



Dupilumab in the treatment of asthma

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Dupilumab is a fully human monoclonal IgG4 antibody that blocks IL-4 and IL-13 signaling. Its efficacy has been assessed across a range of atopic diseases, due to its ability to inhibit T helper cell 2 (Th2) mediated inflammation. It has already been approved in the USA and Europe for the treatment of atopic dermatitis. Recently, it also gained approval in the USA as add-on treatment for moderate-to-severe asthma in adolescents and adults. Phase II and III randomized controlled trials have demonstrated improvements in asthma exacerbation rates, FEV1, oral glucocorticoid use and a range of patient-reported outcomes, with a favorable safety profile. This article will review the available clinical trial data relating to the efficacy and safety of dupilumab in the management of asthma and related atopic respiratory conditions.

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Asthma is a chronic atopic disease prevalent among both adults and children, which is associated with significant morbidity, effects upon health-related quality of life and substantial economic cost [1]. Previously, maintenance therapy was limited mainly to inhaled corticosteroids and beta-agonists, and a proportion of patients remained symptomatic despite these treatments. In recent times, monoclonal antibodies directed against mediators of the T helper cell 2 (Th2) inflammatory pathway have transformed asthma treatment [2]. Agents targeting IgE and IL-5 were the first to be registered; however, dupilumab, an IL-4/IL-13 antagonist jointly developed by Regeneron and Sanofi, has recently secured US FDA approval for treatment of moderate-to-severe asthma in adolescents and adults [3]. Dupilumab has been, and continues to be, studied in a broad range of clinical development programs for diseases driven by type 2 inflammation, including severe asthma, atopic dermatitis, nasal polyps and eosinophilic esophagitis.

Mechanism & pharmacology

Dupilumab is a fully human IgG4 monoclonal antibody directed against the α subunit of the IL-4 receptor. IL-4 signaling occurs via the type I receptor that comprises the IL-4 receptor α subunit and the common γ chain; both IL-4 and IL-13 signal via the type II receptor complex containing the IL-4 receptor α subunit and the IL-13 receptor $\alpha 1$ subunit. Hence, dupilumab inhibits signaling through both type I and II receptors. IL-4 and IL-13 are key cytokines in the T helper type 2 (Th2) dominant immune response that characterizes atopic diseases such as asthma, atopic dermatitis and allergic rhinitis [4–6]. IL-4 has been implicated in the pathogenesis of asthma because of its role in promoting IgE class switching [7], upregulation of vascular adhesion molecules [8] and collagen production leading to airway remodeling [9]. IL-13 has been shown to influence goblet cell differentiation, bronchial hyper-reactivity and mucus production [10–12]. Dupilumab differs in its mechanism of action from the majority of monoclonal antibodies currently in clinical use for asthma, which target IL-5 (mepolizumab, benralizumab and reslizumab) or IgE (omalizumab). Several agents targeting IL-13 alone have been investigated (lebrikizumab; tralokinumab), however, failed to meet primary end points in Phase III trials [13,14]. Alternative IL-4 antagonists that have been investigated include pascolizumab [15], a humanized monoclonal anti-IL-4 antibody, and pitrakinra, a recombinant form of IL-4 that binds to the IL-4 receptor alpha subunit and thus prevents IL-4 and IL-13 signaling [16,17]. These molecules have not been taken into further development programs.

Pharmacodynamics

In vitro studies have demonstrated high affinity binding of dupilumab to the human IL-4R α , as well as functional inhibition of IL-4 and IL-13 signaling in cells expressing IL-4 receptors such as B lymphocytes [18]. Consistent with these *in vitro* effects, clinical studies have found that dupilumab decreases downstream biomarkers of IL-4/IL-13 signaling and Th2-mediated inflammation, such as IgE, fraction of exhaled nitric oxide (FeNO), periostin, eotaxin-3 (CCL26) and CCL17 [19,20]. Peripheral eosinophilia have been reported in a minority of subjects receiving dupilumab [19,20]. The postulated mechanism is that dupilumab prevents IL-4- and IL-13-mediated eosinophil activation and migration to tissues, but not IL-5-mediated bone marrow production of eosinophils [19,21]. This phenomenon will be discussed further later in this paper. A trial assessing the effect of dupilumab compared with placebo on airway inflammation in adult patients with persistent asthma has been completed, but results are yet to be published [22].

Pharmacokinetics

Dupilumab is administered as a subcutaneous injection. The recommended dose in the setting of asthma is either 400 mg as an initial injection, followed by 200 mg every fortnight; or 600 mg initially followed by 300 mg fortnightly. The median time to maximum dupilumab concentrations in serum after an initial dose of 75–600 mg is 3–7 days; clinically sufficient levels are reached within 2 weeks [23]. Bioavailability is estimated at 64% [24]. In those trials which reported anti-drug antibodies, these occurred in a minority of dupilumab-treated patients and did not appear to affect clinical efficacy [19,25].

Efficacy

Although dupilumab has received greatest attention in the setting of atopic dermatitis, the earliest Phase II and III clinical trials assessed its use in difficult-to-treat asthma (Table 1). The initial Phase IIa trial randomized 104 patients with moderate-to-severe asthma to dupilumab 300 mg (52 patients) or placebo (52 patients) subcutaneously weekly for 12 weeks or until they experienced a flare of asthma [20]. Eligibility criteria included a blood eosinophil count ≥ 300 cells/ μ l or a sputum eosinophil count $\geq 3\%$. The patients were required to be on medium-to-high dose inhaled corticosteroids (ICSs) plus long-acting beta adrenoceptor agonists (LABAs) at enrollment, but this background therapy was discontinued at week 4 (LABA) and weeks 6–9 (ICS) of the trial, leaving patients on either dupilumab or placebo monotherapy. There was a statistically significant difference in asthma exacerbations between the dupilumab group (6%, or 3 patients) and the placebo group (44%, or 23 patients). In addition, there was a difference of 0.27 l in change in FEV₁ from baseline at week 12 in dupilumab treated patients in comparison with placebo ($p < 0.001$). The minimal clinically important difference in FEV₁ has not been definitively established for asthma; however, differences of between 100 and 230 ml have been proposed [26–28].

Commentators highlighted the remarkable potential of dupilumab, given its apparent ability to achieve asthma control as monotherapy in this cohort of patients with refractory disease [30]. However, some limitations of the study were also noted: its ‘real world’ applicability was questioned, given that clinicians would not withdraw background ICS and LABA treatment in practice, and because the group of patients eligible for the study likely represents a small fraction of asthmatics (those with persistent symptoms despite conventional therapy, and with an eosinophilic asthma phenotype) [30].

