Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials

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Summary

Background Patients with chronic rhinosinusitis with nasal polyps (CRSwNP) generally have a high symptom burden and poor health-related quality of life, often requiring recurring systemic corticosteroid use and repeated sinus surgery. Dupilumab is a fully human monoclonal antibody that inhibits signalling of interleukin (IL)-4 and IL-13, key drivers of type 2 inflammation, and has been approved for use in atopic dermatitis and asthma. In these two studies, we aimed to assess efficacy and safety of dupilumab in patients with CRSwNP despite previous treatment with systemic corticosteroids, surgery, or both.

Methods LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52 were two multinational, multicentre, randomised, double-blind, placebo-controlled, parallel-group studies assessing dupilumab added to standard of care in adults with severe CRSwNP. SINUS-24 was done in 67 centres in 13 countries, and SINUS-52 was done in 117 centres in 14 countries. Eligible patients were 18 years or older with bilateral CRSwNP and symptoms despite intranasal corticosteroid use, receiving systemic corticosteroids in the preceding 2 years, or having had sinonasal surgery. Patients in SINUS-24 were randomly assigned (1:1) to subcutaneous dupilumab 300 mg or placebo every 2 weeks for 24 weeks. Patients in SINUS-52 were randomly assigned (1:1:1) to dupilumab 300 mg every 2 weeks for 52 weeks, dupilumab every 2 weeks for 24 weeks and then every 4 weeks for the remaining 28 weeks, or placebo every 2 weeks for 52 weeks. All patients were randomly assigned centrally with a permuted block randomisation schedule. Randomisation was stratified by asthma or non-steroidal anti-inflammatory drug-exacerbated respiratory disease status at screening, previous surgery at screening, and country. Patients with or without comorbid asthma were included. Coprimary endpoints were changes from baseline to week 24 in nasal polyp score (NPS), nasal congestion or obstruction, and sinus Lund-Mackay CT scores (a coprimary endpoint in Japan), done in an intention-to-treat population. Safety was assessed in a pooled population of both dupilumab groups in SINUS-52 up to week 24 and the dupilumab group in SINUS-24 and the placebo groups in both studies until week 24. The trials are complete and registered at ClinicalTrials.gov, NCT02912468 and NCT02898454.

Findings Between Dec 5, 2016, and Aug 3, 2017, 276 patients were enrolled in SINUS-24, with 143 in the dupilumab group and 133 in the placebo group receiving at least one study drug dose. Between Nov 28, 2016, and Aug 28, 2017, 448 patients were enrolled in SINUS-52, with 150 receiving at least one dose of dupilumab every 2 weeks, 145 receiving at least one dose of dupilumab every 2 weeks for 24 weeks and every 4 weeks until week 52, and 153 receiving at least one dose of placebo. Dupilumab significantly improved the coprimary endpoints in both studies. At 24 weeks, least squares mean difference in NPS of dupilumab treatment versus placebo was –2·06 (95% CI –2·43 to –1·69; p<0·0001) in SINUS-24 and –1·80 (–2·10 to –1·51; p<0·0001) in SINUS-52; difference in nasal congestion or obstruction score was –0·89 (–1·07 to –0·71; p<0·0001) in SINUS-24 and –0·87 (–1·03 to –0·71; p<0·0001) in SINUS-52; and difference in Lund-Mackay CT scores was –7·44 (–8·35 to –6·53; p<0·0001) in SINUS-24 and –5·13 (–5·80 to –4·46; p<0·0001) in SINUS-52. The most common adverse events (nasopharyngitis, worsening of nasal polyps and asthma, headache, epistaxis, and injection-site erythema) were more frequent with placebo.

Interpretation In adult patients with severe CRSwNP, dupilumab reduced polyp size, sinus opacification, and severity of symptoms and was well tolerated. These results support the benefits of adding dupilumab to daily standard of care for patients with severe CRSwNP who otherwise have few therapeutic options.

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Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP), an important phenotype of chronic rhinosinusitis,[1,2] has an estimated prevalence of 4·2% in the USA and 4·3% in Europe.[3,4] The clinical, economic, and human burden of this condition is poorly recognised despite the high symptom burden, troublesome and difficult-to-treat loss of smell,[5–7] high rates of recurrence or relapse of nasal polyps after surgery, frequent comorbid late-onset asthma, and poor health-related quality of life.[8] CRSwNP predominantly displays type 2 inflammatory signatures including interleukin (IL)-4, IL-5, and IL-13, and infiltration of nasal polyps by eosinophils, basophils, and mast cells.[9,10] Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (also termed Samter's triad, aspirin-exacerbated respiratory disease in the USA, or N-exacerbated respiratory disease in Europe) is a disease phenotype described as aspirin or NSAID hypersensitivity, asthma, and CRSwNP and is associated with a type 2 inflammatory reaction. Asthma and NSAID-exacerbated respiratory disease are frequent type 2 inflammatory comorbidities, with asthma occurring in up to 65% and NSAID-exacerbated respiratory disease occurring in up to 16% of patients with CRSwNP.[11–14] Patients with CRSwNP and comorbid asthma (with and without NSAID-exacerbated respiratory disease) have more severe disease, characterised by high nasal polyp scores, recurrence of nasal polyps after surgery, frequent systemic corticosteroid dependence, poor asthma control, and higher costs and use of healthcare resources.[15]

Novel therapies to improve disease control are needed to spare patients from systemic corticosteroids and repeated sinus surgery. Current standard-of-care options for CRSwNP[1,2] have limitations. Intranasal corticosteroids are the first line of therapy but have small effects on polyp size and symptoms. When symptoms worsen, systemic corticosteroids provide short-term efficacy,[16] but adverse effects prevent long-term use. When pharmacological therapy is unsuccessful, surgery can be effective but, without control of the underlying inflammation disease, recurrence is common,[17] resulting in repeated courses of systemic corticosteroids and surgery in a subgroup of patients with nasal polyps. A therapy that directly targets the fundamental type 2 inflammation driving this disease might provide the opportunity to offer an effective and well

Research in context

Evidence before this study

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a predominantly type 2 inflammation-mediated disease with high disease burden and poor quality of life. In a subgroup of patients with CRSwNP and severe type 2 inflammation, typically associated with comorbid late-onset asthma and disease recurrence after surgical therapy, disease control cannot be achieved by existing standard of care. We searched MEDLINE (via PubMed) and Embase for articles from database inception up to Aug 4, 2016, using search terms including "nasal polyposis", "chronic rhinosinusitis", "chronic rhinosinusitis with nasal polyps", "AERD", "NSAID-ERD", "Samter's". Additionally, we used the Cochrane Library to search other databases, including the Cochrane Central Library of Controlled Trials. Grey literature and other resources were hand-searched to identify any other relevant data. We did a claims-database analysis to ascertain the treatment patterns and cost burden of CRSwNP in the USA. We did extensive analyses on the disease using the GALEN sinusitis cohort of patients with chronic rhinosinusitis in Europe. Dupilumab has been shown to have significant efficacy in diseases driven by type 2 inflammation, such as moderate-to-severe atopic dermatitis and moderate-to-severe asthma in patients aged 12 years or older. In a previous phase 2, proof-of-concept study in patients with CRSwNP, dupilumab showed significant efficacy in reducing nasal polyp burden and was well tolerated.

Added value of this study

To our knowledge, LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52 are the first and largest phase 3 trials to date assessing a monoclonal antibody targeting this type 2 inflammatory condition, investigating dupilumab efficacy as an add-on treatment to standard intranasal corticosteroids in patients with severe uncontrolled CRSwNP. In both studies, dupilumab reduced nasal polyp size and sinus disease burden, reduced severity of symptoms, improved sense of smell, improved health-related quality of life, and reduced the use of systemic corticosteroids and the need for nasal polyp surgery. In patients with comorbid asthma, dupilumab also improved lung function and asthma control. Dupilumab was shown to be well tolerated.

Implications of all the available evidence

Existing therapies for CRSwNP have limitations and do not address the underlying type 2 inflammatory processes that drive this disease with frequent recurrence. Blocking interleukin (IL)-4 and IL-13 signalling with dupilumab, in addition to the use of intranasal corticosteroids, could improve the lives of patients with severe uncontrolled CRSwNP compared with standard of care. Dupilumab treatment also showed efficacy in treating patients with comorbid asthma, a patient population with an increased disease burden that is difficult to treat.

