Dupilumab versus omalizumab in patients with chronic rhinosinusitis with nasal polyps and coexisting asthma (EVEREST): a multicentre, randomised, double-blind, head-to-head phase 4 trial

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Summary

Background Chronic rhinosinusitis with nasal polyps (CRSwNP) is predominantly driven by type 2 inflammation. The biologics dupilumab and omalizumab, which target drivers and mediators of type 2 inflammation (interleukin [IL]-4/IL-13 signaling and immunoglobulin E [IgE], respectively), are efficacious in treating CRSwNP but direct comparisons are few. In EVEREST (EValuating trEatment RESponses of dupilumab versus omalizumab), the first head-to-head trial in respiratory biologics, we aimed to compare the efficacy and safety of dupilumab and omalizumab in patients with severe CRSwNP who had mild, moderate, or severe asthma.

Methods EVEREST was an international, randomised, double-blind, phase 4 trial, conducted at 100 hospitals or clinical centres in 17 countries. Sites were selected with otolaryngology, pneumologist, allergist, and immunologist practices; needed to have previously conducted double-blind studies; and were required have nasal endoscopy and electrocardiogram machines. Eligible patients aged 18 years or older with severe uncontrolled CRSwNP (with a nasal polyp score of 5 or more [and ≥2 for each nostril]), symptoms of nasal congestion and loss of smell for at least 8 weeks before screening, and physician-diagnosed asthma. Patients were randomly assigned (1:1) to subcutaneous dupilumab 300 mg every 2 weeks or omalizumab weight-tiered and IgE-tiered dosing every 2 weeks or 4 weeks for 24 weeks, with background mometasone furoate nasal spray. Patients and investigators were masked to the study drugs. Primary endpoints were change from baseline in endoscopic nasal polyp score and University of Pennsylvania Smell Identification Test (UPSIT) at 24 weeks. Efficacy was assessed in the intention-to-treat population and safety was assessed in patients who received at least one dose of study medication. The trial was registered at ClinicalTrials.gov, NCT04998604.

Findings Between Sept 27, 2021, and Dec 27, 2024, 819 individuals were screened for study inclusion, 459 were excluded (most common screen failures were: 167 did not meet nasal polyp score ≥5 or did not have ongoing symptoms of nasal congestion and loss of smell, 114 did not meet pre-bronchodilator FEV_1 ≤85% predicted normal, and 99 did not meet eligibility as per omalizumab drug-dosing), and 360 participants were randomly assigned (181 assigned to the dupilumab group and 179 assigned to the omalizumab group). Of the 360 participants, 198 (55%) participants were male, 162 (45%) were female, and the mean age of the total population sample was 52 years (SD 13·1). Improvements were significantly greater with dupilumab than omalizumab for all primary and secondary efficacy endpoints at week 24. Least squares mean differences in change from baseline dupilumab over omalizumab were: nasal polyp score –1·60 (95% CI –1·96 to –1·25; p<0·0001) and UPSIT 8·0 (6·3 to 9·7; p<0·0001). 115 (64%) of 179 participants in the dupilumab group and 116 (67%) of 173 participants in the omalizumab group reported treatment-emergent adverse events, the most common of which were nasopharyngitis, accidental overdose, headache, upper respiratory tract infection, and cough. There were no deaths in the study.

Interpretation Dupilumab was superior to omalizumab in patients with severe CRSwNP and coexisting asthma. These findings support the efficacy of dupilumab in patients with type 2 respiratory diseases versus an active biologic comparator, the known safety profiles of dupilumab and omalizumab, and could enable better treatment targeting for patients with CRSwNP and asthma in clinical practice.

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Research in context

Evidence before this study

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a predominantly type 2 inflammatory disease associated with high disease burden and poor quality of life, particularly in patients with coexisting type 2 inflammatory conditions such as asthma or non-steroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD). We searched MEDLINE from database inception (via PubMed) for articles published in English up to Mar 4, 2025, using search terms "nasal polyposis", "chronic rhinosinusitis", "chronic rhinosinusitis with nasal polyps", "asthma", "biologic", "dupilumab", and "omalizumab". Dupilumab and omalizumab have been shown to have significant efficacy in diseases arising from type 2 inflammation, such as CRSwNP, asthma, NSAID-ERD, and atopic dermatitis. In previous phase 3 studies in patients with CRSwNP, dupilumab and omalizumab showed efficacy in reducing nasal polyp burden.

Added value of this study

To our knowledge, EVEREST is the first head-to-head phase 4 trial assessing two biologics, dupilumab and omalizumab, in a large group of patients with severe CRSwNP coexisting with mild, moderate, or severe asthma. Treatment with dupilumab resulted in reduced nasal polyp size and severity of symptoms, and improved sense of smell, asthma control, and both CRSwNP-specific and asthma-specific health-related quality of life compared with omalizumab. Both treatments were well tolerated.

Implications of all the available evidence

Patients with CRSwNP and coexisting asthma have a high disease burden that is challenging to treat. Dupilumab showed a more favourable benefit–risk profile with superior efficacy in treating these patients compared with omalizumab and demonstrated tolerability consistent with the known safety profile. These findings will enable better treatment targeting for patients with CRSwNP and asthma.

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is associated with a high symptom burden including nasal congestion, rhinorrhoea and loss of sense of smell, and a substantial reduction in health-related quality of life, particularly in patients with moderate-to-severe disease.[1–3] Up to 67% of patients with CRSwNP have coexisting asthma, which is associated with more severe disease, a higher risk of polyp recurrence, greater dependence on systemic corticosteroids, reduced health-related quality of life,[4–6] and increased costs.[7–9] Approximately a quarter of patients with CRSwNP and coexisting asthma have non-steroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD), characterised by adult-onset asthma with CRSwNP and hypersensitivity to NSAIDs.[10]

See Online for appendix 1

CRSwNP is a predominantly type 2 inflammatory disease and biologics targeting different key molecules of type 2 inflammation have shown efficacy versus placebo in phase 3 trials. The biologics dupilumab (anti-interleukin [IL]-4Rα), omalizumab (anti-immunoglobulin [Ig]E), and mepolizumab (anti-IL-5) are approved for the treatment of CRSwNP with or without coexisting asthma.[1,10–12] Differences in study designs and study populations between the placebo-controlled trials of these biologics preclude direct comparison of the results, but several meta-analyses[13,14] and indirect treatment comparisons have been published.[15–19] These analyses indicate that dupilumab is a more effective treatment than omalizumab for patients with CRSwNP, including in difficult-to-treat populations such as those with coexisting type 2 inflammatory diseases. However, direct comparisons of these biologics in a head-to-head clinical trial in patients with CRSwNP or asthma have not yet been made.

EVEREST (EValuating trEatment RESponses of dupilumab versus omalizumab) is the first head-to-head study designed to fill the key evidence gap in providing direct comparative data.[20] We aimed to evaluate the efficacy and safety of dupilumab compared with omalizumab in patients with severe CRSwNP coexisting with mild, moderate, or severe asthma.