Three subsequent trials have addressed these concerns (Tables 1 & 2). In 2016, Wenzel *et al.* published the results of their Phase IIb trial which randomized 776 adult patients with poorly controlled asthma to receive dupilumab 200 or 300 mg every 2 or 4 weeks, or placebo, in addition to background ICS and LABA treatment for 24 weeks [29]. Eosinophilia was not an inclusion criterion, although the primary efficacy end point was the change at week 12 in FEV₁ in patients with a blood eosinophil count of ≥ 300 cells/ μ l. In the subgroup with eosinophilia, all patients receiving dupilumab (except the group who received 200 mg every 4 weeks) saw greater improvements in FEV₁ (l) at 12 weeks in comparison with placebo treated patients (least squares mean difference [l] versus placebo: 0.17 [dupilumab 300 mg every 4 weeks; $p = 0.0212$]; 0.26 [dupilumab 200 mg every 2 weeks; $p = 0.0008$]; 0.21 [dupilumab 300 mg every 2 weeks; $p = 0.0063$]). In addition, a statistically significant improvement in change in FEV₁ from baseline at both 12 and 24 weeks was seen in all dupilumab dosing groups in comparison with placebo and in the subpopulation of patients with eosinophils less than 300 cells/ μ l receiving fortnightly dupilumab. All dupilumab groups except dupilumab 300 mg every 4 weeks saw a reduction in the annualized rates of severe asthma exacerbations regardless of eosinophil count (risk reduction vs placebo in adjusted annualized severe exacerbation

Table 1. Characteristics of dupilumab trials in asthma.

Study	Year of publication / study type	Population	Size	Drug regimens	Primary end point	Secondary end points	Biomarkers	Notes
Wenzel et al. [20]	2013 Phase IIa	18–65 years old Moderate-to-severe asthma Elevated blood eosinophils ($\geq 300/\mu\text{l}$) or sputum eosinophils ($\geq 3\%$) Symptoms poorly controlled on medium-high dose ICS + LABA FEV1 $\geq 50\%$ predicted ACQ scores 1.5–3 and ≥ 1 exacerbation in past 2 years	104 patients randomized 52 received placebo 52 received dupilumab 17 withdrew from placebo arm 7 withdrew from dupilumab arm	Dupilumab 300 mg subcutaneously weekly vs placebo subcutaneously weekly for 12 weeks	Occurrence of an asthma exacerbation	Time to asthma exacerbation At each visit and week 12: Change from baseline FEV1, morning and evening PEF, ACQ5 score, morning and evening asthma symptom scores, nocturnal awakenings, use of reliever medication	FE _{NO} CCL17 (TARC) IgE YKL40 CEA Plasma eotaxin-3 Peripheral blood eosinophil levels	LABAs discontinued at week 4 ICS tapered and discontinued week 6–9 Most frequent reported events qualifying as ‘exacerbations’ were reduction in morning PEF and use of reliever medication
Wenzel et al. [29]	2016 Phase IIb	≥ 18 years old Existing treatment with medium-high dose ICS plus LABA (or equivalent) Stable dose of ICS + LABA for a month before treatment Pre-bronchodilator FEV1 of 40–80% ACQ5 score of ≥ 1.5 FEV1 reversibility of $\geq 12\%$ and 200 ml Requirement for severe exacerbation within 1 year of screening	776 patients randomized 158 assigned to placebo (146 completed) 154 assigned to dupilumab 200 mg every 4 weeks (135 completed) 157 assigned to dupilumab 300 mg every 4 weeks (142 completed) 150 assigned to dupilumab 200 mg every 2 weeks (137 completed) 157 assigned to dupilumab 300 mg every 2 weeks (149 completed)	Dupilumab subcutaneously 200 mg every 4 weeks vs 300 mg every 4 weeks vs 200 mg every 2 weeks vs 300 mg every 2 weeks placebo, for 24 weeks	Change from baseline in FEV1 at week 12 in patients with blood eosinophil counts of $\geq 300/\mu\text{l}$: Percentage change in FEV1 from baseline Annualized severe asthma exacerbation rate Time to severe exacerbation events PROs including ACQ-5 score and AQLQ score Requirement for SABA medication	Pre-specified at week 12 and week 24 for both total patient cohort and subgroup with blood eosinophil counts of $\geq 300/\mu\text{l}$: Percentage change in FEV1 from baseline Annualized severe asthma exacerbation rate Time to severe exacerbation events PROs including ACQ-5 score and AQLQ score Requirement for SABA medication	FE _{NO}	No baseline requirement for elevated eosinophil count (or other markers of Th2 inflammation); however, randomization stratified by eosinophil count 42% of patients had baseline blood eosinophil count ≥ 300 eosinophils/ μl
Castro et al. [19]	2018 Phase III LIBERTY ASTHMA QUEST	≥ 12 years Receiving medium-high dose ICS plus up to 2 additional preventers FEV1 $\leq 80\%$ predicted normal value (or $\leq 90\%$ predicted normal value if 12–17 years) FEV1 reversibility of $\geq 12\%$ and 200 ml ACQ5 score ≥ 1.5 Worsening of asthma in previous year	1902 patients randomized 317 assigned to 1.14 ml placebo (38 discontinued) 631 assigned to dupilumab 200 mg (70 discontinued) 321 assigned to 2 ml placebo (35 discontinued) 633 assigned to dupilumab 300 mg (85 discontinued)	Dupilumab 200 mg fortnightly (400 mg loading dose) vs dupilumab 300 mg fortnightly (600 mg loading dose) vs two matched placebo groups (1.14 ml; 2 ml) for 52 weeks; all subcutaneous	Annualized rate of severe exacerbations (number of severe exacerbations per patient year) Absolute change from baseline in the FEV1 before bronchodilator use at week 12	In patients with eosinophils $\geq 300/\text{mm}^3$ and $\geq 150/\text{mm}^3$: annualized rate of severe exacerbations; absolute and percentage change from baseline in FEV1 at week 12 Percentage change from baseline FEV1 at week 12 Absolute and percentage change from baseline FEV1 at week 2, 4, 8, 24, 36, 52 Change from baseline in other lung function measurements Annualized rate of loss of asthma control (LOAC) events Annualized rate of severe exacerbation events Time to first LOAC and severe exacerbation event Change from baseline in PROs at week 12, 24, 36, 52 Change from baseline in healthcare resource utilization at week 4, 8, 12, 24, 36 and 52	FE _{NO} Peripheral blood eosinophil levels Total and antigen specific IgE CCL17 (TARC) Periostin Eosinophil cationic protein Eotaxin-3	Background therapy with ICS and additional preventers was continued No baseline requirement for elevated eosinophil count (or other markers of Th2 inflammation)

ICS: Inhaled corticosteroid; LABA: Long-acting beta adrenoceptor agonist.