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tolerated option that also addresses common comorbid, substantial type 2 inflammatory diseases such as asthma.

Dupilumab is a fully human VelocImmune-derived monoclonal antibody[18,19] that inhibits signalling by IL-4 and IL-13, cytokines that are key drivers of type 2 inflammation.[20] This antibody has been approved by the US Food and Drug Administration as an add-on maintenance treatment in adult patients with inadequately controlled CRSwNP. Dupilumab has also been approved for the treatment of other type 2 inflammatory disorders, including in patients aged 12 years or older in the USA with moderate-to-severe atopic dermatitis inadequately controlled with topical prescription therapies, or for whom those therapies are not advisable; in adults with inadequately controlled moderate-to-severe atopic dermatitis who are candidates for systemic therapy in the EU and other countries;[21–23] in patients aged 12 years or older in Japan as add-on maintenance treatment for moderate-to-severe asthma with an eosinophilic phenotype, or oral corticosteroid-dependent asthma, and for severe or refractory asthma with symptoms that are inadequately controlled with existing therapy; and in patients with type 2 severe asthma characterised by increased blood eosinophils, raised fractional exhaled nitric oxide, or both, who are inadequately controlled with high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment in the EU.[24–26]

In these two phase 3 trials, LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52, we aimed to assess the efficacy and safety of dupilumab when added to standard therapy (intranasal corticosteroids) in adults with severe CRSwNP uncontrolled by standard of care, including patients with a history of comorbid asthma, NSAID-exacerbated respiratory disease, or both.

Methods

Study design

LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52 were two multinational, multicentre, randomised, double-blind, placebo-controlled, parallel-group studies assessing the efficacy and safety of dupilumab in patients with severe uncontrolled CRSwNP. SINUS-24 was done in 67 hospitals or clinical centres in 13 countries (Bulgaria, Czechia, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Ukraine, Russia, the UK, and the USA). SINUS-52 was done in 117 hospitals or clinical centres in 14 countries (Argentina, Australia, Belgium, Canada, Chile, Israel, Mexico, Portugal, Russia, Spain, Sweden, Turkey, Japan, and the USA). Details of the study designs and multiplicity-controlled testing hierarchy are presented in the appendix (pp 11–12). The trials consisted of a 4-week run-in period, a treatment period (24 weeks in SINUS-24 and 52 weeks in SINUS-52), and a follow-up period (24 weeks in SINUS-24 and 12 weeks in SINUS-52). The protocols were developed by the sponsors in collaboration with the principal investigators. The local institutional review board or ethics committee at each study centre oversaw trial conduct and documentation.

See Online for appendix

Patients

Eligibility criteria were the same for both studies (appendix pp 7–8). Eligible patients were aged 18 years or older with bilateral nasal polyps and symptoms of chronic rhinosinusitis despite intranasal corticosteroid therapy before randomisation and had received systemic corticosteroids in the preceding 2 years (or had a medical contraindication or intolerance to systemic corticosteroids) or previous sinonasal surgery. At screening, patients were required to have a bilateral endoscopic nasal polyp score (NPS) of at least 5 (maximum 8), with a minimum score of 2 for each nostril, and exhibit at least two of the following symptoms: nasal congestion or obstruction (patient-assessed symptom severity score of at least 2 of 3, and a weekly average score of at least 1 at randomisation; 0=no symptoms, 1=mild, 2=moderate, and 3=severe) and either loss of smell or nasal discharge (anterior or posterior). These criteria resulted in a study population with severe disease. A prespecified enrolment goal of 50% of patients with asthma, NSAID-exacerbated respiratory disease, or both on the basis of patient-reported history and 50% of patients having had previous surgery was met without the need to cap enrolment. Patients who had a forced expiratory volume in 1 second (FEV_1) of 50% or lower than the predicted normal or participated in other dupilumab studies were excluded. Other key exclusion criteria are detailed in the appendix (p 8).

Saline nasal lavage, systemic antibiotics, short-course systemic corticosteroids, or sinonasal surgery were permitted as needed during the treatment and follow-up periods. All patients provided written informed consent before participating in the trials.

Randomisation and masking

In SINUS-24, patients were randomly assigned (1:1) to dupilumab 300 mg every 2 weeks or to matching placebo. In SINUS-52, patients were randomly assigned (1:1:1) to dupilumab 300 mg every 2 weeks for 52 weeks (group A), the same schedule for the first 24 weeks followed by dupilumab 300 mg every 4 weeks (group B), or placebo (group C).

Patients were randomly assigned centrally with a permuted block randomisation schedule by Interactive Voice Response System or Interactive Web Response System. Randomisations and allocations were done with use of ClinPhone from Parexel (Waltham, MA, USA), which generated the patient randomisation list and treatment assignment. Site personnel had access to the portal, did interactive response technology calls, and received corresponding notifications from ClinPhone. The randomisation block size was four for SINUS-24 and six for SINUS-52. Randomisation was stratified by asthma or NSAID-exacerbated respiratory disease status at screening (visit 1), previous surgery at screening, and country. The sponsor provided the randomisation scheme to the centralised treatment allocation system and treatments were allocated to the patients accordingly. Both patients

and investigators were masked to the assigned drug, with active drug or matching placebo used in identical prefilled syringes labelled with a treatment kit number. Treatment group information was masked in data transfers from Parexel to the sponsor until database lock.

Procedures

During the 4-week run-in period and throughout the trial, patients received 100 µg of mometasone furoate nasal spray (MFNS) in each nostril twice daily. Afterwards, patients in SINUS-24 received either 300 mg of subcutaneous dupilumab every 2 weeks or placebo for 24 weeks. Patients in SINUS-52 received dupilumab 300 mg every 2 weeks for 52 weeks, received dupilumab 300 mg every 2 weeks for the first 24 weeks followed by extending the treatment schedule to dupilumab every 4 weeks until reaching a total of 52 weeks, or received placebo throughout. Patients in SINUS-24 were followed up during an additional 24 weeks, and patients in SINUS-52 were followed up for an additional 12 weeks. In SINUS-24, visits were scheduled every 2 weeks from randomisation to week 8 and at weeks 16 and 24, with follow-up visits at week 36 and 48. From week 10, home administration of the study drug by patients or caregivers occurred every 2 weeks, with optional visits for administration scheduled at weeks 10–14 and 18–22. CT scans were done at baseline, week 24, and week 48. Nasal endoscopy, University of Pennsylvania Smell Identification Test (UPSIT), 22-item Sino-Nasal Outcome Test (SNOT-22), visual analog scale for rhinosinusitis, and spirometry and six-item Asthma Control Questionnaire (ACQ-6) in patients with asthma were administered at weeks 0, 8, 16, 24, and 48. Laboratory tests for biomarkers were done at weeks 0 and 24. In SINUS-52, visits were scheduled every 2 weeks from randomisation to week 8, and at weeks 16, 24, 40, and 52, with a follow-up visit at week 64. From week 10, home administration of study drug by patients or caregivers occurred every 2 weeks, with optional visits for administration scheduled at weeks 10–14, 18–22, 26–38, and 42–50. CT scans were done at baseline, week 24, and week 52. Nasal endoscopy, UPSIT smell test, SNOT-22, and visual analog scale for rhinosinusitis were administered at weeks 0, 4, 8, 16, 24, 40, and 52. Spirometry and ACQ-6 in patients with asthma were administered at weeks 0, 4, 16, 24, 40, and 52. Laboratory tests for blood biomarkers were done at weeks 0, 24, and 52 and for nasal secretion biomarkers were done at weeks 0 and 24.

Both studies used the Medidata Rave system as the data repository for site and patient data. Cognizant Technology Solutions did database setup, data reconciliation, and data review and cleaning. Data were recorded in source documents at the sites for data from electronic case report forms or directly in the systems for some external data. Investigators approved all electronic case report form data by applying electronic signatures directly to the system. Once all data were clean and approved by the site, the database was extracted and locked, and data were transferred to the SAS environment for statistical analysis.

Outcomes

The coprimary endpoints in both studies were change from baseline in both endoscopic NPS and nasal congestion severity (based on monthly average of daily score recorded by patients) at week 24. Preplanned subgroups for assessing consistency in treatment effects are listed in the appendix (pp 9–10).