Methods

Study design

EVEREST was a multicentre, randomised, double-blind, phase 4 trial comparing efficacy and safety of dupilumab versus omalizumab in patients with severe CRSwNP and coexisting asthma. A summary of the study design was reported previously[20] and details are presented in appendix 1 (p 1). EVEREST was conducted in 100 hospitals or clinical centres in 17 countries (Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Mexico, Poland, Portugal, UK, USA, Romania, Spain, and Sweden) with dual CRSwNP and asthma expertise. Sites were selected with otolaryngology, pneumologist, allergist, and immunologist practices; needed to have previously conducted double-blind studies; and needed to have nasal endoscopy and electrocardiogram machines. The trial consisted of a 4-week run-in period, a 24-week treatment period, and a 12-week follow-up period (appendix 1 p 16). The protocol was developed by the funders and sponsors (Sanofi and Regeneron Pharmaceuticals) in collaboration with the principal investigators. The local institutional review board or ethics committee at each study centre approved the protocol and patient information materials and oversaw trial conduct. There was no patient or public involvement in the design, conduct, or reporting of the trial. Details of the protocol are presented in appendix 2

See Online for appendix 2

and the statistical analysis plan is presented in appendix 3. This trial was registered at Clinicaltrials.gov, NCT04998604 on Aug 10, 2021 before patient enrolment, and is now completed.

Participants

Eligible participants were aged 18 years or older with CRSwNP, which despite treatment with systemic corticosteroids in the past 2 years (or contradiction or intolerance to these drugs) or previous surgery for nasal polyps, had a nasal polyp score of 5 or more (and ≥2 for each nostril [a score of 2 in each nostril would be excluded]),[21] and symptoms of nasal congestion and loss of smell for at least 8 weeks before screening, with moderate-to-severe symptoms in the 7 days before randomisation (average daily score >1). Participants also required physician-diagnosed coexisting asthma for at least 12 months on a stable dose of low, medium, or high-dose inhaled corticosteroid and a second controller (long-acting β-2 adrenergic receptor agonist). All participants were required to meet the eligible weight range (30–150 kg) and serum IgE concentrations (30–1500 IU/mL) for omalizumab dosing. Participants who had undergone any endoscopic sinus surgery (including nasal polypectomy) within 6 months before screening were excluded from the study, as were patients with conditions or concomitant diseases such as antrochoanal polyps, nasal septal deviation that would occlude at least one nostril, acute rhinosinusitis, nasal or upper respiratory viral infection, known or suspected diagnosis of cystic fibrosis or eosinophilic granulomatous with polyangiitis. Participants who received a biologic treatment less than 4 weeks (or 5 half-lives) before screening were also excluded. Further details of selection criteria are provided in the protocol (appendix 2 p 41). Data on sex (male or female) and race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, Not Reported, or Unknown) were self-reported by the participants and all participants provided written informed consent before participating in the trial.

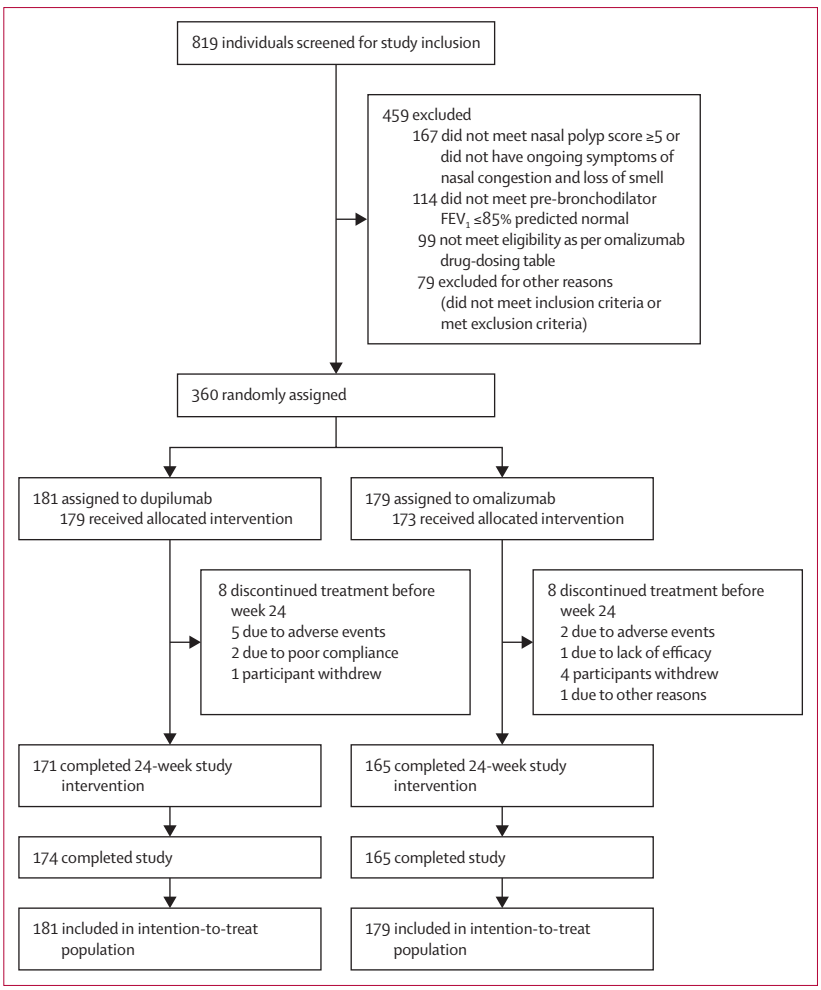

Figure 1: **Trial profile**

Randomisation and masking

Patients were randomly assigned (1:1) to dupilumab or omalizumab. Randomisation was assigned centrally with a stratified block randomisation schedule (block size 4) by Interactive Voice Response Technology. This system generated the participant randomisation list and allocated the intervention number and the corresponding intervention kits to the participants. Before the study was initiated, the log in information and directions for the Interactive Voice Response Technology were provided to each site. Site personnel had access to the portal. Randomisation was stratified by previous endoscopic sinus surgery (yes or no), inhaled corticosteroid dose (low *vs* medium or high according to Global Initiative for Asthma 2020 guidelines), presence of NSAID-ERD (yes or no), and region (eastern Europe or rest of the world). Participants and investigators were masked to the assigned drug, with active drug or placebo injections administered by unmasked study personnel who were not involved in evaluating the participant.

