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Efficacy and safety of dupilumab in patients with uncontrolled severe CRSwNP and a clinical diagnosis of NSAID-ERD: Results from two randomized placebo-controlled phase 3 trials

Short title: Dupilumab treatment in CRSwNP and NSAID-ERD

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Data sharing and availability

Qualified researchers may request access to data and related study documents. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial patients. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: <https://www.clinicalstudydatarequest.com>.

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ABSTRACT

Background: About one-tenth of patients with difficult-to-treat chronic rhinosinusitis with nasal polyps (CRSwNP) have comorbid non-steroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD). Dupilumab, a fully human monoclonal antibody that blocks the shared interleukin (IL)-4/IL-13 receptor component, is an approved add-on treatment in severe CRSwNP. This post hoc analysis evaluated dupilumab efficacy and safety in CRSwNP patients with/without NSAID-ERD.

Methods: Data were pooled from the phase 3 SINUS-24 and SINUS-52 studies in adults with uncontrolled severe CRSwNP who received dupilumab 300 mg or placebo every 2 weeks. CRSwNP, nasal airflow, lung function, and asthma control outcomes at Week 24 were evaluated and treatment–subgroup interactions were assessed for patients with and without NSAID-ERD.

Results: Of 724 patients, 204 (28.2%) had a diagnosis of NSAID-ERD. At Week 24, least squares mean treatment differences demonstrated significant improvements in nasal polyp score, nasal congestion (NC), Lund–Mackay computed tomography, 22-item Sinonasal Outcome Test (SNOT-22), Total Symptom Score, rhinosinusitis severity visual analog scale, peak nasal inspiratory flow (PNIF), six-item asthma control questionnaire score, and improvement in smell with dupilumab vs placebo (all $P < .0001$) in patients with NSAID-ERD. Treatment comparisons demonstrated significantly greater improvements with dupilumab in patients with vs without NSAID-ERD for NC ($P = .0044$), SNOT-22 ($P = .0313$), TSS ($P = .0425$), and PNIF ($P = .0123$).

Conclusions: In patients with uncontrolled severe CRSwNP, dupilumab significantly improved objective measures and patient-reported symptoms to a greater extent in the presence of comorbid NSAID-ERD than without. Dupilumab was well tolerated in patients with/without NSAID-ERD.

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Abbreviations: ACQ-6, 6-item asthma control questionnaire; CRSwNP, chronic rhinosinusitis with nasal polyps; ECP, eosinophil cationic protein; FEV₁, forced expiratory volume in 1 second; IgE, immunoglobulin E; LTE₄, leukotriene E₄; NC, nasal congestion; NP, nasal polyp; NPS, nasal polyp score; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated disease; PNIF, peak nasal inspiratory flow; q2w, every 2 weeks; SCS, systemic corticosteroids; SNOT-22, 22-item Sinonasal Outcome Test; TARC, thymus and activation-regulated chemokine; TEAE, treatment-emergent adverse event; TSS, total symptom score; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog scale.

1 INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory disease of the nasal passages and paranasal sinuses characterized by two or more symptoms, one of which should be either rhinorrhea or nasal congestion/obstruction, with/without facial pain/pressure or loss of sense of smell for at least 12 weeks.^{1,2} The disease is associated with a high symptom burden and poor health-related quality of life (HRQoL).¹⁻⁴ A subgroup of patients suffer from uncontrolled severe CRSwNP, characterized by the polyp mass, symptoms, and the lack of control by the standard of care.⁵ The pathophysiology of CRSwNP is characterized predominantly by type 2 inflammation with interleukin (IL)-4, IL-13, and IL-5 as prominent cytokines, and tissue infiltration by eosinophils, lymphocytes, basophils, and mast cells.^{1,6-9}