Key secondary endpoints were change from baseline at week 24 in sinus opacification, assessed by Lund-Mackay CT score (third coprimary endpoint in Japan); patient-reported total symptom score (a composite severity score consisting of the sum of daily symptoms of nasal congestion, loss of smell, and anterior or posterior rhinorrhoea); daily loss of smell or smell impairment; SNOT-22 score; and UPSIT smell test. Multiplicity-tested key secondary endpoints for SINUS-52 were change from baseline at week 52 in NPS, nasal congestion, and SNOT-22 score (group A alone). NPS and Lund-Mackay CT scan scoring was done centrally by masked review of the video recordings of standardised endoscopies (for NPS) and sinus images (for Lund-Mackay CT).

Data from the two studies were pooled to assess the proportion of patients requiring systemic corticosteroids or sinonasal surgery (done or planned) during the treatment period. Changes from baseline at week 24 in FEV_1 and ACQ-6 scores were assessed in the pooled subset with comorbid asthma.

The proportion of patients with at least a 1-point or 2-point improvement in NPS score was also reported, along with change from baseline in rhinosinusitis disease severity assessed by a visual analog scale (score 0–10 cm, >7 cm indicating severe disease) and peak nasal inspiratory flow.

Safety assessments included vital signs, physical examination, clinical laboratory assessment, 12-lead electrocardiogram findings, and incidence of adverse events and serious adverse events. For SINUS-52, we also assessed changes in blood eosinophil count; serum total IgE; thymus and activation-regulated chemokine (TARC; also known as C-C motif chemokine 17), periostin, and plasma eotaxin-3 (also known as C-C motif chemokine 26) concentrations; and eosinophil cationic protein (ECP) and eotaxin-3 concentrations and total IgE in nasal secretions.

Statistical analysis

On the basis of a previous phase 2 study,[27] we estimated that a sample size of approximately 120 patients per treatment group would give the SINUS-24 study 98% power (two-tailed test at an α level of 0·05) to detect an effect size of 0·588 in NPS (on the basis of assumed mean difference of 1·24 and common SD of 2·11), and 95% power to detect an effect size of 0·534 in nasal congestion (on the basis of assumed mean difference

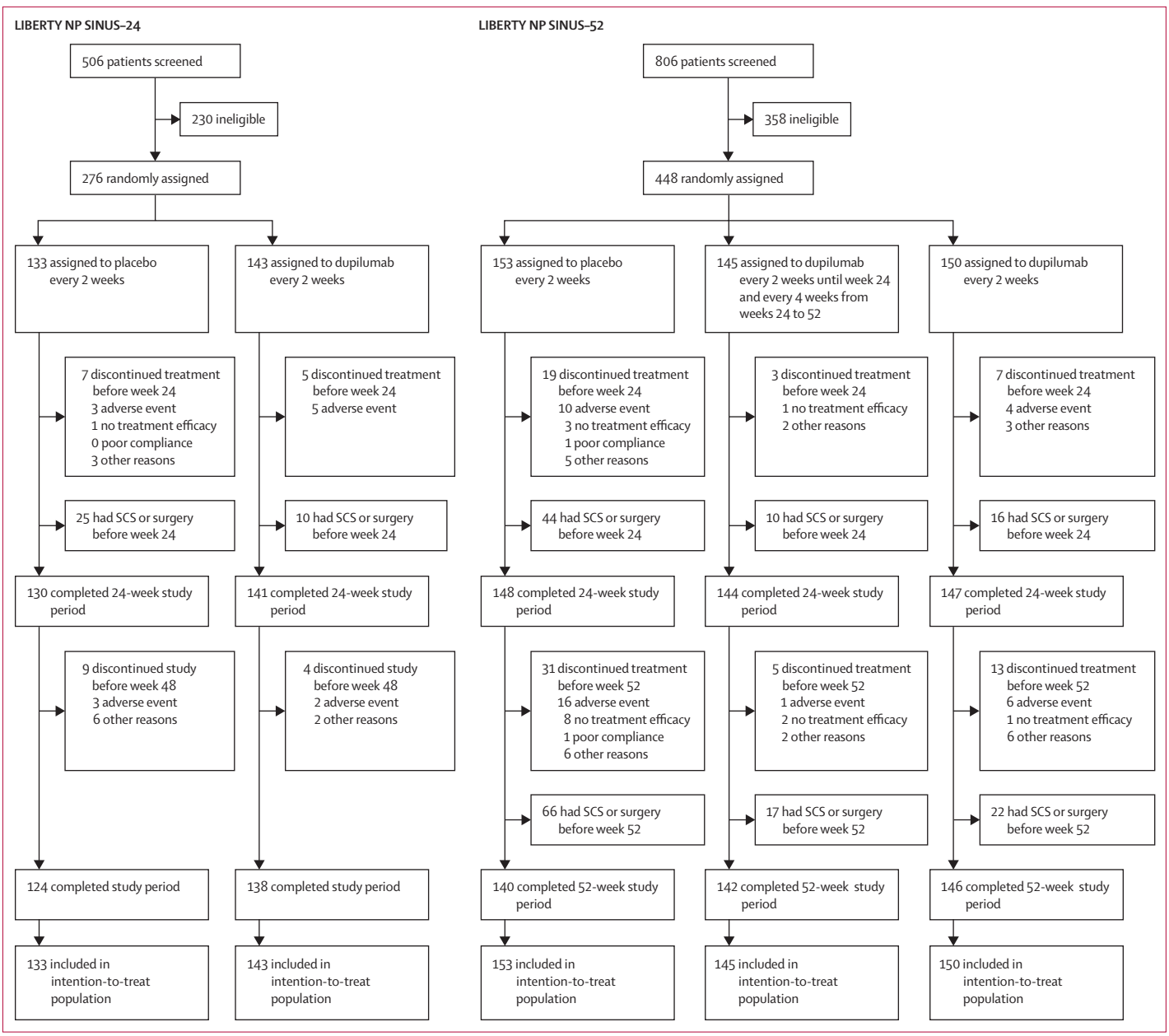

Figure 1: **Patient disposition and trial profile**
Some patients who discontinued treatment before week 24 continued to participate in the study, follow-up, or both. SCS=systemic corticosteroid.

of 0·55 and common SD of 1·03) at week 24 in the dupilumab group, with 93% combined power for both endpoints, assuming no negative correlation between endpoints. SINUS-24 had an equal allocation ratio. SINUS-52 had three arms, randomised 1:1:1. The pooling of groups A and B for the primary analyses resulted in the use of an allocation ratio of 2:1 to assess the sample size. The pooling of groups A and B at week 24 (approximately 240 patients) would give 99% power to detect the same effect size as previously described for NPS and nasal congestion in patients treated with dupilumab, with 98% combined power. All sample size calculations were done with nQuery Advisor 7.

We did efficacy analyses in the intention-to-treat population, defined as all patients who were randomly assigned; data were analysed according to assigned intervention, whether received or not. Primary and key secondary endpoints were prospectively defined, multiplicity-adjusted, and analysed with a hybrid of the worst observation carried forward (WOCF) and multiple imputation methods, followed by an ANCOVA model with the baseline value of the corresponding endpoint,