See **Online** for appendix 3

Procedures

During the 4-week run-in period and throughout the trial, patients received mometasone furoate nasal spray at a stable dose of 400 µg per day as two actuations of 50 µg per nostril twice daily. If this dose was not tolerated or was not approved under local policy, patients followed a once-daily regimen (total daily dose 200 µg). Asthma background therapy (inhaled corticosteroid and second controller medication) had to be maintained at a stable dose for at least 1 month before the screening visit, during the screening and run-in period, and throughout the study intervention period. During the treatment period, patients received either 300 mg of subcutaneous dupilumab every 2 weeks or 75–600 mg subcutaneous omalizumab every 2 weeks or every 4 weeks according to

	Dupilumab group (n=181)	Omalizumab group (n=179)	Total (n=360)
Age, years	51 (13·3)	52 (12·9)	52 (13·1)
Sex			
Male	107 (59%)	91 (51%)	198 (55%)
Female	74 (41%)	88 (49%)	162 (45%)
Race			
American Indian or Alaska Native	0	2 (1%)	2/358 (1%)
Asian	1/179 (1%)	1 (1%)	2/358 (1%)
Black or African American	2/179 (1%)	1 (1%)	3/358 (1%)
White	171/179 (96%)	170 (95%)	341/358 (95%)
Multiple	0	1 (1%)	1/358 (<1%)
Not reported or unknown	5/179 (3%)	4 (2%)	9/358 (3%)
BMI (kg/m²)	27·43 (5·03)	26·85 (3·98)	27·14 (4·54)
CRSwNP duration, years	13·3 (9·64)	13·2 (9·91)	13·3 (9·76)
Previous endoscopic sinus surgery			
No previous surgeries	36 (20%)	34 (19%)	70 (19%)
One previous surgery	59 (33%)	61 (34%)	120 (33%)
Two previous surgeries	35 (19%)	33 (18%)	68 (19%)
Three or more previous surgeries	51 (28%)	51 (29%)	102 (28%)
Age of onset of asthma, years	34·9 (16·48)	36·1 (16·35)	35·5 (16·40)
NSAID-ERD	74 (41%)	71 (40%)	145 (40%)
Ongoing allergic rhinitis	83 (46%)	81 (45%)	164 (46%)
Ongoing seasonal allergic rhinitis	73 (40%)	66 (37%)	139 (39%)
Ongoing perennial allergic rhinitis	60 (33%)	46 (26%)	106 (29%)
Nasal polyp score (scale 0–8)†	6·11 (1·17)	6·15 (1·28)	6·13 (1·22)
Smell test (UPSIT) score (scale 0–40)*	11·10 (5·45)	11·00 (6·13)	11·10 (5·79)
Loss of smell score (scale 0–3)†	2·86 (0·40)	2·83 (0·44)	2·84 (0·42)
Nasal congestion score (scale 0–3)†	2·47 (0·56)	2·44 (0·63)	2·46 (0·59)
Total symptom score (scale 0–9)†	7·38 (1·27)	7·30 (1·49)	7·34 (1·38)
SNOT-22 total score (scale 0–110)†	64·80 (19·06)	66·20 (20·56)	65·50 (19·81)

(Table 1 continues on next page)

weight tier and IgE concentrations. Further information on dosing is provided in the protocol (appendix 2 pp 48–51). Patients receiving omalizumab every 4 weeks also received placebo as needed to mask the number of active injections. Rescue treatment with systemic antibiotics, short-course systemic corticosteroids, or endoscopic sinus surgery was permitted as needed during the treatment. Participants receiving rescue treatment other than endoscopic sinus surgery could continue on the study drug.

Outcomes

The two primary endpoints were change from baseline in endoscopic nasal polyp score (range 0–8, with a higher score indicating greater disease severity) and University of Pennsylvania Smell Identification Test (UPSIT; range 0–40, with a lower score indicating greater disease severity) at week 24. Key secondary endpoints were change from baseline at week 24 in daily loss of smell and nasal congestion severity scores (range 0–3, with a higher score indicating greater disease severity), each recorded in the patient-reported daily nasal symptom diary. Other secondary endpoints were change from baseline at week 24 in total symptom score (range 0–9, with a higher score indicating greater disease severity), 22-item Sino-Nasal Outcome Test (SNOT-22) total score (range 0–110, with a higher score indicating greater disease severity), peak nasal inspiratory flow, and rhinosinusitis severity visual analogue scale (range 0–10 cm, with a higher score indicating greater disease severity). SNOT-22 sub-domain scores will be reported as post-hoc analyses. Tertiary or exploratory endpoints included change from baseline at week 24 in pre-bronchodilator FEV_1, 7-point Asthma Control Questionnaire score (ACQ-7, range 0–6, with a higher score indicating greater disease severity), Asthma Quality of Life Questionnaire (AQLQ, range 1–7, with a higher score indicating greater disease severity), fractional exhaled nitric oxide (FeNO, ppb), forced expiratory flow 25–75%, time to first systemic corticosteroid burst (defined as short, high-dose course) for asthma and nasal polyp, and annualised rate of systemic corticosteroid courses.

Safety was assessed in all participants who received at least one dose of the study drugs and included incidence of adverse events, serious adverse events, and adverse events of special interest (appendix 1 p 2).

Statistical analysis

Originally, a sample size of 422 was targeted to power the two primary endpoints, nasal polyp score and UPSIT, as well as the key asthma secondary endpoint of change from pre-bronchodilator FEV_1. However, the patient inclusion criterion of pre-bronchodilator FEV_1 of 85% or less predicted normal at screening proved to be a barrier to enrolment. To accelerate enrolment, the protocol was therefore amended to remove the inclusion criterion of pre-bronchodilator FEV_1 of 85% or less predicted normal. Due to the low recruitment rate, the protocol was further amended to decrease the sample size to 320 participants and downgrade the key asthma endpoint from secondary to exploratory. Based on the original assumptions, the reduced sample size of 320 patients with approximately 160 patients per group would provide 96% power to detect a treatment difference of –0·7 using a two-sided t-test with an α of 0·025 for change from baseline in nasal polyp score at week 24 in dupilumab 300 mg administered every 2 weeks versus omalizumab administered every 2 weeks or 4 weeks, and more than 99% power to detect a treatment difference of 6·7 with pooled standard deviation of 8·64 (dupilumab) and 6·69 (omalizumab) using a two-sided t-test with an α of 0·025 for change from baseline in UPSIT at week 24 in dupilumab versus omalizumab. Further details are provided in the protocol (appendix 2 pp 77–78; appendix 1 p 1).

Efficacy data for all outcomes were analysed in the intention-to-treat study population (consisting of all randomised patients, regardless of whether they received treatment, and analysed according to the study

intervention group allocated by randomisation). Change from baseline in nasal polyp score and UPSIT at week 24 was analysed in an ANCOVA model with study intervention (dupilumab, omalizumab), corresponding baseline value, previous endoscopic sinus surgery (yes or no), inhaled corticosteroid dose (low *vs* medium or high), presence of NSAID-ERD (yes or no), and region (Eastern Europe or rest of world) as covariates and reported as mean (SD). The adjusted least squares means in change from baseline of each study intervention group, the least squares mean difference between the dupilumab and omalizumab groups, and the corresponding SEs and 95% CI of the differences obtained from the imputed data were combined using Rubin's formula. The safety analysis set included all randomly assigned patients who received at least one dose of treatment. Incidences of adverse events were summarised using descriptive statistics and reported as absolute values with percentages.