Approximately 10% of patients with CRSwNP have a diagnosis of non-steroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD).¹⁰ NSAID-ERD—also known as aspirin-exacerbated respiratory disease or Samter's triad—is a type 2 immune-mediated clinical syndrome associated with aspirin/non-steroidal anti-inflammatory drug (NSAID) sensitivity, asthma, and CRSwNP.¹¹⁻¹³ The syndrome encompasses two distinct phases consisting of a chronic baseline airway inflammation that presents as asthma and recurrent nasal polyps, and an acute hypersensitivity reaction triggered by NSAIDs. Onset and severity of symptoms are dose related and characterized by upper and/or lower airway symptoms, which can vary from mild rhinorrhea, wheezing, and shortness of breath, to severe laryngospasm and bronchospasm.^{13,14} Although these respiratory reactions are the defining feature of the syndrome, the initial inflammatory process begins and continues independently of exposure to NSAIDs. Both airway inflammation and the clinical reactions to NSAIDs are characterized by a potent type 2 immune response with the activation of effector cells, including mast cells, eosinophils, and basophils, and derangements in arachidonic acid metabolism. Lipid mediators, including prostaglandins and leukotrienes, which are central to the pathogenesis of NSAID-ERD, are potent innate lymphoid cell 2 activators, which rapidly and robustly induce the production of T helper 2 (Th2) cytokines upon upregulation.^{11,12}

Patients with CRSwNP and NSAID-ERD have more severe sinus disease and worse HRQoL than those without NSAID-ERD.^{13,15,16} The current standards of care for CRSwNP with NSAID-ERD include corticosteroid use, with sinonasal surgery for patients who are inadequate responders.¹³ However, reoccurrences of polyps are common. Aspirin desensitization post-sinonasal surgery has also been utilized as part of a multifaceted treatment approach.¹⁷ However, aspirin desensitization is not appropriate for all patients due to the risk of exacerbation of underlying asthma and side effects, including laryngeal spasm

and cutaneous and gastrointestinal toxicity.¹⁸⁻²⁰ Thus, an alternative management approach that reduces systemic corticosteroids (SCS) or nasal polyp (NP) surgery need is desirable.

Dupilumab is a fully human VelocImmune®-derived monoclonal antibody that blocks the shared receptor component for IL-4 and IL-13, which are key and central drivers of type 2 inflammation in multiple diseases.²¹⁻²³ In the randomized, double-blind, 24-week SINUS-24 (NCT02912468) and 52-week SINUS-52 (NCT02898454) phase III trials in patients with uncontrolled severe CRSwNP, dupilumab significantly improved endoscopic, radiologic, and clinical outcomes, including sense of smell, vs placebo, and was generally well tolerated.²⁴ In a systematic review, dupilumab treatment after 24 weeks improved disease-specific and general HRQoL vs placebo in patients with uncontrolled severe CRSwNP.²⁵ Dupilumab is approved by the United States Food and Drug Administration²⁶ and European Medicines Agency²⁷ as an add-on treatment in adult patients with inadequately controlled CRSwNP.

In pre-specified subgroup analyses of CRSwNP patients with comorbid NSAID-ERD from SINUS-24 and SINUS-52, dupilumab showed significant improvements in nasal polyp score (NPS), nasal congestion (NC) score, and Lund–Mackay computed tomography (LMK-CT) score at Week 24, compared with placebo (all $P < .0001$).²⁴ The aim of this study was to analyze the efficacy and safety of dupilumab vs placebo across a range of outcome measures in patients with CRSwNP with and without comorbid NSAID-ERD in the pooled SINUS-24 and SINUS-52 studies.

2 METHODS

2.1 Study design

SINUS-24 and SINUS-52 were 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 studies of dupilumab in patients with uncontrolled severe CRSwNP. The study design, randomization process, and methodology for SINUS-24 and SINUS-52 have been reported previously.²⁴ In both studies, randomization was stratified by asthma or NSAID-ERD disease status at screening, previous surgery at screening, and country.