Table 1. Characteristics of dupilumab trials in asthma (cont.).

Study	Year of publication/study type	Population	Size	Drug regimens	Primary end point	Secondary end points	Biomarkers	Notes
Rabe et al. [25]	2018 Phase III LIBERTY ASTHMA VENTURE	≥ 12 years Receiving systemic glucocorticoids (5–35 mg prednisone equivalent/day) in previous 6 months On high dose ICS plus up to 2 additional preventers FEV1 ≤ 80% predicted normal value (or ≤ 90% predicted normal value if 12–17 years) FEV1 reversibility of ≥ 12% and 200 ml (or airway hyperresponsiveness demonstrated in previous 12 months)	210 patients randomized 103 patients received dupilumab 107 patients received placebo 2 patients withdrew from dupilumab arm 5 patients withdrew from placebo arm	Dupilumab 300 mg subcutaneously fortnightly (600 mg loading dose) vs matched placebo for 24 weeks Oral glucocorticoids were continued for a 4 week induction period, and then reduced every 4 weeks between week 4 and 20 according to a pre-specified algorithm	Percentage reduction in oral glucocorticoid dose at week 24 while asthma control was maintained	In patients with maintained asthma control: proportion of patients with a reduction from baseline of at least 50% in glucocorticoid dose; proportion of patients who had a reduction in glucocorticoid dose to less than 5 mg/day Proportion of patients who had the maximum possible reduction in oral glucocorticoid dose Proportion of patients no longer using oral glucocorticoids Absolute reduction in oral glucocorticoid dose Annualized rate of severe exacerbation events during 24 week period Absolute change from baseline in FEV1 at 2, 4, 8, 12, 16, 20, 24 weeks Change from baseline in ACQ5 score at week 24	FE _{NO} Peripheral blood eosinophil levels Total and antigen specific IgE CCL17 (TARC) Periostin Eotaxin-3	No baseline requirement for elevated eosinophils or other markers of Th2 mediated inflammation Background ICS continued

ICS: Inhaled corticosteroid; LABA: Long-acting beta adrenoceptor agonist.

Table 2. Efficacy and safety data.

Study	Improvement in lung function	Exacerbation rates	Use of corticosteroids	Patient reported outcomes	Safety data
Wenzel et al. 2013 [20]	Difference between dupilumab and placebo in change in FEV1 from zero to week 12 0.27 l (p < 0.001) Difference between dupilumab and placebo in change in morning PEF was 34.6 l/min (0.005); no significant difference in change in evening PEF	Exacerbations occurred in 6% of dupilumab vs 44% of placebo patients (p < 0.001) Probability of asthma exacerbation 0.06 (dupilumab) vs 0.46 (placebo) at week 12 (p < 0.001)	Five placebo patients required systemic glucocorticoids vs 1 dupilumab patient Dose of ICS ≥ 4 times previous dose in 3 placebo patients vs 0 dupilumab patients (p-value not supplied as data fell within primary efficacy end point of 'asthma exacerbation')	-0.73 difference between dupilumab vs placebo in change in ACO5 score from baseline to week 12 (p = 0.001) -0.7 difference between dupilumab and placebo in change in both morning and evening asthma scores from baseline to week 12 (p < 0.001)	77% adverse events in placebo group vs 81% in dupilumab group Three serious adverse events in placebo group; 1 in dupilumab group Injection site reactions in 15 (29%) of dupilumab patients vs 5 (10%) of placebo patients Nasopharyngitis, headache, nausea, urticaria more common in dupilumab treated patients (but small overall numbers) 23/43 placebo treated patients experienced either no change or an increase in blood eosinophil levels vs 17/44 dupilumab treated patients; however, 4 dupilumab patients developed an eosinophil rise >200% in comparison with no dupilumab treated patients; no information provided on any clinical manifestations of hypereosinophilia in these patients
Wenzel et al. 2016 [29]	Improvement in mean change in FEV1 (l) from baseline to week 12 between dupilumab and placebo (pre-specified primary efficacy end point) was demonstrated in all dosing groups in the overall cohort: 0.10 (dupilumab 200 mg every 4 weeks; p = 0.0304); 0.12 (dupilumab 300 mg every 4 weeks; p = 0.0048); 0.20 (dupilumab 200 mg every 2 weeks; p < 0.0001); 0.16 (dupilumab 300 mg every 2 weeks; p = 0.0002) Mean difference in change in FEV1(l) for dupilumab vs placebo in patients was generally greater in patients with eosinophils $\geq 300/\mu\text{l}$ (no statistically significant change in the dupilumab 200 mg q4 weekly dosing group): 0.17 (dupilumab 300 mg every 4 weeks; p = 0.0212); 0.26 (dupilumab 200 mg every 2 weeks; p = 0.0008); 0.21 (dupilumab 300 mg every 2 weeks; p = 0.0063) For patients with eosinophils <300/μl, mean difference in change in FEV1(l) was only statistically significant for fortnightly dosing (0.15 for dupilumab 200 mg every 2 weeks; p = 0.0057; 0.12 for dupilumab 300 mg every fortnight; p = 0.0262), not for monthly dosing	Statistically significant differences in annualized severe exacerbation rate for all dupilumab dosing groups compared with placebo, except 300 mg every 4 weeks group. Magnitude of the reduction was higher for fortnightly dosing, and similar for 200 mg and 300 mg fortnightly dosing: dupilumab 200 mg every 4 weeks 53.7% reduction; p = 0.0093; dupilumab 200 mg every 2 weeks 70% reduction; p = 0.0002; dupilumab 400 mg every 2 weeks; 70.5% reduction; p = 0.0001	Not analyzed as a separate end point (use of systemic corticosteroids included as an indicator of a severe asthma exacerbation or loss of asthma control (LOAC) event) Patients remained on baseline ICS and LABA therapy throughout trial	Improvements in ACO5 scores from baseline to week 24 significantly greater in the overall cohort (least-squares mean difference vs placebo -0.35 for 200 mg group [p 0.0015] and -0.31 for 300 mg group [p 0.0049] for patients receiving fortnightly dosing). No statistically significant difference in improvement in ACQ scores was observed between placebo and dupilumab groups for patients receiving monthly dupilumab dosing. The only cohort with a difference in ACQ scores exceeding the minimal clinically important difference of 0.5 was the 300 mg/fortnight dupilumab group in the subgroup of patients with eosinophils $\geq 300/\mu\text{l}$ (LS mean difference vs placebo -0.55; 95% CI: -0.9 to -0.2). In the subgroup with eosinophils <300/μl, a statistically significant improvement in ACO5 scores relative to placebo at week 24 was only seen in the 200 mg fortnightly dosing group (LS mean difference vs placebo -0.33; 95% CI: -0.61 to -0.05)	Rates of adverse events similar for dupilumab (79% combined) vs placebo (75%) Rates of serious adverse events similar (7% dupilumab combined vs 6% placebo) No evidence of a dose-response relationship for overall adverse events among dupilumab-treated patients Injection site reactions (majority mild) reported in 18% dupilumab patients vs 13% placebo, with evidence of a dose response 2 deaths in 300 mg every 4 week dosing group; thought unrelated to dupilumab (acute cardiac failure in one, and gastric cancer, organizing pneumonia and cor pulmonale in another) Post-hoc analysis showed significant increase in blood eosinophil counts for dupilumab patients vs placebo from week 4 to 16 but not thereafter. One patient with a past history of eosinophilia developed hypereosinophilic syndrome requiring systemic corticosteroids No significant increase in rates of upper respiratory tract infections, nasopharyngitis, herpes virus infections or bacterial infections for dupilumab-treated patients compared with placebo