For patients discontinuing the study intervention before week 24 not due to any reason related to the COVID-19 pandemic, off-study intervention efficacy assessments measured up to week 24 were included in this analysis. By contrast, for any patients discontinuing the study intervention due to any reason related to the COVID-19 pandemic, off-study intervention data were set to missing. For patients who underwent endoscopic sinus surgery for CRSwNP or received systemic corticosteroids for any reason during the study, data collected afterwards were set to missing, and the worst post-baseline value on or before the time of endoscopic sinus surgery or systemic corticosteroid intake was used to impute the missing week 24 value (for patients whose post-baseline values are all missing, the baseline was used to impute the value). For patients who discontinued the treatment without being rescued by endoscopic sinus surgery or receiving systemic corticosteroid, a multiple imputation approach was used to impute the missing week 24 value by using all patients excluding those who had undergone endoscopic sinus surgery or received systemic corticosteroids on or before week 24 under an assumption of missing at random. Further details are provided in the statistical analysis plan (appendix 3 pp 22–23). Subgroup analyses were conducted for the two primary endpoints (appendix 1 p 1).

The changes from baseline in the continuous secondary endpoints to week 24 were analysed using the ANCOVA model in the same way as for the primary endpoints. Significance was only possible at p=0·05 for each key secondary and selected secondary endpoints in the hierarchy if both comparisons had p<0·05 for the primary endpoints. The following key secondary endpoints and the selected secondary endpoint were included in the multiplicity adjustment scheme and tested in the following order: change from baseline to week 24 in loss of smell, change from baseline to week 24 in nasal congestion, and change from baseline to week 24 in total severity score. This fixed hierarchical approach controlled the overall type I error rate at the 0·05 level. Secondary and other endpoints not in the hierarchy were not included in multiplicity adjustments and p values for these are nominal and for descriptive purpose. Statistical analyses were done with SAS (version 9.4).

	Dupilumab group (n=181)	Omalizumab group (n=179)	Total (n=360)
(Continued from previous page)			
Peak nasal inspiratory flow, L/min*	79·78 (50·16)	77·68 (59·44)	78·74 (54·89)
Rhinosinusitis disease severity (visual analogue scale, 0–10 cm)†	8·63 (1·50)	8·75 (1·41)	8·69 (1·45)
Pre-bronchodilator FEV_1, L	2·68 (0·92)	2·59 (0·82)	2·63 (0·87)
Pre-bronchodilator FEV_1, % predicted	77·4 (19·68)	77·9 (16·06)	77·6 (17·96)
ACQ-7 score (scale 0–6)†	2·82 (0·99)	2·69 (0·96)	2·76 (0·97)
Forced expiratory flow 25–75%, L/s	1·84 (1·11)	1·72 (0·91)	1·78 (1·02)
AQLQ (scale 1–7)†	4·13 (1·20)	4·23 (1·25)	4·18 (1·22)
Blood eosinophil count, cells per µL	562 (385)	550 (351)	556 (368)
Baseline serum total immunoglobulin E, IU/mL	212 (181)	220 (185)	216 (183)
FeNO (ppb)	54·30 (40·78)	54·60 (38·52)	54·40 (39·65)
Number of severe asthma exacerbations in the year before screening	0·6 (1·9)	0·9 (2·7)	0·7 (2·3)
Inhaled corticosteroid dose level‡			
Low	64 (35%)	63 (35%)	127 (35%)
Medium or high	117 (65%)	116 (65%)	233 (65%)
Systemic corticosteroid use in the previous 2 years	86 (48%)	90 (50%)	176 (49%)
Indication for previous systemic corticosteroid use			
CRSwNP	67/86 (78%)	77/90 (86%)	144/176 (82%)
Asthma	18/86 (21%)	15/90 (17%)	33/176 (19%)
Other	5/86 (6%)	5/90 (6%)	10/176 (6%)

Data are n (%), n/N (%), or mean (SD). Additional demographic data are presented in appendix 1 (p 5). CRSwNP=chronic rhinosinusitis with nasal polyps. NSAID-ERD=non-steroidal anti-inflammatory drug-exacerbated respiratory disease. SNOT-22=22-item Sino-Nasal Outcome Test. UPSIT=University of Pennsylvania Smell Identification Test. ACQ-7=asthma control questionnaire 7-item version. AQLQ=asthma quality of life questionnaire with standardised activities. FeNO=fractional exhaled nitric oxide. ppb=parts per billion. *Higher scores indicate lower disease severity. †Higher scores indicate greater disease severity. ‡According to The Global initiative for Asthma 2020 guidelines.

Table 1: **Baseline characteristics**

Role of the funding source

The study sponsors participated in the study design, data analysis, data interpretation, and writing of the report, and approved the decision to submit for publication.

Results

Between Sept 27, 2021, and Dec 27, 2024, 819 individuals were screened for inclusion in the study. 459 were ineligible, the most common reasons being not meeting the inclusion criteria of nasal polyp score ≥5 and ongoing symptoms of nasal congestion and loss of smell (n=167); not meeting the inclusion criterion of pre-bronchodilator FEV_1 ≤85% of predicted normal (n=114); and not meeting

	Dupilumab group (n=181)			Omalizumab group (n=179)			Least squares mean difference of dupilumab over omalizumab (95% CI; p-value)
	Baseline	Week 24		Baseline	Week 24		
	Mean (SD)	Mean (SD)	Least squares mean change from baseline (SE)	Mean (SD)	Mean (SD)	Least squares mean change from baseline (SE)	
Primary endpoints							
Nasal polyp score (scale 0–8)	6·11 (1·17)	3·56 (2·01)	−2·65 (0·15)	6·15 (1·28)	5·19 (1·83)	−1·05 (0·15)	−1·60 (−1·96 to −1·25; p<0·0001)
Smell test score (UPSIT; scale 0–40)	11·10 (5·45)	23·40 (8·80)	12·70 (0·72)	11·00 (6·13)	15·20 (8·86)	4·70 (0·74)	8·00 (6·30 to 9·70; p<0·0001)
Secondary endpoints							
Nasal congestion score (scale 0–3)	2·47 (0·56)	0·86 (0·66)	−1·63 (0·07)	2·44 (0·63)	1·43 (0·91)	−1·05 (0·07)	−0·58 (−0·74 to −0·42; p<0·0001)
Loss-of-smell score (scale 0–3)	2·86 (0·40)	1·41 (1·03)	−1·55 (0·08)	2·83 (0·44)	2·23 (0·96)	−0·74 (0·09)	−0·81 (−1·01 to −0·61; p<0·0001)
Total symptom score (scale 0–9)	7·38 (1·27)	3·03 (1·83)	−4·48 (0·17)	7·30 (1·49)	4·79 (2·26)	−2·73 (0·18)	−1·74 (−2·15 to −1·33; p<0·0001)
SNOT-22 total score (scale 0–110)	64·80 (19·06)	20·80 (16·75)	−44·60 (1·66)	66·20 (20·56)	34·60 (22·77)	−31·90 (1·71)	−12·70 (−16·70 to −8·80; nominal p<0·0001)
Peak nasal inspiratory flow (L/min)	79·78 (50·16)	150·88 (61·72)	68·96 (4·11)	77·68 (59·44)	118·18 (67·48)	37·69 (4·29)	31·27 (21·40 to 41·15; nominal p<0·0001)
Rhinosinusitis disease severity (visual analogue scale, 0–10 cm)	8·63 (1·50)	3·22 (2·97)	−5·43 (0·27)	8·75 (1·41)	5·21 (3·21)	−3·56 (0·28)	−1·87 (−2·52 to −1·23; nominal p<0·0001)
Other endpoints							
Pre-bronchodilator FEV_1 (L)	2·68 (0·92)	2·99 (0·88)	0·29 (0·04)	2·59 (0·82)	2·79 (0·91)	0·14 (0·05)	0·15 (0·05 to 0·26; nominal p=0·0030)
ACQ-7 score (scale 0–6)	2·82 (0·99)	0·90 (0·74)	−1·92 (0·07)	2·69 (0·96)	1·37 (1·00)	−1·44 (0·08)	−0·48 (−0·65 to −0·31; nominal p<0·0001)
FeNO (ppb)	54·30 (40·78)	25·60 (14·24)	−30·0 (2·48)	54·60 (38·52)	48·90 (42·74)	−4·60 (2·65)	−25·40 (−31·40 to −19·40; nominal p<0·0001)
Forced expiratory flow 25–75% (L/s)	1·84 (1·11)	2·27 (1·12)	0·41 (0·07)	1·72 (0·91)	1·99 (1·04)	0·21 (0·07)	0·20 (0·04 to 0·36; nominal p=0·013)
AQLQ (scale 1–7)	4·13 (1·20)	6·14 (0·83)	2·00 (0·08)	4·23 (1·25)	5·58 (1·14)	1·44 (0·08)	0·56 (0·37 to 0·75; nominal p<0·0001)