2.2 Participants

The eligibility criteria were identical for both studies and previously published (see Supplementary Table 1).²⁴ Briefly, adults with bilateral NPs and symptoms of chronic rhinosinusitis despite intranasal corticosteroid therapy, who had received SCS in the preceding 2 years (or had a medical contraindication or intolerance to SCS) or previous sinonasal surgery were included. A prespecified enrollment goal was to have at least 50% of patients with asthma, NSAID-ERD, or both, and 50% of patients having had previous polyp surgery. Written informed consent was provided by all patients in the SINUS-24 and SINUS-52 trials.²⁴

To ascertain a diagnosis of NSAID-ERD, a two-question survey based on a diagnostic algorithm endorsed by an expert panel¹³ was administered during the medical/surgery history interview. The 2 questions were: *Have you ever had respiratory, nasal, and/or bronchial symptoms following the intake of aspirin or/and NSAID?*; and *While having a positive clinical history of NSAID-ERD, have you ever undergone an aspirin provocation test, either nasal, bronchial, or oral?* An affirmative response to either question was considered to indicate a clinical diagnosis of NSAID-ERD.

Details of study sites have been previously published.²⁴

2.3 Interventions

Patients were randomly assigned (1:1) to receive subcutaneous (SC) dupilumab 300 mg or placebo every 2 weeks (q2w) for 24 weeks in SINUS-24, and (1:1:1) to receive dupilumab 300 mg q2w for 52 weeks, dupilumab q2w for 24 weeks and then every 4 weeks (q4w) for the remaining 28 weeks, or placebo q2w for 52 weeks in SINUS-52. Patients received 100 mg of mometasone furoate nasal spray (MFNS) in each nostril twice daily throughout the trial starting from 4 weeks prior to randomization. Patients were permitted to use saline nasal lavage as needed, systemic antibiotics, short-course SCS, or to undergo sinonasal surgery during treatment and follow-up.

2.4 Outcome measures

The coprimary endpoints in the SINUS-24 and SINUS-52 studies were change from baseline in NPS and NC, at Week 24.²⁴ In this post hoc analysis, changes from baseline at Week 24 in NPS, patient-assessed symptom severity score for nasal congestion (NC score 0–3; 0 = no symptoms, 1 = mild, 2 = moderate, and 3 = severe), LMK-CT score, 22-item Sinonasal Outcome Test (SNOT-22) score, patient-reported Total Symptom Score (TSS; a composite severity score consisting of the sum of daily symptoms of nasal congestion, loss of smell, and anterior or posterior rhinorrhea), and visual analog scale (VAS) for rhinosinusitis severity were analyzed. Changes in smell were determined using University of Pennsylvania Smell Identification Test (UPSIT) score, proportion of patients who were anosmic (UPSIT score ≤ 18), loss of smell score, and SNOT-22 smell/taste item scores. The need for rescue intervention was assessed as time to first SCS use or need for NP surgery over 52 weeks of the treatment period. In patients with concomitant asthma, nasal obstruction, lung function, and asthma control were assessed by peak nasal inspiratory flow (PNIF), forced expiratory volume in 1 second (FEV₁), and 6-item Asthma Control Questionnaire (ACQ-6) score, respectively.

Eosinophil count, serum total immunoglobulin E (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 were assessed in blood samples taken at baseline and Week 24. Eosinophil cationic protein (ECP), eotaxin-3, and total IgE were assessed in nasal secretion samples taken at baseline and Week 24, and urinary leukotriene E₄ (LTE₄) was measured in samples taken at baseline and Week 24. Serum periostin, serum TARC, eotaxin-3 in both blood and nasal secretion samples, and total IgE and ECP in nasal secretion samples were also assessed at Week 24 in the SINUS-52 population.

Safety measures included assessments of vital signs, physical examination, clinical laboratory assessment, 12-lead electrocardiogram findings, and incidence of treatment-emergent adverse events (TEAEs).

2.5 Sample size, randomization, and masking

The sample size calculation, randomization process, and masking procedures for the SINUS-24 and SINUS-52 studies have been described previously.²⁴

2.6 Statistical methods

Analyses of the efficacy endpoints (NPS, NC score, LMK-CT score, SNOT-22 score, TSS, rhinosinusitis VAS), nasal airflow (PNIF), lung function (FEV₁), and asthma control (ACQ-6) used the same imputed dataset

using worst observation carried forward and multiple imputation methods, as done for the primary analysis.²⁴ Further details on statistical methods are given in the Supplementary Materials.