Table 2. Efficacy and safety data (cont.).

Study	Improvement in lung function	Exacerbation rates	Use of corticosteroids	Patient reported outcomes	Safety data
Castro et al. 2018 [19]	Absolute change in FEV1 from baseline at week 12 was 0.32 l for 200 mg dupilumab vs 0.18 l for matched placebo (difference 0.14 l; $p < 0.001$) and 0.34 l for dupilumab 300 mg vs 0.21 l for matched placebo (difference 0.13 l; $p < 0.001$) Greater improvements in FEV1 for dupilumab-treated patients were seen in those with higher baseline eosinophil counts: difference in change at week 12 between dupilumab and placebo was 0.21 l (95% CI: 0.13–0.29) for patients with eosinophils $\geq 300 \text{ mm}^3$ treated with 200 mg dupilumab/fortnight and 0.24 l (95% CI: 0.16–0.32) for those treated with 300 mg dupilumab/fortnight. In patients with eosinophils between 150 and 300 mm^3, a difference of 0.11 l was seen in improvement in FEV1 at week 12 for lower dose dupilumab patients (95% CI: 0.01–0.21), and no significant difference was seen for higher dose dupilumab patients No statistically significant difference was seen in improvement in FEV1 between dupilumab and placebo at week 12 for patients with eosinophils $< 150 \text{ mm}^3$ Greater improvements in FEV1 against placebo were also seen for dupilumab patients with a higher baseline FEV0	Annualized adjusted rate of severe exacerbations 0.46 in dupilumab 200 mg group vs 0.87 in 1.14 ml placebo group ($p < 0.001$); 0.52 in dupilumab 300 mg group vs 0.97 in 2 ml placebo group ($p < 0.001$) Annualized adjusted rate of severe exacerbations in patients with eosinophils $< 150 \text{ mm}^3$ was similar for dupilumab 200 mg (0.47; 95% CI: 0.36–0.62) vs matched placebo (0.51; 95% CI: 0.35–0.76); and for dupilumab 300 mg (0.74; 0.58–0.95 95% CI) vs matched placebo (0.64; 95% CI: 0.44–0.93)	Not analyzed as a separate end point (use of systemic corticosteroids included as an indicator of a severe asthma exacerbation) Patients remained on baseline ICS and other preventer medication throughout the trial	ACQ-5 scores improved for dupilumab vs matched placebo groups from week 2 (least squares mean difference vs placebo -0.34 for dupilumab 200 mg [95% CI: -0.46 to -0.22]; -0.31 for dupilumab 300 mg [95% CI: -0.42 to -0.19]) and sustained at week 52 (least squares mean difference vs placebo -0.39 for dupilumab 200 mg [95% CI: -0.53 to -0.25]; -0.22 for dupilumab 300 mg [95% CI: -0.36 to -0.08])	Similar rates of adverse events for dupilumab (81%) and placebo (83.1%) groups Serious adverse events similar for combined dupilumab (8.2%) and combined placebo (8.4%) groups 5 deaths in dupilumab group; 3 deaths in placebo group; none considered related to trial drug Eosinophilia in 52 (4.1%) of dupilumab-treated patients vs 4 (0.6%) of placebo patients. 4 dupilumab patients symptomatic secondary to eosinophilia; two serious adverse events Injection site reactions more common in dupilumab-treated patients (16.8%) vs placebo-treated patients (7.9%) Infections (viral upper respiratory tract infections, upper respiratory tract infections, bronchitis, influenza, sinusitis) were all more common in pooled placebo patients vs pooled dupilumab Rates of conjunctivitis similar (2.3% dupilumab vs 3.3% placebo) Numeric imbalance in cardiovascular events was observed (13 patients in combined dupilumab group vs 4 in combined placebo group); after blinded assessment no difference in rates of major adverse cardiac events
Rabe et al. 2018 [25]	In overall population, improvement in FEV1 higher in dupilumab group vs placebo group at week 24 (least squares mean value 0.22 l [95% CI: 0.09–0.34]). Improvements in FEV1 were seen as early as week 2 Improvements were more marked in patients with higher baseline eosinophil counts; for example least squares mean difference in FEV1 for dupilumab treated patients with eosinophil count of $\geq 300 \text{ mm}^3$ was 0.32 l (95% CI: 0.10–0.54), compared with 0.24 l for patients with eosinophils $< 150 \text{ mm}^3$	59% lower rate of severe asthma exacerbations in dupilumab vs placebo group (95% CI: 37–74%) Improvements were more marked in patients with higher baseline eosinophil counts: 71% reduction in severe exacerbation rates vs placebo treated patients for dupilumab patients with eosinophil count $\geq 300 \text{ mm}^3$ (95% CI: 40–86%); vs 60% improvement for patients with eosinophils $< 150 \text{ mm}^3$ (95% CI: 5–83%)	Least squares mean percentage change in oral glucocorticoid dose from baseline to week 24 was -70.1 ($\pm 4.9\%$) in the dupilumab group vs -41.9 $\pm 4.6\%$ in the control group ($p < 0.001$) Percentage of patients who had a reduction in oral glucocorticoid dose to $< 5 \text{ mg/day}$ was 69% in dupilumab group vs 33% in placebo group ($p < 0.001$) Greater benefit observed in patients with higher baseline eosinophil counts; odds ratio 6.59 (95% CI: 2.13–20.42) for dupilumab patients vs placebo patients with eosinophils $\geq 300 \text{ cells/mm}^3$ achieving a glucocorticoid dose reduction of $\geq 50\%$ as opposed to 2.91 (95% CI: 1.28–6.63) for those with $< 300 \text{ cells/mm}^3$	Least-squares mean difference in ACQ5 scores at week 24 between dupilumab and placebo was -0.47 (95% CI: -0.76 to -0.18) Other PROs such as AQLQ scores, Hospital Anxiety and Depression Scale and SNOT-22 scores were listed as secondary end points but data not included in the published paper or supplementary materials	Incidence of adverse events similar (62% dupilumab group vs 64% placebo group) Serious adverse events in 9% of dupilumab group vs 6% of placebo group Eosinophilia observed in 14% of dupilumab treated patients vs 1% of placebo; 13% of dupilumab treated patients experienced at least one eosinophil count $\geq 3000 \text{ cells/mm}^3$ (vs 1% in placebo group); no cases of biochemical eosinophilia were associated with clinical manifestations Injection site reactions more common in dupilumab group vs placebo (9 vs 4%) Bronchitis (7 vs 6%) and sinusitis (7 vs 4%) slightly more common in dupilumab group vs placebo Viral upper respiratory tract infections more common in placebo group (18 vs 9%), as was influenza (6 vs 3%)