UPSIT=University of Pennsylvania Smell Identification Test. SNOT-22=22-item Sino-Nasal Outcome Test. ACQ-7=asthma control questionnaire 7-item version. FeNO=fractional exhaled nitric oxide. ppb=parts per billion. AQLQ=asthma quality of life questionnaire with standardised activities.

Table 2: **Summary of primary, secondary, and other efficacy endpoints**

the eligibility requirements of the omalizumab drug-dosing table (n=99; figure 1). 360 participants were enrolled in EVEREST and randomly assigned to dupilumab every 2 weeks (n=181) or omalizumab every 2 weeks or 4 weeks (n=179; figure 1). The database lock occurred on Jan 27, 2025. Eight participants were randomly assigned to a group but were not treated and eight participants in each treatment group discontinued treatment before week 24 (figure 1). The most common reason for treatment discontinuation was adverse events.

Baseline demographics and patient characteristics were balanced across the treatment groups and were consistent with a population with severe, uncontrolled CRSwNP coexisting with mild, moderate, or severe asthma (table 1). 198 (55%) participants were male, 162 (45%) were female, and most of the participants were white (95%). The mean age of the total population sample was 52 years (SD 13·1). 176 (49%) participants used systemic corticosteroids in the 2 years before enrolment, predominantly for CRSwNP. Most (81%) participants had undergone at least one endoscopic sinus surgery before enrolment. The mean baseline nasal polyp score was 6·13 (SD 1·22), UPSIT was 11·10 (5·79), nasal congestion was 2·46 (0·59), and loss of smell was 2·84 (0·42). The mean baseline pre-bronchodilator FEV_1 was 2·63 L (SD 0·87) and ACQ-7 score was 2·76 (0·97), indicating inadequately controlled asthma. The overall study population showed a mean baseline pre-bronchodilator FEV_1 percent predicted value of 77·6% corresponding to moderate asthma. The distribution of pre-bronchodilator FEV_1 percent predicted value for mild (≥80%), moderate (60% to <80%), and severe (<60%) asthma was 44%, 42%, and 14% of the study population, respectively. Around two-thirds (65%) of patients were on medium or high dose inhaled

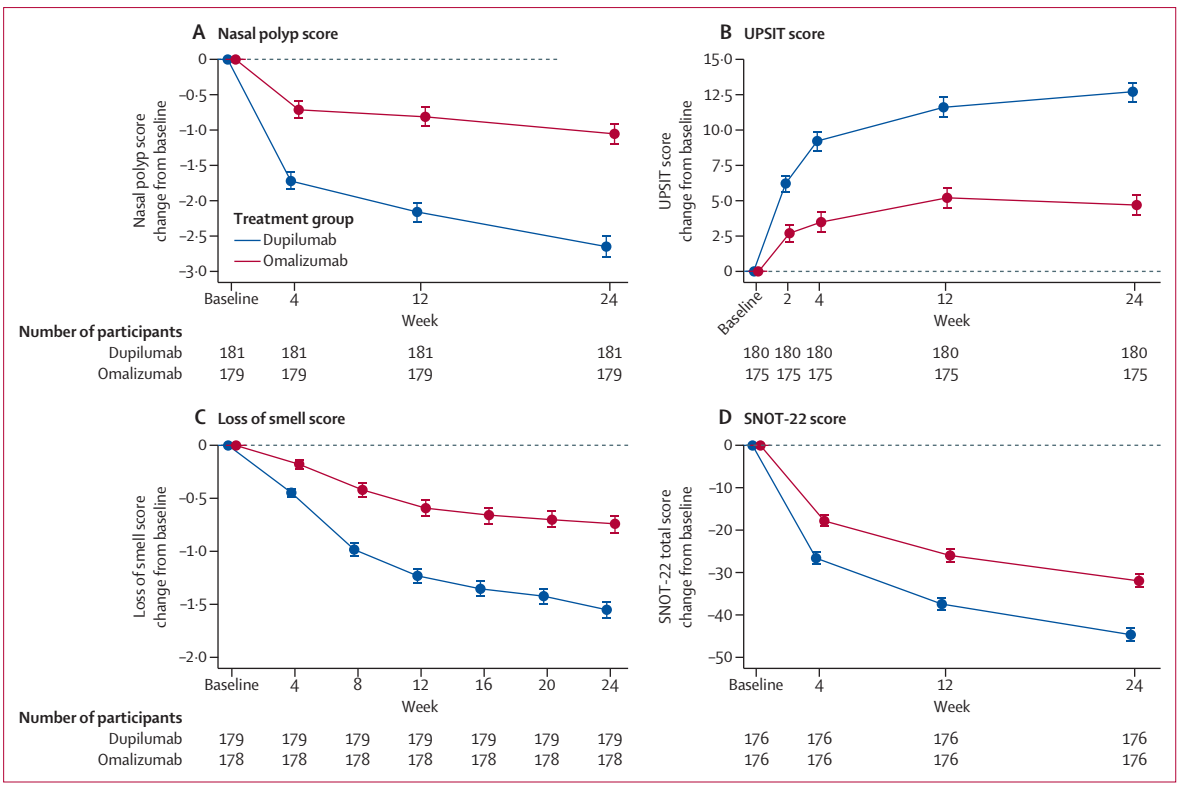

Figure 2: **Change from baseline in nasal polyp score (A), UPSIT (B), loss of smell score (C), and SNOT-22 (D) up to week 24**
Data are least squares mean (SE). UPSIT=University of Pennsylvania Smell Identification Test. SNOT-22=22-item Sino-Nasal Outcome Test.

corticosteroids at baseline, and 35% were on a low dose inhaled corticosteroid, according to the Global Initiative for Asthma 2020 guidelines.[22] 145 patients (40%) had NSAID-ERD.