	LIBERTY NP SINUS-24		LIBERTY NP SINUS-52			Overall population (n=724)
	Placebo (n=133)	Dupilumab, q2w (n=143)	Placebo (n=153)	Dupilumab, q2w–q4w (n=145)	Dupilumab, q2w (n=150)	
Age (years)	50 (41–60)	52 (39–61)	53 (44–61)	53 (42–63)	51 (42–61)	52 (42–61)
Sex						
Men	70 (53%)	88 (62%)	95 (62%)	87 (60%)	97 (65%)	437 (60%)
Women	63 (47%)	55 (38%)	58 (38%)	58 (40%)	53 (35%)	287 (40%)
Body-mass index (kg/m²)	28·36 (5·76)	27·49 (5·11)	27·91 (5·50)	27·96 (5·51)	27·96 (5·53)	27·93 (5·47)
Nasal polyp duration (years)	10·77 (8·57)	11·42 (9·69)	10·88 (9·40)	10·67 (9·12)	11·28 (10·38)	11·01 (9·45)
Nasal polyp surgery						
≥1 previous surgery	99 (74%)	99 (69%)	88 (58%)	85 (59%)	88 (59%)	459 (63%)
≥3 previous surgeries	29 (22%)	33 (23%)	18 (12%)	9 (6%)	22 (15%)	111 (15%)
Time since most recent nasal polyp surgery (years)	5·54 (5·07)	5·93 (5·57)	8·77 (7·15)	8·41 (6·83)	7·54 (7·02)	7·16 (6·44)
Systemic corticosteroid use in the preceding 2 years	87 (65%)	92 (64%)	122 (80%)	116 (80%)	121 (81%)	538 (74%)
Bilateral endoscopic nasal polyp score* (scale 0–8)	5·86 (1·31)	5·64 (1·23)	5·96 (1·21)	6·29 (1·20)	6·07 (1·22)	5·97 (1·25)
Nasal congestion or obstruction score* (scale 0–3)	2·45 (0·55)	2·26 (0·57)	2·38 (0·54)	2·44 (0·59)	2·48 (0·62)	2·40 (0·58)
SNOT-22 total score* (scale 0–110)	50·87 (20·22)	48·00 (20·16)	53·48 (21·85)	51·89 (21·05)	50·16 (19·72)	50·94 (20·66)
Smell test (UPSIT) score* (scale 0–40)	14·44 (8·31)	14·68 (8·66)	13·78 (8·31)	13·60 (7·57)	13·46 (8·20)	13·98 (8·21)
Loss-of-smell score* (scale 0–3)	2·73 (0·51)	2·70 (0·57)	2·72 (0·52)	2·73 (0·59)	2·81 (0·46)	2·74 (0·53)
Lund-Mackay CT total score* (scale 0–24)	19·55 (4·26)	18·55 (4·55)	17·65 (3·76)	17·81 (3·89)	18·42 (3·61)	18·37 (4·06)
Rhinosinusitis disease severity* (visual analog scale 0–10 cm)	7·96 (2·06)	7·42 (2·01)	7·98 (2·22)	7·78 (2·20)	8·24 (1·77)	7·88 (2·07)
Baseline peak nasal inspiratory flow* (L/min)	83·52 (56·30)	98·59 (56·70)	87·47 (56·14)	84·86 (59·98)	80·96 (50·15)	87·07 (56·08)
Baseline blood eosinophils (×10⁹ cells per L)	0·44 (0·31)	0·44 (0·35)	0·45 (0·36)	0·40 (0·30)	0·45 (0·39)	0·43 (0·34)
Baseline total IgE (IU/mL)	222·55 (269·11)	202·06 (282·37)	227·80 (267·13)	282·28 (463·72)	210·82 (256·78)	229·21 (318·13)
Baseline eotaxin-3 (pg/mL)	67·36 (73·53)	74·94 (63·36)	90·84 (111·25)	83·36 (164·07)	70·61 (45·16)	77·72 (101·81)
Any type 2 medical history, including asthma or NSAID-exacerbated respiratory disease	99 (74%)	109 (76%)	127 (83%)	120 (83%)	122 (81%)	577 (80%)
Asthma	79 (59%)	82 (57%)	91 (59%)	91 (63%)	85 (57%)	428 (59%)
NSAID-exacerbated respiratory disease	38 (29%)	46 (32%)	44 (29%)	41 (28%)	35 (23%)	204 (28%)
Any type 2 medical history, excluding asthma or NSAID-exacerbated respiratory disease	75 (56%)	81 (57%)	98 (64%)	99 (68%)	96 (64%)	449 (62%)
Age of onset of asthma in patients with comorbid asthma (years)	33·42 (15·42)	38·28 (13·96)	33·29 (16·14)	33·57 (18·18)	35·54 (15·57)	34·78 (16·01)

Data are n (%) or mean (SD), unless otherwise specified. Region was a covariate in these studies and is not reported in this table. Direct statistical comparisons between the groups for demographics and characteristics were not prespecified, and therefore were not done. q2w=every 2 weeks. q4w=every 4 weeks. SNOT-22=22-item Sino-Nasal Outcome Test. UPSIT=University of Pennsylvania Smell Identification Test. NSAID=non-steroidal anti-inflammatory drug. *Higher scores indicate greater disease severity except for UPSIT and peak nasal inspiratory flow, for which higher scores indicate lower disease severity.

Table 1: **Patient baseline demographics and clinical characteristics (intention-to-treat population)**

treatment, asthma or NSAID-exacerbated respiratory disease status, surgery history, and study region as covariates. Statistical inference, including the least squares means obtained from all 40 imputed data, were combined by use of Rubin's rule.

For patients who underwent nasal polyps surgery or received systemic corticosteroids for any reason, data collected post-surgery (actual date) or post-systemic corticosteroid treatment were set to missing in the WOCF-multiple imputation approach, and the worst post-baseline value on or before the time of surgery or systemic corticosteroid treatment was used to impute missing week 24 or 52 values (depending on the study; baseline values were used for patients whose post-baseline values were all missing). For patients who discontinued treatment without rescue by surgery or systemic corticosteroids, we used a multiple imputation approach to impute missing values, using all patients who had not been rescued by surgery or were not receiving systemic corticosteroids.

We implemented a hierarchical multiplicity procedure to control the overall type 1 error rate for testing the coprimary and selected key secondary endpoints. The overall α was 0·05. We tested comparisons with placebo on the basis of a hierarchical order (appendix p 12), with two-sided α=0·05. In SINUS-52, groups A and B were pooled at week 24 for analysis. At week 52, each of the active treatment groups were compared only with placebo.

We preplanned a pooled integrated assessment of the efficacy data from SINUS-24 and SINUS-52 before the

database lock. In this single-stage, fixed-effect individual data meta-analysis, we did two multiplicity-adjusted analyses: change from baseline at week 24 in FEV_1 and proportion of patients requiring systemic corticosteroids or nasal polyp surgery (actual or planned) during the entire treatment period (dupilumab every 2 weeks and placebo) of both studies.

For the pooled analysis of the change from baseline at week 24 in FEV_1, all dupilumab groups and placebo groups in both studies were pooled at week 24. We used the same method of WOCF-multiple imputation followed by an ANCOVA model for statistical analysis, with an additional covariate of the study indicator in the ANCOVA model.

For the proportion of patients requiring systemic corticosteroids or nasal polyp surgery (actual or planned) during the treatment period, we pooled the entire dupilumab every 2 weeks treatment period (group A up to 52 weeks and B up to 24 weeks from SINUS-52 and the dupilumab group from SINUS-24) from both studies, and we included a forced censor for the SINUS-52 group B at week 24. The entire placebo treatment period, of up to 52 weeks for SINUS-52 and up to 24 weeks for SINUS-24, was pooled as well. The probability that a patient in each treatment group would require rescue at week 52 was determined with the Cox proportional hazards model and the Kaplan-Meier method. The Cox model used the event as the dependent variable and the study indicator, treatment group, asthma or NSAID-exacerbated respiratory disease strata, previous surgery strata, and study region as covariates. We estimated hazard ratios (HRs) and corresponding 95% CIs and p values for dupilumab every 2 weeks versus placebo. We used a Kaplan-Meier curve to derive the probability that a patient would have an event up to week 52, with point probabilities and corresponding 95% CIs calculated.

We planned a pooled integrated assessment of the safety adverse event data from SINUS-24 and SINUS-52, focusing on the first 24 weeks of treatment, combining both dupilumab groups in SINUS-52 up to week 24 with the dupilumab group in SINUS-24 and the placebo groups in both studies until week 24. The safety population was defined as all patients exposed to the investigational medicinal product, regardless of the amount of exposure. We assessed long-term safety up to week 52 of treatment in SINUS-52.

An independent data monitoring committee reviewed safety data throughout the trial, meeting every 3 to 6 months. These trials are registered at Clinicaltrials.gov, NCT02912468 (SINUS-24) and NCT02898454 (SINUS-52). We used SAS, version 9.4, for statistical analyses. The appendix (pp 9–10) gives further details of these analyses.