rate: dupilumab 200 mg every 4 weeks 53.7% reduction; $p = 0.0093$; dupilumab 200 mg every 2 weeks 70% reduction; $p = 0.0002$; dupilumab 400 mg every 2 weeks; 70.5% reduction; $p = 0.0001$).

In 2018, the results of a large Phase III trial (LIBERTY ASTHMA QUEST) assessing dupilumab (200 or 300 mg) every fortnight against placebo for 1 year as add-on therapy in patients over the age of 12 with uncontrolled asthma were published [19]. As with the 2016 study, patients were enrolled regardless of eosinophil count. There was a significant difference in the annual adjusted rate of severe asthma exacerbations for both dupilumab dosing groups in comparison with the matched placebo groups across all participants. On an intention-to-treat analysis, patients who received 200 mg of dupilumab fortnightly had an annualized exacerbation rate of 0.46 in comparison with matched placebo patients with a rate of 0.87 ($p < 0.001$). Patients in the 300 mg per fortnight dupilumab group had an annualized exacerbation rate of 0.52, in comparison with a rate of 0.97 in matched placebo patients ($p < 0.001$). On subgroup analysis, however, there was no statistically significant difference in exacerbation rates between dupilumab and placebo for patients with blood eosinophils of <150 cells/mm³, whereas a difference was present for patients with higher eosinophil counts.

A statistically significant improvement in FEV1 for dupilumab-treated patients in comparison to placebo was also seen as early as 2 weeks, and was maintained throughout the trial period. At week 12, the mean improvement in FEV1 was 0.14 l greater for patients in the overall trial population treated with dupilumab in comparison with placebo (95% CI: 0.08–0.19 l), and 0.13 l greater for patients who received 300 mg dupilumab in comparison with placebo (95% CI: 0.08–0.18 l). Greater improvements in FEV1 were seen for patients with a higher baseline eosinophil count: at week 12, there was a 0.21 l difference in change in FEV1 between patients receiving dupilumab 200 mg versus matched placebo who had a baseline eosinophil count ≥ 300 /mm³ (95% CI: 0.13–0.29 l), and a 0.24 l difference for patients receiving dupilumab 300 mg vs matched placebo (95% CI: 0.16–0.32 l). In comparison, for patients with a baseline eosinophil count under 150/mm³, there was no statistically significant difference in improvement in FEV1 between dupilumab- and placebo-treated patients. Similarly, greater improvements in FEV1 were seen for dupilumab-treated patients with higher baseline FeNO values. In patients with the highest baseline FeNO values of ≥ 50 ppb, there was a 0.3 l (95% CI: 0.17–0.44 l) difference in improvement in FEV1 between patients receiving dupilumab 200 mg/fortnight and placebo, and a 0.39 l difference (95% CI: 0.26–0.52 l) for patients receiving dupilumab 300 mg/fortnight versus placebo. Smaller improvements were seen for patients with FeNO values of between 25 and 50 ppb: there was a 0.19 l improvement (95% CI: 0.09–0.28 l) in FEV1 for lower dose dupilumab-treated patients as compared with matched placebo, and a 0.12 l improvement (95% CI: 0.03–0.21 l) for higher dose dupilumab-treated patients as against placebo. In those patients with baseline FeNO <25 ppb, no statistically significant difference in change in FEV1 was seen for dupilumab treated patients in comparison with placebo.

A second Phase III study, the LIBERTY ASTHMA VENTURE trial, also published in 2018, assessed dupilumab 300 mg subcutaneously fortnightly (following a 600 mg initial dose) against placebo as add-on therapy over 24 weeks in 210 patients aged 12 years or older requiring oral glucocorticoids for asthma [25]. Patients treated with dupilumab achieved a greater, statistically significant, reduction in oral glucocorticoid dose regardless of eosinophil count ($-70.1\% \pm 4.9\%$ change, in comparison to $-41.9\% \pm 4.6\%$ in the placebo group; $p < 0.001$). A total of 80% of patients in the dupilumab-treated group achieved at least a 50% reduction in oral glucocorticoid dose at week 24, in comparison with 50% of patients in the placebo group ($p < 0.001$). A total of 69% of dupilumab-treated patients reached an oral glucocorticoid dose of under 5 mg/day, in comparison with 33% of those in the placebo group ($p < 0.001$). A total of 48% of dupilumab-treated patients were able to discontinue oral glucocorticoids, in comparison with 25% of patients receiving placebo ($p 0.002$). In general, the magnitude of the reduction was greatest for patients with higher baseline blood eosinophils, but significantly greater reductions were still seen in dupilumab-treated patients regardless of baseline eosinophils.