Improvements were significantly greater with dupilumab than omalizumab for all primary and secondary efficacy endpoints at week 24 (table 2; figure 2). Least squares mean differences in change from baseline dupilumab over omalizumab at week 24 were: nasal polyp score –1·60 (95% CI –1·96 to –1·25; p<0·0001) and UPSIT 8·0 (6·3 to 9·7; p<0·0001). The magnitudes of the mean differences in improvement with dupilumab over omalizumab for the primary endpoints met or exceeded reported thresholds for meaningful within-patient change in clinical settings (appendix 1 p 6). The treatment benefit of dupilumab over omalizumab was largely consistent across the prespecified patient subgroups (appendix 1 pp 17–19). Dupilumab superiority for each primary endpoint was evident at 24 weeks irrespective of age, sex, bodyweight, inhaled corticosteroid dose level, region, presence or absence of NSAID-ERD, presence or absence of previous endoscopic sinus surgery, age of onset of asthma, presence or absence of severe asthma exacerbations in the year before the study, smoking history, and use of systemic corticosteroids in the 2 years before the study. In the subgroups with baseline blood eosinophil counts of <150 cells/μL (n=8 and n=5 in the dupilumab and omalizumab arms, respectively) and <300 cells/μL (n=33 and n=40 in the dupilumab and omalizumab arms, respectively), the superiority of dupilumab over omalizumab was evident at week 24 for UPSIT but was non-significant for nasal polyp score (appendix 1 pp 17–19). Nominally greater improvement with dupilumab over omalizumab was evident from the first post-baseline assessment for each primary endpoint; at week 4, nasal polyp score least squares mean difference in change from baseline for dupilumab over omalizumab was –1·01 (95% CI –1·32 to –0·71; nominal p<0·0001); at week 2, UPSIT least squares mean difference for dupilumab over omalizumab was 3·5 (2·0 to 5·0; nominal p<0·0001; figure 2A, B).

Similarly, patients receiving dupilumab showed significantly greater improvements in loss of smell, nasal congestion, total symptom score (all p<0·0001, table 2, figure 2), and nominally greater improvements in SNOT-22, peak nasal inspiratory flow, and rhinosinusitis severity visual analogue scale (all nominal p<0·0001, table 2) at week 24 than patients receiving omalizumab. The least squares mean differences in change from baseline dupilumab over omalizumab at week 24 of –12·70 (95% CI –16·70 to –8·80; nominal p<0·0001) for SNOT-22 and 31·27 (21·40 to 41·15; p<0·0001) for peak nasal inspiratory flow were greater than the minimally important clinical differences of at least

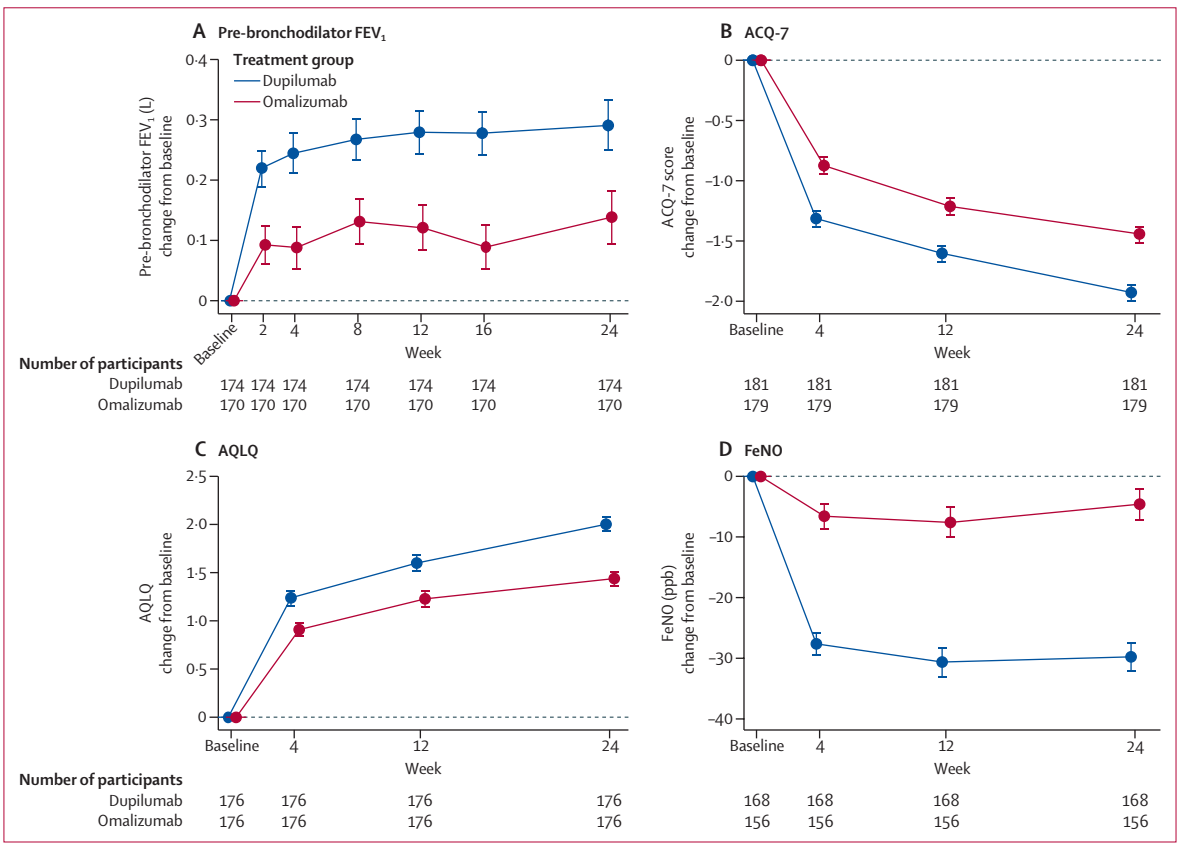

Figure 3: **Change from baseline in pre-bronchodilator FEV_1 (A), ACQ-7 (B), AQLQ (C), and FeNO (ppb) (D) up to week 24**
Data are least squares mean (SE). ACQ-7=asthma control questionnaire. AQLQ=asthma quality of life questionnaire. FeNO=fractional exhaled nitric oxide. ppb=parts per billion.

8·9 points for SNOT-22 and at least 20 L per min for peak nasal inspiratory flow (appendix 1 p 6). Nominally greater improvements with dupilumab over omalizumab were evident from week 4 with least squares mean differences in change from baseline of –0·27 (95% CI –0·37 to –0·17) for loss of smell, –0·35 (–0·46 to –0·24) for nasal congestion, –0·83 (–1·09 to –0·58) for total symptom score, –8·60 (–12·20 to –5·10) for SNOT-22, 14·30 L per min (9·20 to 19·50) for peak nasal inspiratory flow, and –1·56 (–2·10 to –1·03) for rhinosinusitis severity visual analogue scale.