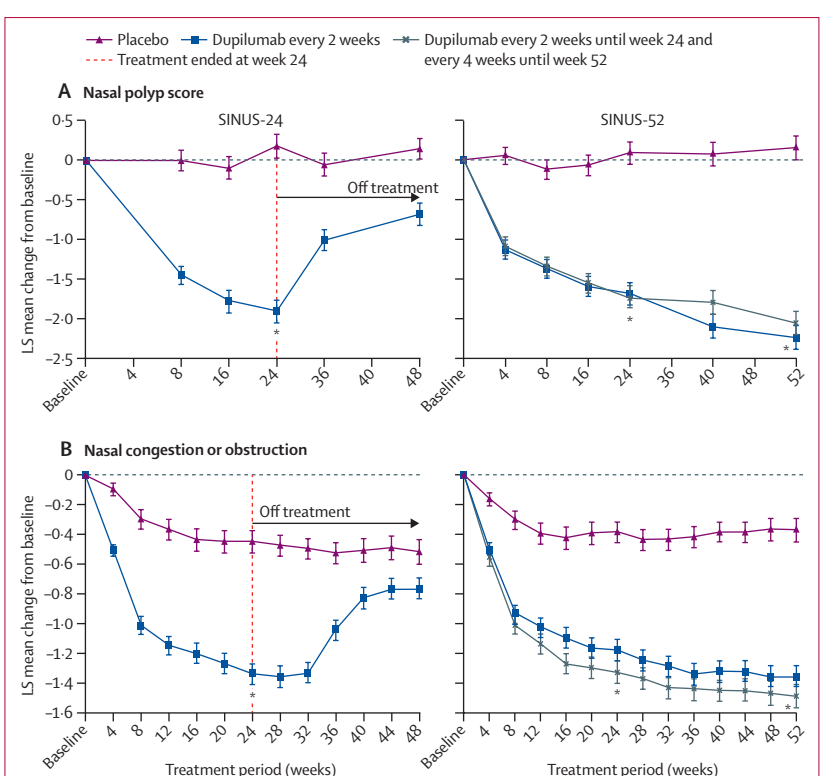

Figure 2: **Change from baseline over time in nasal polyp score (A) and nasal congestion or obstruction (B) in SINUS-24 and SINUS-52**
Error bars denote SE. LS=least squares. *p<0·0001.

Role of the funding source

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

Results

Between Dec 5, 2016, and Aug 3, 2017, patients were enrolled in SINUS-24, with 276 patients randomly assigned to dupilumab every 2 weeks (n=143) or placebo (n=133; figure 1). The final patient treatment was done on July 5, 2018. Between Nov 28, 2016, and Aug 28, 2017, patients were enrolled in SINUS-52, with 448 patients randomly assigned to placebo (n=153), dupilumab every 2 weeks (n=150), or dupilumab every 2 weeks until week 24 and every 4 weeks until week 52 (n=145; figure 1). The final patient treatment was done on Aug 29, 2018. Both trials were unmasked simultaneously once the SINUS-52 treatment period and SINUS-24 study were completed.

In SINUS-24, 12 (4%) of 276 patients discontinued treatment before week 24, and 13 (5%) patients discontinued from the study; one patient was randomly assigned, but not treated, and the primary reason for discontinuation was occurrence of adverse events (figure 1). In SINUS-52, 29 (6%) of 448 patients discontinued before week 24, and 49 (11%) patients discontinued treatment before

	Testing hierarchy position	LIBERTY NP SINUS-24					LIBERTY NP SINUS-52				
		Placebo (n=133)		Dupilumab q2w (n=143)		LS mean difference *vs* placebo (95% CI; p value)	Placebo (n=153)		Dupilumab q2w (n=295)*		LS mean difference *vs* placebo (95% CI; p value)
		Mean (SD)	LS mean change from baseline (SE)	Mean (SD)	LS mean change from baseline (SE)		Mean (SD)	LS mean change from baseline (SE)	Mean (SD)	LS mean change from baseline (SE)	
Primary endpoints at week 24											
Bilateral nasal polyp score (scale 0–8)	1	5·94 (1·44)	0·17 (0·15)	3·75 (1·98)	−1·89 (0·14)	−2·06 (−2·43 to −1·69; p<0·0001)	6·09 (1·19)	0·10 (0·14)	4·46 (1·89)	−1·71 (0·11)	−1·80 (−2·10 to −1·51; p<0·0001)
Nasal congestion or obstruction score (scale 0–3)	1	1·90 (0·85)	−0·45 (0·07)	0·94 (0·75)	−1·34 (0·07)	−0·89 (−1·07 to −0·71; p<0·0001)	2·02 (0·77)	−0·38 (0·07)	1·19 (0·90)	−1·25 (0·06)	−0·87 (−1·03 to −0·71; p<0·0001)
Key secondary endpoints at week 24											
Lund–Mackay CT score (scale 0–24)	2	18·97 (4·51)	−0·74 (0·37)	10·89 (4·82)	−8·18 (0·34)	−7·44 (−8·35 to −6·53; p<0·0001)	17·73 (3·81)	−0·09 (0·31)	12·86 (3·87)	−5·21 (0·24)	−5·13 (−5·80 to −4·46; p<0·0001)
Total symptom score (scale 0–9)	3	6·02 (2·02)	−1·17 (0·17)	3·16 (1·93)	−3·77 (0·16)	−2·61 (−3·04 to −2·17; p<0·0001)	6·08 (1·97)	−1·00 (0·20)	3·77 (2·44)	−3·45 (0·15)	−2·44 (−2·87 to −2·02; p<0·0001)
Smell test score (UPSIT; scale 0–40)	4	14·56 (8·58)	0·70 (0·71)	25·39 (9·49)	11·26 (0·67)	10·56 (8·79 to 12·34; p<0·0001)	13·30 (7·96)	−0·81 (0·71)	23·89 (9·21)	9·71 (0·56)	10·52 (8·98 to 12·07; p<0·0001)
Loss-of-smell score (scale 0–3)	5	2·50 (0·77)	−0·29 (0·07)	1·35 (0·99)	−1·41 (0·07)	−1·12 (−1·31 to −0·93; p<0·0001)	2·49 (0·79)	−0·23 (0·08)	1·55 (1·02)	−1·21 (0·06)	−0·98 (−1·15 to −0·81; p<0·0001)
SNOT-22 score (scale 0–110)	6	40·49 (23·06)	−9·31 (1·62)	18·58 (14·92)	−30·43 (1·54)	−21·12 (−25·17 to −17·06; p<0·0001)	42·16 (23·26)	−10·40 (1·61)	23·89 (18·77)	−27·77 (1·26)	−17·36 (−20·87 to −13·85; p<0·0001)
Key secondary endpoints at week 52											
Bilateral nasal polyp score (scale 0–8)	7	..	..	..	..	..	6·10 (1·52)	0·15 (0·15)	3·76 (2·20; n=150)†	−2·24 (0·15; n=150)†	−2·40 (−2·77 to −2·02; p<0·0001)
Nasal congestion or obstruction score (scale 0–3)	8	..	..	..	..	..	2·04 (0·78)	−0·37 (0·08)	1·10 (0·92; n=150)†	−1·35 (0·07; n=150)†	−0·98 (−1·17 to −0·79; p<0·0001)
SNOT-22 score (scale 0–110)	9	..	..	..	..	..	44·05 (22·66)	−8·88 (1·61)	21·67 (19·16; n=150)†	−29·84 (1·63; n=150)†	−20·96 (−25·03 to −16·89; p<0·0001)

Endpoints were multiplicity-tested. More details on position within testing hierarchy can be found in the appendix (p 12). On the basis of published thresholds for clinical meaningfulness for SNOT-22,[28] changes in the outcomes can be considered clinically meaningful. q2w=every 2 weeks. LS=least squares. UPSIT=University of Pennsylvania Smell Identification Test. SNOT-22=22-item Sino-Nasal Outcome Test. *Pooling of groups A (patients treated up to 52 weeks) and B (patients treated up to 24 weeks from SINUS-52 and SINUS-24). †Group A.

Table 2: **Summary of primary and key secondary efficacy endpoints for each intention-to-treat population of SINUS-24 and SINUS-52**

week 52; one patient was randomly assigned, but not treated. Occurrence of adverse events was the most common reason for treatment discontinuation (figure 1).

Baseline demographics and characteristics were balanced across the treatment groups within each study and across both studies and were consistent with a population with severe, inadequately controlled CRSwNP, on the basis of the ubiquity of chronic rhinosinusitis symptoms, bilateral obstructive polyps, and extensive involvement of the sinuses (table 1). Most patients (705 [97%] of 724) had either previously received systemic corticosteroids (64–81%) or sinonasal surgery (58–74%). Approximately 551 (76%) of 724 patients had anosmia at baseline, 428 (59%) had comorbid asthma, and 204 (28%) had NSAID-exacerbated respiratory disease. Mean baseline FEV_1 in patients with asthma was 2·61 L (percent predicted 84% [18·70]) and ACQ-6 score was 1·59, suggesting inadequately controlled asthma. Most patients (388 [91%] of 427) in this subgroup had received asthma medications, primarily inhaled corticosteroids and long-acting β-agonists (282 [74%] of 382), in the preceding year.