In terms of other efficacy end points, a 59.3% reduction in the rate of severe asthma exacerbations was seen in dupilumab-treated patients in comparison with placebo (95% CI: 37–74). A greater improvement in FEV1 (least squares mean difference 0.22 l [95% CI: 0.09–0.34 l]) was also seen among dupilumab-treated patients.

A meta-analysis has aggregated data from the four trials discussed above [31]. On pooled analysis, dupilumab was associated with a significant reduction in the annualized severe asthma exacerbation rate, with a relative risk of 0.44 in comparison with placebo ($p < 0.01$). This difference persisted when data were stratified according to baseline eosinophil count: patients with baseline eosinophils of >300 /mm³ treated with dupilumab saw a relative risk of 0.33 of the annualized severe exacerbation rate ($p < 0.01$) in comparison with placebo, while patients with baseline eosinophils of <300 /mm³ saw a smaller, but still statistically significant improvement (RR: 0.5; $p < 0.01$).

However, a subgroup of dupilumab-treated patients with an eosinophil count $<150/\text{mm}^3$ had no reduction in annualized severe asthma exacerbation rate in comparison with placebo. A statistically significant improvement was also seen in FEV1 on meta-analysis: dupilumab-treated patients had a mean improvement of 0.14 l in FEV1 in comparison with placebo-treated patients ($p < 0.01$). On subgroup analysis, an improvement in FEV1 persisted regardless of baseline eosinophil count, although patients with higher baseline eosinophils experienced a greater magnitude of change (eosinophils $>300/\text{mm}^3$: FEV1 mean difference 0.21 l ($p < 0.01$); eosinophils $<300/\text{mm}^3$: FEV1 mean difference 0.12 l; eosinophils $<150/\text{mm}^3$: mean difference 0.10 l; $p = 0.01$). There have been no head-to-head analyses of different monoclonal antibodies for asthma; however, a recent publication performed an indirect statistical analysis of data from randomized controlled trials assessing dupilumab and mepolizumab, and concluded that dupilumab-treated patients experienced a greater improvement in FEV1 from baseline in comparison with mepolizumab-treated patients (mean difference in change in FEV1 [l] 0.133; 95% CI: 0.016–0.252 l) [32]. In addition, no significant difference was seen in the incidence of severe adverse events between the dupilumab- and mepolizumab-treated patients [32].

The optimal dose of dupilumab for asthma has not been definitively identified. The Wenzel 2016 trial was the only study to assess 4 weekly dosing as well as fortnightly dosing; it found a statistically significant improvement in FEV1 across all dupilumab dosing groups in comparison with placebo; however, the magnitude of the improvement was larger for the fortnightly dosing groups. In addition, in the subgroup of patients with eosinophil counts $<300/\mu\text{l}$, a statistically significant difference in improvement in FEV1 was only seen in dupilumab patients who received fortnightly dosing [29]. The recent meta-analysis was not powered to detect differences in outcome based on dose.

As is apparent from the data discussed above, the major trials assessing dupilumab in asthma focused upon lung function as measured by FEV1, and on asthma exacerbations, as well as on biomarkers of Th2-mediated inflammation such as the fraction of exhaled nitric oxide (FE_{NO}), eosinophil count and serum IgE level. However, improvements in patient-reported outcomes were also seen. Asthma Control Questionnaire (ACQ5) scores improved in all four trials in comparison with placebo (Table 2); however, the magnitude of the difference in most assessments did not exceed the minimal clinically important difference of 0.5 [33]. Exceptions were the Wenzel 2013 trial (assessing a cohort of patients with baseline elevated blood or sputum eosinophils): a -0.73 mean difference in change in ACQ5 score from baseline was seen between dupilumab-treated patients in comparison with placebo-treated patients ($p = 0.001$) [20]. In addition, in the Wenzel 2016 trial, the subgroup of patients with a baseline eosinophil count $\geq 300/\mu\text{l}$ who received the highest dupilumab dose (300 mg/fortnight) saw a -0.55 least squares mean difference in comparison with placebo in their change in ACQ5 score ($p = 0.0021$) [29]. A statistically significant improvement in Asthma Quality of Life Questionnaire (AQLQ) scores was seen in both the Wenzel 2016 and the QUEST trials [19,29]. In the QUEST trial at week 52, the mean difference in AQLQ scores was 0.29 for the 200 mg/fortnightly dupilumab group in comparison with placebo (95% CI: 0.15–0.44 l) and 0.26 in the 300 mg/fortnight group versus matched placebo (95% CI: 0.12–0.40 l) [19]. In the Wenzel 2016 trial, a statistically significant improvement was seen in AQLQ scores at week 24 for dupilumab treated patients in the overall cohort for all dosing groups, except the 200 mg per month group: least squares mean difference versus placebo 0.3 (300 mg/month dupilumab; $p 0.0120$); 0.31 (200 mg/fortnight dupilumab; $p 0.0090$); 0.36 (300 mg/fortnight dupilumab; $p 0.0027$) [29]. The magnitude of improvement, therefore, fell below the threshold for the minimal clinically important difference in AQLQ score (0.5) among the overall cohort [34]. In the subgroup of patients with a baseline eosinophil count $\geq 300/\mu\text{l}$, however, results for all but one of the dosing groups reached clinical significance (LS mean difference vs placebo: 0.53 [200 mg/month; $p 0.0054$]; 0.67 [200 mg/fortnight; $p 0.0003$]; 0.78 [300 mg/fortnight; $p < 0.0001$]). In contrast, patients in the 2016 Wenzel trial with eosinophils $< 300/\mu\text{l}$ did not achieve a statistically significant improvement in AQLQ scores over placebo. The Wenzel 2013 trial [20] did not assess AQLQ scores; change in AQLQ scores from baseline at 12 and 24 weeks was listed as a secondary end point for the VENTURE trial but this outcome was not included in the published material [25].

A separate study performed a *post-hoc* analysis of the 2016 Wenzel trial looking specifically at patient-reported outcomes; it found significant improvements in asthma symptoms and quality of life, as well as workplace productivity (assessed through surrogate markers such as time off work for severe exacerbation events) [35].

Although adolescent patients were included in the LIBERTY ASTHMA QUEST and VENTURE trials, there are no published Phase III data pertaining to patients younger than 12. Several pediatric trials are currently proceeding: the VOYAGE trial aims to assess the efficacy of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma [36]; and the Excursion study is evaluating the long-term safety and tolerability of dupilumab in

pediatric patients who participated in the VOYAGE trial [37]. A Phase II trial is also assessing response to dupilumab in children with asthma according to polymorphisms in the IL-4R α , to see whether genotype can predict treatment success [38].

