolled persistent asthma despite the use of inhaled corticosteroids plus long-acting β_2-agonist therapy, irrespective of baseline eosinophil count. Thus, this study extends the findings of the previous study,[7] confirming

that dupilumab treatment is efficacious as add-on therapy to medium-to-high-dose inhaled corticosteroids plus long-acting β_2-agonist therapy, compared with inhaled corticosteroids plus long-acting β_2-agonist therapy alone, even in patients with lower eosinophil counts (<300 eosinophils per μL). Although this study was not powered to directly compare the different dosing levels of dupilumab, thus limiting conclusions about the dose–response association, the dose regimens given every 2 weeks were consistently more efficacious than those given every 4 weeks, and have therefore been selected for further efficacy and safety assessment in an ongoing pivotal phase 3 clinical trial (NCT02414854). Another limitation of this study was the short duration of the study in patients with uncontrolled persistent asthma and the small number of patients per dose regimen.

Approved treatment options remain limited for patients with uncontrolled persistent asthma. At present, these medications are used as add-on therapy to standard inhaled corticosteroids plus long-acting β_2-agonist combinations. Tiotropium, a long-acting, inhaled, anticholinergic agent, significantly improved lung function (FEV_1) after 8 weeks when added to inhaled corticosteroids plus long-acting β_2-agonist therapy in patients with severe, uncontrolled asthma.[24] In two subsequent phase 3 trials in patients whose asthma was being poorly controlled with inhaled corticosteroids plus long-acting β_2-agonist therapy, add-on tiotropium significantly reduced the risk of severe exacerbation (21%) relative to placebo (p=0·03).[24,25] Omalizumab, which inhibits the binding of IgE to the IgE receptor, is only indicated for adults and adolescents (aged ≥12 years) with moderate-to-severe persistent asthma who have a positive skin test or in-vitro reactivity to a perennial aeroallergen. Additionally, studies with omalizumab have not shown effects on FEV_1 with variable and modest improvements in exacerbation rates (25–26%).[26,27] Reslizumab, a humanised α anti-interleukin-5 $IgG4_K$ monoclonal antibody, has been approved as add-on maintenance treatment for patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype. In a phase 3 trial, reslizumab was associated with improvements in FEV_1, 7-item Asthma Control Questionnaire (ACQ-7), rescue short-acting β_2-agonist use, and forced vital capacity, compared with placebo, in the subgroup of patients with eosinophil counts of at least 400 eosinophils per μL.[28] Mepolizumab, an antagonist of the type 2 cytokine interleukin 5, has been approved for use in patients with poorly controlled severe eosinophilic asthma (MENSA study inclusion criteria: eosinophil count ≥150 eosinophils per μL at screening or ≥300 eosinophils per μL at some time during the year before study entry). The annualised rate of clinically significant exacerbations (primary study outcome) was reduced by 47% and 53% in patients receiving intravenous and subcutaneous mepolizumab, respectively (p<0·001 for both comparisons *vs* placebo).[29]

A post-hoc analysis of the DREAM study[30] showed that patients with a baseline blood eosinophil count of fewer than 150 eosinophils per μL did not have a significant exacerbation benefit (30% reduction) with mepolizumab. Similarly, early studies with interleukin-13 blockers suggested more moderate efficacy only in type 2/Th2-high subgroups defined by biomarkers,[13,14] whereas recent phase 3 studies did not provide confirmatory effects on exacerbations.[24–29] By contrast to approved biologics, dupilumab treatment showed significant improvements in both lung function and annualised exacerbation rates across a broad range of patients with asthma. The increase in FEV_1 change from baseline occurred rapidly, which might have been a result of the rapid reduction in mucus production and secretion induced by dupilumab, a known potential effect of interleukin-13 inhibition. Even in patient-reported outcomes such as AQLQ, ACQ-5, and morning and evening asthma symptom scores, dupilumab achieved a substantial improvement in patients with baseline blood eosinophils counts of at least 300 eosinophils per μL, which so far has been considered unachievable with add-on therapy.[30] This substantial, broad response suggests that targeting both interleukin 4 and interleukin 13 can have a crucial role in improving lung function, exacerbation rates, and patient-reported outcomes in patients with uncontrolled persistent asthma. Moreover, the addition of dupilumab resulted in near-maximum decreases in FeNO, a type 2 inflammatory biomarker, at week 2 that were sustained throughout the treatment period, showing suppression of type 2 inflammation beyond that which is achievable with medium-to-high-dose inhaled corticosteroids plus long-acting β_2-agonist therapy alone. These results clearly show that there is a patient group with a need for additional medications such as dupilumab to decrease the clinical burden of asthma.

Dupilumab has now been studied in at least 3000 patients with asthma, atopic dermatitis, nasal polyps, and eosinophilic oesophagitis, and has shown an acceptable safety profile in placebo-controlled studies across indications.[4,16–18,30] In this study, the incidence of adverse events was generally similar across treatment groups, although an apparent dose–response relationship was observed for injection-site reactions. No clinically important safety signals were observed, and results are consistent with the safety profile of dupilumab in other studies.[7,16,17,22] Overall, mean blood eosinophil counts remained stable over the duration of treatment. However, in patients with baseline blood eosinophil counts of at least 300 eosinophils per μL, a transient increase in blood eosinophil levels was observed after treatment initiation, which did not seem to affect efficacy and quickly declined after treatment withdrawal. The effect of dupilumab on eosinophils will be further investigated in the ongoing phase 3 clinical trial (NCT02414854).

Most commonly encountered treatment-emergent adverse events (≥10% in all dupilumab regimens combined) were balanced between the dupilumab

regimens and the placebo group. In this study, injection-site reactions occurred in 18% of patients in all dupilumab regimens combined and in 13% of placebo recipients. Rates of bacterial and opportunistic infections such as herpes viral infections in the dupilumab-treated groups were low and similar to those observed with placebo. Overall, there is strong evidence that dupilumab, an anti-interleukin-4 receptor α agent that inhibits both interleukin-4 and interleukin-13 signalling, might benefit patients with uncontrolled persistent asthma despite use of inhaled corticosteroids plus long-acting β_2-agonist therapy, irrespective of blood eosinophil count.

Contributors

SW, GP, ERS, RRE, NMHG, NS, GDY, ML-T, and AT contributed to the conception and design of the study. MC, JC, and JM acquired the data. LW and BZ provided statistical analysis of the data. All authors contributed to the analysis and interpretation of the data and the critical revision of the publication, are accountable for the accuracy and integrity of the publication, and provided final approval to submit for publication.

Declaration of interests

SW declares research support received from AstraZeneca, Genentech, GlaxoSmithKline, and Sanofi and is a consultant for Actelion, Aerocrine, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Regeneron Pharmaceuticals (unpaid). MC has received funding from Washington University for participation in dupilumab clinical trial from Sanofi. JC has received funding for dupilumab clinical trial from Sanofi. JM is a consultant for Sanofi, Teva, and AstraZeneca; has received research grants from Novartis; and has received speaker fees from GlaxoSmithKline, Novartis, Uriach, and Menarini. LW, BZ, GP, ERS, LE, ML-T, and AT are employees of Sanofi and might hold stock or stock options, or both, in the company. RRE, VNJ, NMHG, NS, and GDY are employees and shareholders of Regeneron Pharmaceuticals.

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