3 RESULTS

3.1 Patient characteristics

Of the 724 patients included in the pooled ITT population, 204 (28.2%) had a clinical diagnosis consistent with NSAID-ERD (Supplementary Table 2). Of these, 203 patients had a history of intolerance to aspirin and/or NSAIDs, and 30 patients had undergone an aspirin provocation test, of which 26 had a positive test (Supplementary Table 2). There were more female patients ($P < .0001$) among those with NSAID-ERD than among those without NSAID-ERD. Patients with NSAID-ERD had more severe CRSwNP than those without, as reflected by the significant differences in baseline disease characteristics shown between the 2 groups (Table 1). A greater proportion of patients with NSAID-ERD had undergone prior sinonasal surgery compared with those without NSAID-ERD (78% vs 58%, respectively; $P < .001$). Patients with NSAID-ERD had greater sinus opacification (higher LMK-CT score), worse sense of smell (lower UPSIT score, greater percentage of patients with anosmia, higher daily loss of smell score, and higher SNOT-22 smell/taste item score), and higher TSS than those without NSAID-ERD (all $P < .05$). The type 2 inflammatory biomarkers including blood eosinophils, serum periostin, plasma eotaxin-3, nasal secretion eotaxin-3, and urinary LTE_4 were higher in patients with NSAID-ERD compared with those without NSAID-ERD (all $P < .05$). There was no significant difference in serum total IgE. In the subgroup of CRSwNP patients with comorbid asthma ($n = 428$), patients with NSAID-ERD ($n = 181$) had poorer lung function (FEV_1) compared with patients without NSAID-ERD ($n = 247$) (Table 1).

3.2 Changes in disease control and symptom burden

Dupilumab treatment, compared with placebo, demonstrated meaningful improvements in assessed outcome measures of CRSwNP in both patients with and without NSAID-ERD at Week 24 (nominal $P < .0001$; Figure 1). Improvement vs placebo was evident from the first assessment time point for each endpoint.

When compared, improvement vs placebo for NPS, LMK-CT score, rhinosinusitis VAS, UPSIT, loss of smell score, and SNOT-22 decrease in smell/taste scores were similar in patients with or without NSAID-ERD status (Table 2). Improvements in NC score, TSS, and SNOT-22 total score were greater with dupilumab in patients with NSAID-ERD than in patients without NSAID-ERD (all nominal $P < .05$ for interaction; Table 2).

As loss of smell is a cardinal symptom of CRSwNP, the impact of dupilumab on sense of smell was further examined. Among patients in the NSAID-ERD subgroup, the proportion of anosmic patients

(UPSIT $\leq$ 18) at baseline was similar in the dupilumab and placebo arms. At Week 24, significantly greater proportions of dupilumab-treated patients improved sense of smell (UPSIT > 18) vs placebo-treated patients (60.2% vs 11.0%, respectively; $P < .0001$) (Supplementary Table 3). Among CRSwNP patients without NSAID-ERD, 76.7% of dupilumab-treated patients vs 28.0% in placebo-treated patients improved UPSIT > 18 at Week 24 (Supplementary Table 3). Among patients with anosmia at baseline, the proportions of patients who regained some sense of smell (UPSIT > 18) at Week 24 were comparable in patients with and without NSAID-ERD (35.4% vs 44.0%, respectively; $P = .1133$) (Supplementary Table 4).