The improvement in endoscopic NPS at week 24 was significantly greater with dupilumab treatment than with placebo in both studies (figure 2, table 2). In the placebo group treated with standard of care, NPS worsened at week 24 and week 52. Dupilumab treatment also significantly improved patient-reported nasal congestion scores compared with placebo (figure 2, table 2). We observed improvements in NPS and nasal congestion as early as the first assessment timepoint after the start of dupilumab treatment (within the first 4 to 8 weeks), with continued improvement evident up to the end of treatment in both studies.

We also observed improvements in NPS and nasal congestion in patient subgroups with comorbid asthma, NSAID-exacerbated respiratory disease, or previous surgery (appendix pp 25–27). The proportion of patients achieving at least a 2-point improvement in NPS at week 24 was higher with dupilumab (66 [46%] of 143 patients in SINUS-24, and 136 [46%] of 295 patients with SINUS-52) than with placebo (6 [5%] of 133 patients in SINUS-24, and 1 [1%] of 153 in SINUS-52; appendix p 28).

All multiplicity-adjusted key secondary endpoints showed significant and clinically relevant improvements with dupilumab treatment (p<0·0001 in both studies; table 2, appendix pp 13–14), with all effects having an early onset (in the first 2 to 4 weeks of treatment). The magnitude of improvements in patient subgroups with comorbid asthma, NSAID-exacerbated respiratory disease, or previous surgery was similar to that of improvements in the overall treatment population. Patients treated with dupilumab in SINUS-52 had progressive improvement up to week 52 (figure 2, table 2, appendix pp 13–14), whereas symptoms worsened after discontinuation of dupilumab at week 24 in patients in SINUS-24.

Lund-Mackay CT scores improved significantly in dupilumab groups at week 24 compared with those of placebo groups (table 2, appendix p 13), with improvements seen in all sinuses (appendix p 15). Patients with comorbid asthma, NSAID-exacerbated respiratory disease, or previous surgery showed similar improvements (appendix pp 25–27). Improvements in SNOT-22 scores with dupilumab treatment exceeded the minimal clinically important difference of an 8·9-point improvement or higher[28] and were significant compared with those with placebo (table 2, appendix p 13). Results of the UPSIT smell test showed that the proportion of patients with anosmia (UPSIT score of ≤18) in the dupilumab groups decreased in SINUS-24 from 104 (74%) of 140 patients at baseline to 33 (24%) of 138 at week 24 and in SINUS-52 from 228 (79%) of 287 patients to 84 (30%) of 280 at week 24, with almost no change observed in the placebo group (appendix p 29). Patients treated with dupilumab in both studies had a substantial reduction in rhinosinusitis disease severity assessed with visual analog scale and improvement in peak nasal inspiratory flow and rhinorrhoea daily symptom score at week 24 (prespecified secondary analyses; appendix p 30).

The magnitude of additional improvements observed for NPS and Lund-Mackay CT scan scores from week 24 to week 52 in SINUS-52 were numerically greater in patients who continued the dupilumab every 2 weeks regimen (group A) than in those who switched to a dose every 4 weeks (group B; NPS: –0·53 for group A and –0·31 for group B; Lund-Mackay CT scan score –1·37 for group A and –0·62 for group B). Additional improvements for nasal congestion and the other secondary endpoints from week 24 to week 52 were similar between groups (appendix p 31).

In a prespecified pooled analysis, the proportion of patients who received treatment with systemic corticosteroids or effectively underwent sinonasal surgery during

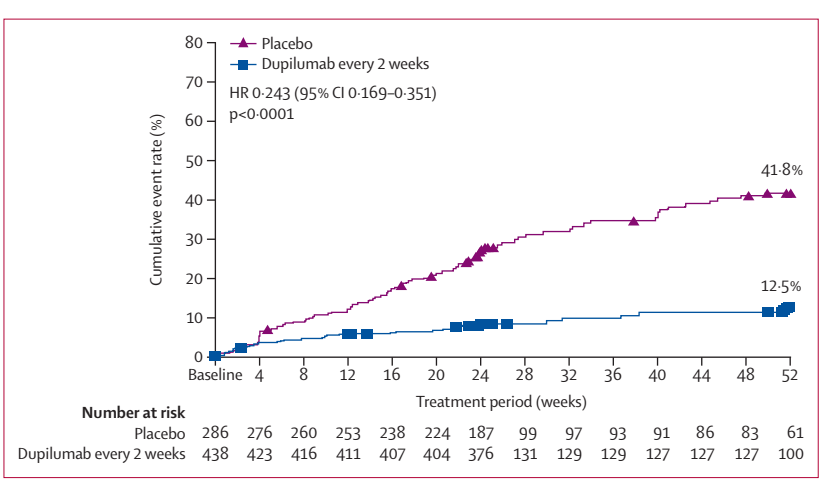

Figure 3: **Time to first systemic corticosteroid use or nasal polyp surgery during the treatment period in the pooled analysis of SINUS-24 and SINUS-52**
HR=hazard ratio.

	Testing hierarchy position	Pooled placebo (n=286)	Pooled dupilumab q2w (n=438)	HR *vs* placebo (95% CI; p value)	Pooled placebo with comorbid asthma (n=170)		Pooled dupilumab q2w with comorbid asthma (n=258)		
					Week 24 mean (SD)	LS mean change from baseline at week 24 (SE)	Week 24 mean (SD)	LS mean change from baseline at week 24 (SE)	LS mean difference *vs* placebo (95% CI; p value)
Prespecified pooled analysis									
Patients requiring rescue with systemic corticosteroids or nasal polyp surgery (n [%])	10	97 (34%)	42 (10%)	0·243 (0·169 to 0·351; p<0·0001)	..	..	..	..	..
Total patient-years followed up (years)	..	208·4	280·1	..	..	..	..	..	..
Prespecified pooled asthma analyses									
FEV_1 (L)	11	..	..	..	2·57 (0·80)	−0·07 (0·04)	2·76 (0·91)	0·14 (0·03)	0·21 (0·13 to 0·29; p<0·0001)
ACQ-6 (scale 0–6)	..	..	..	..	1·52 (1·11)	−0·02 (0·07)	0·70 (0·82)	−0·84 (0·06)	−0·82 (−0·98 to −0·67; p<0·0001)

On the basis of published thresholds for clinical meaningfulness for ACQ-6,[29] changes in the outcome can be considered clinically meaningful. Comparisons of dupilumab versus placebo for endpoints from outside the testing hierarchy are shown with 95% CI. q2w=every 2 weeks. HR=hazard ratio. LS=least squares. FEV_1=forced expiratory volume in 1 s. ACQ-6=six-item Asthma Control Questionnaire.

Table 3: **Prespecified efficacy endpoints in the pooled SINUS-24 and SINUS-52 population**

the treatment period was significantly lower in the pooled dupilumab every 2 weeks group than in the pooled placebo group (figure 3). This reduction reflects the reductions seen in the separate HRs for patients who received systemic corticosteroids (74% lower in the dupilumab group than in placebo) and surgery (83% lower in the dupilumab group than in placebo; appendix p 32).

In prespecified analyses of the pooled subset of patients with comorbid asthma (258 in the dupilumab group and 170 in the placebo group) at week 24, dupilumab significantly improved lung function (assessed with FEV_1 in a multiplicity-controlled analysis) and asthma control (assessed with ACQ-6) compared with placebo (table 3). Median baseline eosinophil count in patients with comorbid asthma was $0{\cdot}43\times10^9$ cells per L (IQR 0·26–0·65). Improvements in lung function and asthma control were similar in patients with comorbid asthma with high ($\geq0{\cdot}3\times10^9$ cells per L) and low ($<0{\cdot}3\times10^9$ cells per L) baseline blood eosinophil counts (appendix pp 33–34). Prespecified exploratory analyses of biomarkers in patients treated with dupilumab in SINUS-52 showed a consistent decrease in concentrations of serum total IgE, periostin, TARC, and plasma eotaxin-3 at weeks 24 and 52 and in concentrations of ECP, total IgE, eotaxin-3, and IL-5 in nasal secretions at week 24. In both studies, and consistent with previous dupilumab studies, we observed a transient, but not significant, increase in mean (but not median) blood eosinophil counts in patients treated with dupilumab. In SINUS-52, eosinophil counts returned to baseline levels by the end of the 52-week treatment period (appendix pp 35–37).