Improvements were also greater with dupilumab than omalizumab for asthma endpoints, with least squares mean differences at week 24 of 0·15 L (95% CI 0·05 to 0·26; nominal p=0·0030) for pre-bronchodilator FEV_1, 0·20 L/s (0·04 to 0·36; nominal p=0·013) for forced expiratory flow 25–75%, –0·48 (–0·65 to –0·31; nominal p<0·0001) for ACQ-7 score, –25·40 ppb (–31·40 to –19·40; nominal p<0·0001) for FeNO, and 0·56 (0·37 to 0·75; nominal p<0·0001) for AQLQ (figure 3, table 2). The least squares mean differences for AQLQ were greater than the minimally important clinical differences of at least 0·5 points (appendix 1 p 6). At week 4, least squares mean differences in change from baseline were –0·45 (95% CI –0·62 to –0·28) for ACQ-7 score, 0·16 (0·08 to 0·24) for pre-bronchodilator FEV_1, –21·10 (–25·90 to –16·30) for FeNO, and 0·33 (0·14 to 0·52) for AQLQ. One (1%) patient in the dupilumab group and two (1%) patients in the omalizumab group had one severe asthma exacerbation during the study.

The number of participants with a first systemic corticosteroid burst during the study treatment period was none for nasal polyps and three (2%) for asthma in the dupilumab group, and 14 (8%) for nasal polyps and four (2%) for asthma in the omalizumab group (appendix 1 p 8). The annualised rates of systemic corticosteroid courses for any reason were 4% in the dupilumab group and 20% in the omalizumab group, and the relative risk of requiring systemic corticosteroids was 18% (95% CI 6·25 to 54·15; nominal p=0·0020) for dupilumab versus omalizumab, indicating a reduced risk of requiring systemic corticosteroids with dupilumab. The risk of worsening CRSwNP or asthma was assessed based on the need for initiation with rescue therapy. The risk of CRSwNP worsening was higher for omalizumab than dupilumab but there was little difference between groups in the worsening of asthma (appendix 1 p 9). No patient in the dupilumab group and three patients in the omalizumab group needed endoscopic sinus surgery during the 24-week treatment period.

Blood eosinophil count showed a transient increase in the dupilumab group, returning towards baseline levels by week 24, whereas in the omalizumab group there was a generally sustained decrease (appendix 1 p 20). Patients in the dupilumab group had a decrease in serum total IgE concentrations between baseline and week 24, while patients in the omalizumab group showed an increase (appendix 1 p 20). Efficacy improvements were greater with dupilumab than omalizumab in nasal polyp score and UPSIT irrespective of baseline IgE concentration (<100 *vs* ≥100 IU/mL; appendix 1 pp 11–12).

In the safety population, which included all patients who were randomly assigned and received at least one dose of study medication, the number of patients with any treatment-emergent adverse events was similar in the dupilumab and omalizumab groups (115 [64%] of 179 *vs* 116 [67%] of 173; table 3). The most commonly reported adverse events were nasopharyngitis, accidental overdose, headache, upper respiratory tract infection, and cough. Three (2%) patients in the dupilumab group and seven (4%) patients in the omalizumab group reported at least one serious treatment-emergent adverse event (table 3, appendix 1 p 13). Four (2%) patients in the dupilumab group and two (1%) patients in the omalizumab group reported at least one adverse event of special interest (appendix 1 p 14). The adverse events of special interest reported in the dupilumab group were seasonal allergy, urticaria, and pregnancy, and in the omalizumab group were helminthic infection and keratitis. The participant who became pregnant withdrew from the study per protocol. Five (3%) participants in the dupilumab group and two (1%) participants in the omalizumab group permanently discontinued treatment due to treatment-emergent adverse events (appendix 1 p 15). No adverse events led to death.

	Dupilumab group (n=179)	Omalizumab group (n=173)
Treatment-emergent adverse events		
Any	115 (64%)	116 (67%)
Any serious	3 (2%)	7 (4%)
Any leading to death	0	0
Any leading to permanent study intervention discontinuation	5 (3%)	2 (1%)
Treatment-emergent adverse events occurring in ≥5% of patients*		
Nasopharyngitis	21 (12%)	20 (12%)
Accidental overdose	12 (7%)	21 (12%)
Headache	10 (6%)	13 (8%)
Upper respiratory tract infection	10 (6%)	8 (5%)
Cough	9 (5%)	2 (1%)

Data are n (%). Following randomisation, two patients in the dupilumab group and six patients in the omalizumab group did not receive treatment and were therefore not included in the safety population. *According to the preferred terms of the Medical Dictionary for Regulatory Activities.

Table 3: **Treatment-emergent adverse events in the safety population**

Discussion

In patients with severe CRSwNP that is inadequately controlled with standard of care treatment and coexists with mild, moderate, or severe asthma, adding dupilumab to daily mometasone furoate nasal spray provided significant and clinically meaningful improvements over those seen with omalizumab. This broad and significant effect was reflected in reduced polyp size and improved sense of smell. The improved benefit with dupilumab over omalizumab was seen within 4 weeks and sustained over 24 weeks.

In this first head-to-head comparison of dupilumab and omalizumab in patients with severe CRSwNP and coexisting asthma, dupilumab showed superiority over omalizumab in meeting the primary endpoints and demonstrating significant improvement in all secondary endpoints, including asthma endpoints. Baseline characteristics were generally balanced across treatment groups, although there were slightly more women in the dupilumab group compared with the omalizumab group (49% *vs* 41%). Rapid improvements as early as week 4 in nasal polyp score and week 2 in UPSIT scores were evident with dupilumab compared with omalizumab. The differences between nasal polyp score and UPSIT scores on dupilumab treatment compared with omalizumab were sustained and significant at week 24 and were clinically meaningful with the mean differences meeting or exceeding the thresholds for clinically meaningful within-patient change.[23] Additionally, the superiority of dupilumab over omalizumab was demonstrated across all the CRSwNP-specific secondary efficacy endpoints, namely, loss of smell, nasal congestion, total symptom score, SNOT-22, peak nasal inspiratory flow, and rhinosinusitis severity visual analogue score. Notably, the mean UPSIT score of patients in the dupilumab group crossed the anosmia threshold (>18) between weeks 2–4, maintaining this improvement throughout the study, while the mean UPSIT score for patients in the omalizumab group remained below the UPSIT anosmia threshold (≤18) throughout the study. Dupilumab treatment also substantially improved asthma control compared with omalizumab as measured by improvements in pre-bronchodilator FEV_1, ACQ-7, AQLQ, and FeNO. Dupilumab superiority to omalizumab manifested in both CRSwNP (upper airways) and asthma (lower airways) outcomes, supporting the unified airway concept model of interlinked respiratory diseases.[24] These head-to-head results corroborate previous indirect treatment comparisons of phase 3 randomised controlled trials that showed dupilumab resulted in significantly greater improvements in nasal polyp score (mean –1·09 [95% CI –1·60 to –0·57]) and nasal congestion score (–0·52 [–0·84 to –0·20]) at week 24 compared with omalizumab in patients with CRSwNP and coexisting asthma.[15,19]