Fewer patients required rescue with SCS or sinonasal surgery with dupilumab than with placebo, irrespective of NSAID-ERD status. In patients with NSAID-ERD, 15/122 (12.3%) in the dupilumab group and 33/82 (40.2%) in the placebo group required rescue with SCS (HR 0.219; 95% confidence interval [CI] 0.116–0.412; nominal $P < .0001$). In patients without NSAID-ERD, SCS rescue was used for 26/316 dupilumab-treated patients (8.2%) vs 55/204 of placebo-treated patients (27.0%) (HR 0.281; 95% CI 0.175–0.450; nominal $P < .0001$) (Figure 2A). In patients with NSAID-ERD, rescue NP surgery was performed in 2/122 patients (1.6%) in the dupilumab group and 9/82 patients (11.0%) in the placebo group (HR 0.204; 95% CI 0.044–0.948; nominal $P < .05$). In patients without NSAID-ERD, rescue NP surgery was performed in 3/316 patients (0.9%) in the dupilumab group and 13/204 patients (6.4%) in the placebo group (HR 0.162; 95% CI 0.046–0.573; nominal $P < .005$) (Figure 2B).

3.3 Changes in airway function and asthma control

Nasal airflow as assessed by PNIF was significantly improved by dupilumab treatment vs placebo in patients with CRSwNP with and without NSAID-ERD at all time points up to Week 24 (nominal $P < .0001$ for all time points; Figure 3A). Treatment effect with dupilumab was greater in patients with NSAID-ERD than those without NSAID-ERD (overall interaction $P = .0123$) (Table 2).

In patients with CRSwNP with comorbid asthma, dupilumab treatment resulted in greater improvements in lung function (assessed by FEV₁) and asthma control (assessed by ACQ-6) than placebo, irrespective of NSAID-ERD status (nominal $P \leq .001$ for all time points in both subgroups; Figure 3B and 3C). Treatment effect with dupilumab at Week 24 did not differ in asthma patients with or without NSAID-ERD for FEV₁ (overall interaction $P = .3434$) or ACQ-6 (overall interaction $P = .1630$) (Table 2).

3.4 Changes in biomarkers

There were more pronounced decreases from baseline to Week 24 in the following biomarkers in dupilumab-treated NSAID-ERD patients than in those without NSAID-ERD: urinary LTE₄ (median

percentage change –76.2% vs –37.2%); nasal secretion total IgE (–70.8% vs –18.3% [SINUS-52]); and nasal ECP (–70.6% vs –35.3% [SINUS-52]) (Supplementary Table 5 and Supplementary Table 6).

Significantly ($P < .01$) greater reductions in serum total IgE, TARC and periostin, plasma eotaxin-3, nasal fluid eotaxin-3, and urinary LTE₄ were observed with dupilumab treatment compared with placebo in patients with or without NSAID-ERD. There were no significant differences in the change from baseline in blood eosinophils or nasal ECP at Week 24 between dupilumab-treated patients vs placebo-treated patients, irrespective of NSAID-ERD status (Supplementary Table 5 and Supplementary Table 6).

3.5 Safety

Dupilumab was well tolerated among patients with CRSwNP with or without NSAID-ERD (Table 3). In patients with CRSwNP and NSAID-ERD, adverse events (AEs) were reported in 70.2% and 79.3% of dupilumab-treated and placebo-treated patients, respectively. The most commonly reported TEAEs (> 5%) among patients with CRSwNP and NSAID-ERD were nasopharyngitis, injection-site erythema, headache, and arthralgia. In patients without NSAID-ERD, AEs were reported in 69.0% and 71.5% of dupilumab- and placebo-treated patients, respectively, over the same period, and nasopharyngitis, headache, and epistaxis were the most commonly reported TEAEs (Table 3). There were no deaths. Serious AEs occurred in ≤ 5.0% of patients with or without NSAID-ERD who received dupilumab – an incidence that was lower than that in the placebo group.

4 DISCUSSION

This analysis of pooled data from the SINUS-24 and SINUS-52 trials demonstrated that patients with CRSwNP with comorbid NSAID-ERD had more severe disease at baseline compared with patients without NSAID-ERD, including worse LMK-CT, TSS, UPSIT, and daily loss of smell scores, more prior surgeries, and higher levels of some biomarkers of type 2 inflammation than those without NSAID-ERD. Higher percentages of patients with NSAID-ERD were anosmic, had comorbid asthma, and had reduced lung function (FEV₁). These findings substantiate those of other studies which reported that patients with CRSwNP with NSAID-ERD generally have more severe and difficult-to-treat disease than those who are NSAID-ERD tolerant.^{13,15,16} This analysis demonstrated that dupilumab treatment resulted in clinically relevant improvements in patient-reported symptoms and objective measures in patients with CRSwNP and comorbid NSAID-ERD. The improvements in NPS, CT sinus opacification scores, rhinosinusitis symptoms, and sense of smell in both patients with and without NSAID-ERD were rapid, evident at the first assessment time points (Weeks 2–4) and sustained over the study duration. Dupilumab also improved lung function and asthma control in CRSwNP patients with NSAID-ERD and asthma.