Results of post-hoc analysis that excluded patients with major or crucial deviations potentially affecting efficacy analyses were consistent with the primary analysis (appendix pp 20–23). Sensitivity analyses including as-observed analysis (accounting for all post-systemic corticosteroid data in patients who received systemic corticosteroids for any reason) done in the intention-to-treat population in both studies supported the robustness of the results (appendix p 24).

	Placebo (n=282)	Dupilumab q2w (n=440)	Risk difference (% [95% CI]) dupilumab q2w *vs* placebo
Treatment-emergent adverse events			
Any	208 (74%)	305 (69%)	−6·48 (−13·04 to 0·08)
Any serious	16 (6%)	15 (3%)	−2·80 (−6·30 to 0·70)
Any leading to death	0	0	0
Any leading to permanent treatment discontinuation	15 (5%)	11 (3%)	−2·66 (−6·01 to 0·69)
Treatment-emergent adverse events occurring in ≥5% of patients*			
Asthma	20 (7%)	7 (2%)	..
Epistaxis	20 (7%)	25 (6%)	..
Headache	24 (9%)	32 (7%)	..
Injection-site erythema†	22 (8%)	28 (6%)	..
Nasal polyps	33 (12%)	12 (3%)	..
Nasopharyngitis	41 (15%)	55 (13%)	..

Data are n (%) unless otherwise specified. q2w=every 2 weeks. *According to the preferred terms of the Medical Dictionary for Regulatory Activities; asthma refers to a worsening of asthma, and nasal polyps refers to a worsening of nasal polyps leading to surgery or systemic corticosteroid use. †Injection-site reaction was a prespecified adverse event of interest in the protocol.

Table 4: **Adverse events that emerged during the intervention period (pooled safety population at week 24)**

In the pooled safety population, the incidence of adverse events emerging during the 24-week treatment period was lower in the dupilumab group than in the placebo group (table 4). The most commonly reported adverse events were nasopharyngitis, nasal polyps (worsening nasal polyps, need for nasal polyp surgery or systemic corticosteroids, or both), headache, asthma (worsening of asthma), epistaxis, and injection-site erythema; these events were more frequent with placebo

than with dupilumab (table 4, appendix pp 38–39). Over the 52-week period in SINUS-52, incidences of cough, bronchitis, arthralgia, accidental overdose, and injection-site reactions were slightly more frequent in the two dupilumab groups than in placebo (appendix pp 40–41). Treatment-emergent adverse events of worsening of nasal polyps and asthma and of sinusitis, arthralgia, and accidental overdose occurred more frequently in patients who switched from dupilumab every 2 weeks to every 4 weeks than in those who remained on dupilumab every 2 weeks for the full 52 weeks (appendix pp 40–41).

In the pooled 24-week safety population, serious adverse events were more common in the placebo group than in the dupilumab group (table 4). Two deaths occurred during the study period that were deemed unrelated to the study drug: one patient given placebo in SINUS-24 had suspected acute myocardial infarction occurring after the period of treatment-emergent adverse events, and one treated with dupilumab in SINUS-52 had intracranial haemorrhage after a fall, occurring within the period of treatment-emergent adverse events. Conjunctivitis was reported in seven patients receiving dupilumab and in one patient receiving placebo; none of these cases were serious, severe, or associated with treatment discontinuation. Four patients had eosinophilia with clinical symptoms reported as treatment-emergent adverse events: one patient had eosinophilic granulomatosis with polyangiitis (EGPA) during treatment with dupilumab; one had eosinophilia associated with arthralgia, asthma exacerbation, and insomnia during dupilumab treatment; one had EGPA more than 300 days after a single dupilumab dose; and one had EGPA while receiving placebo. Further adverse event data can be found in the appendix (pp 42–55).

Discussion

Patients with CRSwNP generally have a high symptom burden, including anosmia, high polyp recurrence rates, asthma comorbidity, and poor health-related quality of life. In patients with severe CRSwNP inadequately controlled with standard of care, adding dupilumab to daily MFNS provided early, significant, and clinically meaningful improvements across all aspects of disease, including a reduction in systemic corticosteroid treatment and surgery. This broad and significant effect was reflected in reduced polyp size and disease in all sinuses, and relief in major symptoms of CRSwNP (nasal congestion, loss of smell, and rhinorrhoea). In patients with comorbid asthma, regardless of baseline eosinophil count, dupilumab treatment improved lung function and asthma control. In SINUS-24, treatment effects diminished after dupilumab discontinuation, whereas in SINUS-52, treatment effects continued to improve up to week 52, underscoring the need for continued suppression of type 2 inflammation for sustained disease control. The magnitude of the additional reductions in nasal polyp size and sinus disease observed from week 24 to week 52 in SINUS-52 was greater in patients who received dupilumab every 2 weeks for 52 weeks than in those who switched to dupilumab every 4 weeks after week 24. In patients in the placebo groups who received daily MFNS alone, no meaningful improvements were noted in polyp size, CT scan score, or sense of smell.

The existing treatment approach for severe CRSwNP is characterised by continuous topical and repeated systemic corticosteroid use and surgery, resulting in high risk for morbidity, poor health-related quality of life, and significant economic burden.[15,17,30] The goals of CRSwNP treatment are to achieve effective and sustained symptom control, minimise recurrence of polyps, and attain better control of comorbid lower airway disease while minimising the risk of side-effects associated with systemic corticosteroid use and repeated sinus surgery. Almost all patients (97%) in SINUS-24 and SINUS-52 had received systemic corticosteroids or sinonasal surgery before entering the studies. Compared with placebo, dupilumab treatment greatly reduced the use of systemic corticosteroids and the proportion of patients who had sinonasal surgery in the prespecified pooled analyses. Dupilumab also improved symptoms and health-related quality of life, as reflected by an improvement in SNOT-22 scores that largely exceeded the threshold for a clinically relevant change.[28] Impairment of the sense of smell, one of the most troublesome symptoms in patients with CRSwNP, correlates with disease severity and recurrence and has a substantial effect on health-related quality of life.[5,6] Approximately 75% of patients in SINUS-24 and SINUS-52 had anosmia at baseline, whereas only 24–30% had anosmia after dupilumab treatment; no change was observed in the placebo groups.

Of importance, the efficacy of dupilumab was shown both in the overall population and in subgroups with higher disease burden that is difficult to control, such as patients with comorbid asthma, NSAID-exacerbated respiratory disease, or previous sinonasal surgery. In patients with CRSwNP and comorbid asthma, dupilumab not only improved upper airway outcome measures, but also significantly improved lung function and achieved better asthma control, whereas patients in the placebo groups showed little or no improvement despite use of asthma medication, including inhaled therapies. Patients with CRSwNP have been noted in the literature to have a predominant type 2 endotype.[9,10] The robust FEV_1 improvement after dupilumab treatment in patients with CRSwNP and asthma, regardless of baseline eosinophil count, supports this finding and suggests that blood eosinophils provide no further specificity in identifying dupilumab responsiveness in this population. This concomitant benefit for lower airway disease highlights the value of a therapy that can simultaneously address multiple comorbid manifestations of type 2 inflammatory diseases in the upper and lower airways. Dupilumab was generally well tolerated and had an acceptable safety

profile for the treatment of patients with severe CRSwNP. One patient had EGPA while being treated with dupilumab, and two patients in placebo groups had EGPA in the context of steroid withdrawal; the causal relationship of EGPA with dupilumab has not been established.

The reductions in type 2 biomarkers in serum (total IgE, TARC, eotaxin-3, and periostin) and in nasal secretions (ECP, eotaxin-3, and total IgE) observed in these studies were consistent with the method of action of dupilumab and with previous dupilumab studies in asthma and atopic dermatitis. The transient increase in the blood eosinophil counts observed in both studies is consistent with the hypothesis that dupilumab blocks eosinophil tissue migration by inhibiting the production of eotaxins mediated by IL-4 and IL-13 (supported by an observed reduction of eotaxin-3 concentrations in the serum and in the target organ [nasal secretion]), but not the production of eosinophils or egress from bone marrow. This mechanism results in the observed transient increase in circulating eosinophils, consistent with other clinical studies of dupilumab.

Our studies had some limitations. The treatment effects showed progressive improvement during the randomised treatment period, and maximum effects were not reached at week 52 in SINUS-52, therefore it is not clear what the full treatment effect of dupilumab might be beyond 52 weeks. We also did not assess dupilumab efficacy as a monotherapy without background MFNS treatment.