The increase of total IgE concentration in the omalizumab group following treatment is consistent with previous pharmacokinetic studies in which the

more stable omalizumab-IgE complexes were slower to eliminate than free IgE.[25] Consistent with previous studies, blood total IgE concentrations decreased in the dupilumab group.[1] Changes in eosinophil counts were consistent with previously observed studies and the known mechanism of action of both biologic agents, and therefore expected. These biomarker observations were conducted exclusively for research purposes. Notably, these changes in biomarkers appear to have no effect on clinical outcomes, as reported in the existing literature.[26]

The superiority of dupilumab over omalizumab was evident across a range of prespecified baseline subgroups, including subgroups with and without NSAID-ERD, with and without previous endoscopic sinus surgery, and with and without the use of systemic corticosteroids in the previous 2 years. NSAID-ERD is a challenging disease in which biologics have shown good efficacy,[27,28] and the current findings provide important new evidence relevant to its pathophysiology and management. The requirement for systemic corticosteroids was low in both groups during the study, consistent with the imputed steroid-sparing effect of biologics.[29] Incidence of systemic steroid use was numerically lower in the dupilumab group than the omalizumab group for both CRSwNP and asthma. However, the number of systemic corticosteroid bursts per treatment group was too small to make comparisons of time to first systemic corticosteroid burst.

The safety profiles of dupilumab and omalizumab were generally similar in this trial and were consistent with their previously reported profiles in CRSwNP and asthma indications. These findings add to the body of evidence supporting the tolerable safety profiles of these biologic treatments.

Limitations of our study include the relatively short treatment duration, which might not have given treatment effects time to plateau, and the absence of efficacy assessments at the end of the 12-week follow-up. Evidence from longer-term studies of dupilumab and omalizumab suggest that their treatment effects continue to increase beyond 24 weeks.[1,30] Small sample sizes in some pre-specified subgroups mean that conclusions cannot be drawn about the influence of some characteristics on treatment effects. The low numbers of patients who had severe asthma exacerbations or endoscopic sinus surgery in both groups made median times to these events difficult to calculate, and would require larger comparative studies. When this study was designed, omalizumab and dupilumab were the only biologics approved for CRSwNP. Since then, another biologic has been approved: mepolizumab. Although the current study demonstrates clinically important differences between dupilumab and omalizumab, to date, there is still no head-to-head comparison for CRSwNP that includes mepolizumab. Recent indirect treatment comparisons indicate that there might be clinically significant differences between dupilumab and mepolizumab outcomes in CRSwNP, highlighting the need for a head-to-head trial including dupilumab and mepolizumab.[18] Further studies will be necessary to identify subgroups of patients with CRSwNP by phenotype who might respond better to omalizumab than to dupilumab.

In conclusion, dupilumab demonstrated superiority over omalizumab for both CRSwNP and asthma outcomes in patients with severe CRSwNP and coexisting asthma. This study supports the efficacy of dupilumab in comorbid type 2 respiratory diseases versus an active biologic comparator and supports the known safety profiles of dupilumab and omalizumab.

Contributors

EDC, GWC, EH, MS, TG, MV, ZH, JMu, PG, JMi, ATP, MW, MZ, and PWH acquired data. EDC, EH, PG, ATP, MW, SZ, MC, SN, JTA, AR, YD, AM, and PWH contributed to the conception and design of the study. EDC and PG verified the underlying data. SZ, MC, JTA, and MZ interpreted the data. MZ did the statistical analysis. All authors had access to the data, provided critical feedback and final approval for submission, and accept responsibility for the accuracy, completeness, and protocol adherence of data and analyses. All authors made the decision to submit this manuscript. All investigators had confidentiality agreements with the funders and sponsors (Sanofi and Regeneron Pharmaceuticals).

Declaration of interests

EDC is an advisory board member for and has received speaker fees or honoraria from AstraZeneca, Firma, GSK, Novartis, Regeneron, and Sanofi. GWC has received research or clinical trials grants from AstraZeneca, GSK, Menarini, and Sanofi Genzyme, and fees for lectures or advisory board participation from AstraZeneca, CellTrion, Chiesi, Faes Farma, Firma, Genentech, GSK, Guidotti-Malesci, HAL Allergy, Innovacaremd, Menarini, Novartis, OM-Pharma, Red Maple, Sanofi-Aventis, Sanofi-Genzyme, Stallergenes-Greer, and Uriach Pharma. EH reports consulting fees from Allergy Therapeutics, Almirall, Apogee Therapeutics, AstraZeneca, Bosch, Celltrion Healthcare, Chiesi, Lofarma, Novartis, Regeneron, and Sanofi; research grants from AstraZeneca and Chiesi; speaker fees or honoraria from AstraZeneca, Chiesi, GSK, Lofarma, and Sanofi; and travel support from AstraZeneca and GSK. MS reports research grants from Eli Lilly, Insmed, and Sanofi. MV has received speaker fees from Sanofi and advisory board and speaker fees from GSK. JMu is an advisory board member for, and has received research grants and speaker fees from Almirall, AstraZeneca, GSK, Glenmark, Lilly, Menarini, MSD, Noucor and Uriach Group, Regeneron Pharmaceuticals, Sanofi, and Viatris and MEDA. PG is an advisory board member for and has received clinical trial funding from AstraZeneca, Eli Lilly, Genentech, Insmed, Novartis, Regeneron Pharmaceuticals, Roche, and Sanofi. JMi is an advisory board member for and has received speaker fees or honoraria from AstraZeneca, GSK, Novartis, and Sanofi. ATP has received research support from AstraZeneca, Insmed, Regeneron Pharmaceuticals, and Sanofi, and is an advisory board member for AstraZeneca, Chiesi, Eli Lilly, GSK, Regeneron Pharmaceuticals, and Sanofi. MW reports research grants from ALK-Abelló, AstraZeneca, GSK, Novartis, Sanofi, and Takeda; is an advisory board member for ALK-Abelló, AstraZeneca, GSK, Novartis, and Sanofi; has received lecture fees from ALK-Abelló, Allergopharma, AstraZeneca, CSL Behring, Genzyme, GSK, HAL Allergie, Infectopharm, LETI Pharma, MSD, NeilMed, Novartis, Sanofi, Stallergenes Greer, and Takeda; and is a member of the executive committee of the German Society of Allergology and Clinical Immunology (DGAKI). SZ, MZ, MC, JTA, and AM are employees of Sanofi and may hold stock or stock options. SN, AR, and YD are employees of Regeneron Pharmaceuticals and may hold stock or stock options. PWH is an advisory board member for and has received lecture fees and research grants from Regeneron Pharmaceuticals and Sanofi, and has received consulting and speaker fees from GSK, Regeneron Pharmaceuticals, Sanofi, and Viatris. All other authors declare no competing interests.

Data sharing

Qualified researchers can request access to patient-level data and related documents (including the clinical study report, study protocol with any amends, blank case report form, and dataset specifications). The protocol is provided in appendix 2 and the statistical analysis plan is provided in appendix 3. Patient-level data will be anonymised, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://www.vivli.org.

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