Although statistically significant treatment-subgroup interactions were observed for NC score, SNOT-22 score, TSS, and PNIF outcomes in patients with CRSwNP and NSAID-ERD compared with those without NSAID-ERD, the treatment effect was statistically and clinically meaningful in either sub-group. It is possible that as the patients with NSAID-ERD had more severe disease that they were more likely to perceive improvement in symptoms. Although mean improvements in NPS were not different in patients with and without NSAID-ERD, the magnitude of increase in PNIF was greater in patients with NSAID-ERD. This finding may be related to a greater improvement in nasal congestion in patients with NSAID-ERD compared with those without NSAID-ERD. Less congested and less edematous nasal passages thereby may have been translated into a better PNIF in patients with NSAID-ERD. These results suggest that there is a benefit for the addition of dupilumab for patients with CRSwNP and NSAID-ERD. The magnitude of treatment effects across both subgroups was generally aligned with the overall primary analysis in patients with CRSwNP.²⁴ Dupilumab was generally well tolerated in CRSwNP, irrespective of the presence of comorbid NSAID-ERD.

This analysis has some limitations, which may impact the interpretation of its findings. In this post hoc analysis, endpoints were not adjusted for multiplicity. In addition, there are several interesting research questions that this study was unable to address. While the effect of dupilumab on upper and lower airway inflammation and function is clear from these data, acute exacerbation following exposure

to NSAIDs – a component of the syndrome – was not assessed. It is also unknown from the findings of this study if dupilumab modulates leukotriene receptor expression or its effect on prostaglandin D2 (PGD2) production. PGD2 is a potent driver in NSAID-ERD as a major recruiter of Th2 cells, eosinophils, and basophils.²⁸ Further clinical studies are warranted to investigate the effects of dupilumab on these aspects of the disease. Even though the diagnosis of NSAID-ERD was based on a two-item questionnaire established by an expert panel, is consistent with current approaches for diagnosing NSAID-ERD,^{2,13} and administered by healthcare professionals, it is possible that some patients may not have understood the question about “respiratory” and “bronchial” symptoms and may have been mis-categorized.

In this RCT, patients with CRSwNP and NSAID-ERD require frequent courses of SCS and are more likely to undergo repeated surgeries.¹³ There is a need for interventions for uncontrolled severe CRSwNP that can reduce the need for systemic corticosteroids and NP surgery.¹³ Dupilumab treatment was associated with substantial systemic corticosteroid-sparing benefits, reducing the use of SCS by 78.1% and 71.9% among those with and without NSAID-ERD, respectively. Similarly, for patients receiving dupilumab, the risk of NP surgery was reduced by 79.6% and 83.8%, respectively.

Urinary LTE_4 is a marker of more severe CRSwNP,²⁹ levels of which are reduced after endoscopic sinus surgery.³⁰ As found in other studies, baseline urinary LTE_4 levels were significantly greater in patients with NSAID-ERD than in patients without NSAID-ERD, with greater reductions from baseline observed with dupilumab treatment in patients with NSAID-ERD vs those without NSAID-ERD. The greater reduction in patients with NSAID-ERD might be accounted for by differences in the contribution of IL-4R α signaling in these patients. IL-4R α signaling inhibits prostaglandin (PG) E_2 production, resulting in increased constitutive production of cysteinyl leukotrienes (CysLTs) and increased excretion of LTE_4 in the urine. By inhibiting IL-4/IL-13, dupilumab lowers production of LTE_4 , as reflected by a greater decrease in urinary LTE_4 in patients with NSAID-ERD than without.¹² This more dramatic reduction in urinary LTE_4 levels might explain the differences in the magnitude of clinical response observed for some endpoints; however, the exact mechanisms remain unexplained. A small study of ten patients in clinical practice has also demonstrated a reduction in urinary LTE_4 levels with dupilumab in patients with uncontrolled CRSwNP and comorbid NSAID-ERD.³¹ reductions in type 2 biomarkers both in systemic circulation (total IgE, TARC, eotaxin-3, and periostin) and locally in nasal secretions (eotaxin-3) observed in these studies were consistent with the mode of action of dupilumab and with previous dupilumab studies in asthma and atopic dermatitis.⁸