Dupilumab in respiratory conditions other than asthma

Th2-mediated inflammation has been implicated in upper airway diseases including allergic rhinitis, chronic sinusitis and nasal polyposis [39]. Few, if any, disease-modifying therapies are available to treat these conditions. As such, researchers have postulated a potential role for dupilumab. A randomized, double blind trial published in 2016 examined dupilumab against placebo in 60 patients with bilateral nasal polyposis and chronic sinusitis [40]. As a pre-specified enrolment target, greater than half of the study participants had comorbid asthma. After 4 weeks of lead-in therapy with intranasal mometasone, patients received 16 weeks of placebo or dupilumab 300 mg weekly (following an initial loading dose of 600 mg). A greater improvement in endoscopic nasal polyp scores was seen in dupilumab-treated patients in comparison with the placebo group. On subgroup analysis by asthma status, however, a statistically significant difference in endoscopic polyp score was only seen for patients with asthma. Statistically significant differences were also seen in radiographic assessments of sinus disease severity, nasal inspiratory flow, sense of smell and SNOT-22 scores in dupilumab-treated patients compared with placebo in the overall population [40,41]. The change in SNOT-22 score was -18.1 (least squares mean difference; $p < 0.001$) between dupilumab- and placebo-treated patients, exceeding the minimal clinically important difference of 8.9 [42]. The study has promising findings for chronic sinusitis sufferers, although limitations include the short duration of follow-up and burden of the weekly dosing schedule.

Recently, the results of two large Phase III trials assessing dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP) were announced. Sinus-24 randomized 276 patients with CRSwNP who had previously required systemic corticosteroids or surgery to dupilumab 300 mg or placebo every 2 weeks for 24 weeks [43]. Sinus-52 randomized 448 patients with CRSwNP who had previously received systemic corticosteroids or surgery 1:1:1 to either dupilumab 300 mg every 2 weeks for 52 weeks, dupilumab 300 mg every 2 weeks for 24 weeks followed by every 4 weeks for 28 weeks, or placebo every 2 weeks for 52 weeks [44]. Both trials reported statistically significant improvements in nasal polyp scores, patient-reported nasal congestion, UPSIT (University of Pennsylvania Smell Identification Test) scores, SNOT-22 scores and CT Lund-Mackay assessments of radiographic severity.

A *post-hoc* analysis of the 2016 Phase IIb trial assessing dupilumab in asthma has also been published, examining the efficacy of dupilumab among participants with perennial allergic rhinitis (PAR) [45]. These patients were identified retrospectively on the basis of specific IgE to typical PAR allergens (such as house dust mite). Only patients in the placebo and second weekly dupilumab (200 and 300 mg) dosing groups were included. In patients with PAR, dupilumab 300 mg fortnightly (but not 200 mg) was associated with a greater improvement in the SNOT-22 score. The major limitation of this analysis is its definition of PAR, as elevated specific IgE to typical perennial allergens does not necessarily equate to clinical allergic rhinitis. In addition, approximately 50% of the patients in the non-PAR subgroup had a reported history of allergic rhinitis symptoms, potentially confounding any comparison.

Finally, a Phase II clinical trial is currently recruiting to assess the role of dupilumab as an adjunct to subcutaneous grass immunotherapy [46].

Safety data & adverse effects

Clinical trials assessing dupilumab in the setting of asthma and other conditions have confirmed it to be a safe and well-tolerated medication. Across the Phase II and III trials in asthma, rates of both adverse events and serious adverse events have been similar between dupilumab- and placebo-treated patients. This has been confirmed in a meta-analysis of the four trials assessing dupilumab in asthma, with no significant difference found between rates of adverse events, or serious adverse events, for dupilumab-treated patients as opposed to placebo [31]. The most consistent adverse event related to dupilumab across trials in all diseases has been an increased risk of injection site reactions in dupilumab-treated patients in comparison with placebo [31], with evidence of a dose-response pattern in some trials [29]. Most injection site reactions have been mild; rarely have they led to discontinuation.

One potential issue that has emerged in the assessment of dupilumab for asthma is that of eosinophilia: elevated eosinophil counts were seen in a minority of patients receiving dupilumab in comparison with placebo-treated patients across a number of trials [19,25,29] and in several cases, clinical symptoms such as pneumonitis and myositis

were attributed to the elevated eosinophil count [19]. As noted earlier in this paper, a proposed mechanism is that dupilumab inhibits IL-4- and IL-13-mediated eosinophil activation and migration to tissues, but does not suppress IL-5-mediated bone marrow production of eosinophils. However, the vast majority of patients who did develop eosinophilia remained asymptomatic, and in the Wenzel 2016 trial, the eosinophilia did not persist beyond week 16. Some of the trials assessing dupilumab for atopic dermatitis have reported similar findings: in the SOLO1 and 2 trials, a very small mean increase in eosinophil counts was observed in the dupilumab-treated patients at weeks 4 and 8; this had resolved by week 16 [47]. In the LIBERTY AD CHRONOS trial, 21% of patients in the 300 mg weekly dosing dupilumab group had developed an eosinophil count above the upper limit of normal, in comparison with 14% in the dupilumab 300 mg fortnightly dosing group and 15% in the placebo group [48]. No reports of symptomatic eosinophilia were noted in the atopic dermatitis trials.

There were no consistent data to suggest an increased infection risk with dupilumab-treated patients in the asthma trials. The increased risk of conjunctivitis documented in Phase II and III trials assessing dupilumab for atopic dermatitis (8% of dupilumab treated patients vs 3.6% of placebo treated patients in a meta-analysis) [49] has not been reported in the setting of asthma. The reason for this disparity is unclear.

Regulatory affairs

On 19 October 2018, the FDA approved dupilumab for use as add-on maintenance treatment in patients aged 12 years or older with moderate-to-severe asthma, if they have an eosinophilic phenotype or are dependent upon oral corticosteroids [3]. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has also recently recommended an extension of indication to permit use of dupilumab in a similar patient cohort [50]. Dupilumab has also received FDA approval for use in adolescent and adult patients with moderate-to-severe atopic dermatitis whose disease is not well controlled with topical therapies [51,52], and is approved in Europe for adult atopic dermatitis patients who would be candidates for systemic therapy [53]. It is approved for similar categories of atopic dermatitis patients in a number of other countries including Australia [54], Canada [55] and Japan [56].