These data support the benefits of adding dupilumab to daily standard of care in patients with CRSwNP as a novel approach in treating the entire spectrum of clinical manifestations of the disease, a predominantly type 2 inflammatory condition, as well as the frequently associated type 2 lower airway comorbidities. Dupilumab treatment also resulted in substantial reductions in the need for systemic corticosteroids and surgery, offering an efficacious treatment for patients with severe CRSwNP who otherwise have few therapeutic options.

Contributors

CB, JKH, MD, PWH, SEL, JM, LSG, JVB, TML, AUC, JFM, CH, HO, GWC, PP, SHC, WJF, MZ, XL, CF, SD, and LPM acquired data. CB, MD, NA, JM, CF, SAK, AK, GP, NMHG, HS, DW, NS, GDY, and LPM contributed to the conception and design of the study. CF, MZ, and XL did statistical analyses. All authors participated in the interpretation of the data, provided critical feedback and final approval for submission, and took responsibility for the accuracy, completeness, and protocol adherence of data and analyses. All investigators had confidentiality agreements with the sponsors.

Declaration of interests

CB has been an advisory board member for ALK, ASIT Biotech, AstraZeneca, Intrexon Actobiotics, GlaxoSmithKline, Novartis, Sanofi, and Stallergenes Greer. JKH has been an advisory board member for Regeneron Pharmaceuticals and Sanofi. MD has received clinical trial funding from AstraZeneca, GlaxoSmithKline, Probionase Therapies, and Sanofi; has been an advisory board member for Regeneron Pharmaceuticals and Sanofi; and has equity ownership in Probionase Therapies. NA, SAK, NMHG, MR, DW, and NS are employees and shareholders of Regeneron Pharmaceuticals. SEL has received clinical trial funding from Allakos, AstraZeneca, Knopp Biosciences, and Sanofi; and has been an advisory board member for Novartis, Regeneron Pharmaceuticals, and Sanofi. JM has received speaker fees from GlaxoSmithKline, Meda-Mylan Pharmaceuticals, Menarini, Merck Sharp & Dohme, Novartis, Regeneron Pharmaceuticals, Sanofi, UCB Pharma, and Uriach; has received clinical trial funding from Genentech-Roche, Regeneron Pharmaceuticals, and Sanofi; has received research grants from Meda-Mylan Pharmaceuticals and Uriach; and has been an advisory board member for Genentech-Roche, Meda-Mylan Pharmaceuticals, Novartis, Regeneron Pharmaceuticals, Sanofi, and Uriach. LSG has received research grants from Glenmark Pharmaceuticals, Novartis, Roxane Laboratories, Sandoz, and Sanofi-Aventis. JVB has received clinical trial funding from Cumberland Pharmaceuticals and Sanofi and has been an advisory board member for Novartis-Genentech, Regeneron Pharmaceuticals, and Optinose. TML has been a national and international scientific advisory board member for Allakos, GlaxoSmithKline, and Sanofi-Aventis. AUC has been an advisory board member for Intrexon Actobiotics. JFM has been a consultant for AstraZeneca, GlaxoSmithKline, Novartis, Sanofi, and Teva; has received speaker fees from Boehringer Ingelheim, Menarini, Novartis, and Uriach; and has received research grants from AstraZeneca, Novartis, and Sanofi. CH has been an advisory board member for GlaxoSmithKline, Optinose, Sanofi Genzyme, and Smith & Nephew. GWC has received speaker fees and been an advisory board member for ALK, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, HAL Allergy, Menarini, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi, Stallergenes Greer, and Uriach. PP has received research grants and been an advisory board member for AstraZeneca, Chiesi, GlaxoSmithKline, Novartis, and Sanofi. SHC has received research grants from AOBiome, National Institutes of Health, and Sanofi; and has received a research network grant from the American Lung Association. WJF has received research grants from GlaxoSmithKline, Meda Pharmaceuticals, Novartis, and Sanofi. SF has been an advisory board member for GlaxoSmithKline, Kyowa Hakko Kirin, and Sanofi; and has received speaker fees from Kyorin, Taiho, and Mitsubishi Tanabe Pharma. MZ, XL, CF, SD, AK, GP, NP, HS, and LPM are Sanofi employees and might hold stock, stock options, or both in Sanofi. GDY is an employee, shareholder, and board of directors' member of Regeneron Pharmaceuticals. PWH and HO declare no competing interests.

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References

1 Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinol Suppl* 2012; **23:** 1–299.

2 Orlandi RR, Kingdom TT, Hwang PH, et al. International consensus statement on allergy and rhinology: rhinosinusitis. *Int Forum Allergy Rhinol* 2016; **6** (suppl 1)**:** S22–209.

3 Settipane GA, Chafee FH. Nasal polyps in asthma and rhinitis. A review of 6,037 patients. *J Allergy Clin Immunol* 1977; **59:** 17–21.

4 Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol* 1999; **28:** 717–22.

5 Kohli P, Naik AN, Harruff EE, Nguyen SA, Schlosser RJ, Soler ZM. The prevalence of olfactory dysfunction in chronic rhinosinusitis. *Laryngoscope* 2017; **127:** 309–20.

6 Chung JH, Lee YJ, Kang TW, et al. Altered quality of life and psychological health (SCL-90-R) in patients with chronic rhinosinusitis with nasal polyps. *Ann Otol Rhinol Laryngol* 2015; **124:** 663–70.

7 Alobid I, Cardelús S, Benítez P, et al. Persistent asthma has an accumulative impact on the loss of smell in patients with nasal polyposis. *Rhinology* 2011; **49:** 519–24.

8 Alobid I, Bernal-Sprekelsen M, Mullol J. Chronic rhinosinusitis and nasal polyps: the role of generic and specific questionnaires on assessing its impact on patient's quality of life. *Allergy* 2008; **63:** 1267–79.

9 Tomassen P, Vandeplas G, Van Zele T, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol* 2016; **137:** 1449–56.

10 Han JK. Subclassification of chronic rhinosinusitis. *Laryngoscope* 2013; **123** (suppl 2)**:** S15–27.

11 Håkansson K, Thomsen SF, Konge L, Mortensen J, Backer V, von Buchwald C. A comparative and descriptive study of asthma in chronic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy* 2014; **28:** 383–87.

12 Stevens WW, Peters AT, Hirsch AG, et al. Clinical characteristics of patients with chronic rhinosinusitis with nasal polyps, asthma, and aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract* 2017; **5:** 1061–70.

13 Laidlaw TM, Boyce JA. Aspirin-exacerbated respiratory disease—new prime suspects. *N Engl J Med* 2016; **374:** 484–88.

14 Robinson D, Humbert M, Buhl R, et al. Revisiting type 2-high and type 2-low airway inflammation in asthma: current knowledge and therapeutic implications. *Clin Exp Allergy* 2017; **47:** 161–75.

15 Bhattacharyya N, Villeneuve S, Joish VN, et al. Cost burden and resource utilization in patients with chronic rhinosinusitis and nasal polyps. *Laryngoscope* 2019; **129:** 1969–75.

16 Alobid I, Benítez P, Cardelús S, et al. Oral plus nasal corticosteroids improve smell, nasal congestion, and inflammation in sino-nasal polyposis. *Laryngoscope* 2014; **124:** 50–56.

17 DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *Laryngoscope* 2017; **127:** 550–55.

18 Macdonald LE, Karow M, Stevens S, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. *Proc Natl Acad Sci USA* 2014; **111:** 5147–52.

19 Murphy AJ, Macdonald LE, Stevens S, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. *Proc Natl Acad Sci USA* 2014; **111:** 5153–58.

20 Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. *Expert Rev Clin Immunol* 2017; **13:** 425–37.

21 Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet* 2017; **389:** 2287–303.

22 Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 2016; **375:** 2335–48.

23 Thaçi D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet* 2016; **387:** 40–52.

24 Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet* 2016; **388:** 31–44.

25 Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018; **378:** 2486–96.

26 Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018; **378:** 2475–85.

27 Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA* 2016; **315:** 469–79.

28 Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol* 2009; **34:** 447–54.

29 Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005; **99:** 553–58.

30 Bachert C, Pawankar R, Zhang L, et al. ICON: chronic rhinosinusitis. *World Allergy Organ J* 2014; **7:** 25.