Conclusion

As in atopic dermatitis, clinical trials have demonstrated dupilumab to be an effective and safe medication for patients with difficult to control asthma, with improvements seen in FEV1, exacerbation rates, use of oral glucocorticoids, Th2-mediated inflammatory markers and patient-reported outcomes. Benefits are most marked in those who have an eosinophilic asthma phenotype, but have also been demonstrated in patients with normal baseline eosinophil counts. Safety data are reassuring; however, a minority of patients appears to develop eosinophilia which in rare cases has been marked and possibly associated with clinical manifestations. This phenomenon will need to be monitored in post-marketing studies. With recent FDA approval, dupilumab appears likely to secure a role in the treatment of refractory asthma in adolescents and adults; ongoing trials will assess its utility in younger patients. In contrast to atopic dermatitis, however, where dupilumab occupies a relatively unique position in terms of approved biological therapies, the asthma space is more crowded and includes several agents aimed at other targets in Th2-mediated inflammatory pathways. As such, useful directions for future research will include refinement of asthma phenotypes to identify those patients who are more likely to benefit from particular biologics, and head-to-head comparisons of biological therapies which to date have been compared only against conventional treatment [57].

Executive summary

- Asthma is a highly prevalent, chronic atopic disease associated with significant morbidity, impaired quality of life and substantial economic cost.
- Conventional maintenance treatment has been limited to inhaled beta agonists and corticosteroids.
- Dupilumab is one of a number of biologics directed at the Th2 pathway that has been assessed as a potential therapy in asthma.
- Dupilumab has demonstrated success in the setting of other atopic diseases, particularly atopic dermatitis.

Mechanism & pharmacology

- Dupilumab is a fully human IgG4 monoclonal antibody directed against the α subunit of the IL-4 receptor.
- Both IL-4 and IL-13 signal through the α subunit of the IL-4 receptor hence dupilumab inhibits IL-4 and IL-13 signaling.
- IL-4 and IL-13 are key cytokines in the T helper type 2 (Th2) dominant immune response that characterizes atopic diseases.
- Dupilumab differs from other biologics currently in clinical use for asthma which target IL-5 or IgE.

Pharmacodynamics

- Dupilumab has been shown to decrease downstream biomarkers of IL-4/IL-13 signaling and Th2-mediated inflammation including IgE, fraction of exhaled nitric oxide (FeNO), periostin, eotaxin-3 (CCL26) and CCL17.

Pharmacokinetics

- Dupilumab is administered as a subcutaneous injection.
- The recommended dose in the setting of asthma is either 400 mg as an initial injection, followed by 200 mg every fortnight; or 600 mg initially followed by 300 mg fortnightly.
- Clinically sufficient dupilumab levels in serum are reached within 2 weeks.

Efficacy

- The results of four major Phase II or III double blind, placebo-controlled randomized controlled clinical trials assessing dupilumab as treatment for asthma have been published.
- Two of these trials (Wenzel *et al.* 2013 and Wenzel *et al.* 2016) assessed dupilumab in adult patients only, and two (QUEST; VENTURE) included adolescents (over the age of 12 years).
- All trials demonstrated a statistically significant improvement in FEV1 and rate of asthma exacerbations or severe exacerbations in dupilumab-treated patients compared with placebo.
- A meta-analysis has confirmed a relative risk of 0.44 ($p < 0.01$) for annualized severe exacerbation rate. An improvement was seen in patients with baseline peripheral blood eosinophils both above and below 300 cells/mm³, although it was more marked in patients with a higher eosinophil count. In addition, a difference was not seen in the pooled data in annualized severe exacerbation rate for patients with an eosinophil count <150 cells/mm³.
- Pooled data in the meta-analysis found statistically significant improvements in FEV1 from baseline to the longest follow-up period in dupilumab-treated patients, with the mean difference being 0.14 l ($p < 0.01$). A larger improvement in FEV1 was seen in subgroups with higher eosinophil counts, but an improvement persisted even in the subgroup with baseline eosinophils <150 cells/mm³.
- All trials demonstrated an improvement in ACQ scores in dupilumab-treated patients compared with placebo; however, this improvement only reached the MCID threshold in the Wenzel *et al.* 2013 trial, and in a subgroup of patients with baseline eosinophils ≥ 300 /mm³ receiving dupilumab 300 mg/fortnight in the Wenzel *et al.* 2016 trial.
- In the Wenzel *et al.* 2013 trial, background long-acting beta adrenoceptor agonist and inhaled corticosteroid therapy was withdrawn during the trial. In the other three studies, patients were permitted to remain on inhaled corticosteroid and long-acting beta adrenoceptor agonist medications.
- The VENTURE trial assessed dupilumab in asthma patients requiring oral glucocorticoids and found a statistically and clinically significant reduction in glucocorticoid requirement for patients receiving dupilumab in comparison with placebo-treated patients.
- Trials in pediatric patients are ongoing.

Dupilumab in respiratory conditions other than asthma

- A 2016 randomized, double blind placebo-controlled trial assessed dupilumab 300 mg weekly against placebo in patients with nasal polyposis and chronic sinusitis.
- It found an improvement in endoscopic nasal polyp scores at week 16 in dupilumab-treated patients; however, on subgroup analysis, a statistically significant difference was only seen for patients with comorbid asthma.
- Improvements in SNOT-22 scores were also seen, exceeding the MCID of 8.9.
- Positive results from two Phase III trials assessing dupilumab in severe chronic rhinosinusitis with nasal polyps have also recently been announced.

Safety

- Overall rates of both adverse events and serious adverse events were similar between dupilumab- and placebo-treated patients.
- Injection site reactions were more common in dupilumab-treated patients, the majority of which were mild.
- No increased risk of infections was seen in dupilumab-treated patients in comparison with placebo.
- The increased risk of conjunctivitis that has been seen in some patients with atopic dermatitis receiving dupilumab was not apparent in the asthma trials.
- A small number of patients developed a peripheral blood eosinophilia with dupilumab treatment. This was marked and/or symptomatic in a few individuals.

Regulatory affairs

- In 2018, the US FDA approved dupilumab as add-on maintenance treatment in adult and adolescent patients with moderate-to-severe asthma, if they have an eosinophilic phenotype or are dependent upon oral corticosteroids.
- The European Medicines Agency human medicines committee (CHMP) has made a similar recommendation.

Conclusion

- Four major clinical trials have confirmed dupilumab to be a safe, effective therapy for refractory asthma, particularly in patients with an eosinophilic subtype.
- Head-to-head trials assessing the relative efficacy of different biologics in asthma, and predicting response based on asthma phenotype, are needed.

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