Dupilumab was generally well tolerated in patients with CRSwNP with and without NSAID-ERD, with nasopharyngitis being the most common TEAE. The safety data were consistent with those of the primary analysis and studies of dupilumab in other patient populations,^{24,32-34} although patients with CRSwNP and NSAID-ERD who received dupilumab had an increased incidence of arthralgia compared with patients without NSAID-ERD (6.6% vs 0%, respectively). There have been other reports of arthralgia experienced in patients receiving dupilumab outside of clinical trials.^{35,36} The exact mechanisms of these AEs are unclear. Another adverse drug reaction previously observed with dupilumab in patients with uncontrolled asthma is increased levels of eosinophils; these increases were transient and resolved to baseline levels at 1 year after starting treatment.³⁴ In the current study, increases in eosinophils were not observed in the subgroup with no clinical diagnosis of NSAID-ERD, but a median increase of 40% from baseline was reported among the subgroup of patients with NSAID-ERD at Week 24. The exact reasons for such a differential response between the groups are unclear. However, it is important to note that the median percentage increase in eosinophil counts observed in the dupilumab-treated group was statistically not different from that of the placebo-treated group, irrespective of NSAID-ERD status, and eosinophil levels returned to baseline by Week 52 in patients with and without NSAID-ERD (data not shown). Increase in blood eosinophil levels is consistent with the hypothesis that by IL-4 and IL-13 blockade, dupilumab suppresses the production of eotaxin-3 and VCAM, and inhibition of trafficking of eosinophils from blood into tissues, but not the production and release of eosinophils from bone marrow and thereby resulting in the observed transient increase in circulating eosinophils, a finding consistent with other clinical studies of dupilumab.^{24,34}

5 CONCLUSIONS

Patients with CRSwNP and comorbid NSAID-ERD are the most severe and difficult-to-treat subset of patients with CRSwNP, with high rates of nasal polyp recurrence and high disease burden. Dupilumab improved symptoms, endoscopic and radiological outcomes, HRQoL, and airway function, and suppressed underlying type 2 inflammation compared with placebo in patients with CRSwNP and NSAID-ERD. A greater improvement was observed with dupilumab for some outcomes in patients with comorbid NSAID-ERD compared with those without. Dupilumab was generally well tolerated in patients with CRSwNP with and without NSAID-ERD. These observations suggest that even greater consideration should be given to the use of dupilumab as a treatment option in the CRSwNP and NSAID-ERD patient population.

Conflicts of interest

J. MulloI reports non-financial support from Regeneron Pharmaceuticals, Inc., and non-financial support from Sanofi, during the conduct of the study; grants, personal fees and other from ALK-Abelló, grants, personal fees and other from AstraZeneca, grants, personal fees and other from Genentech, grants, personal fees and other from GlaxoSmithKline, grants, personal fees and other from Glenmark, grants, personal fees and other from Menarini, grants, personal fees and other from Merck Sharp & Dohme, grants, personal fees and other from Mitsubishi Tanabe Pharma, grants, personal fees and other from Mylan-Meda Pharmaceuticals (Viatris), grants, personal fees and other from Novartis, grants, personal fees and other from Proctor & Gamble, grants, personal fees and other from Regeneron Pharmaceuticals, Inc., grants, personal fees and other from Sanofi Genzyme, grants, personal fees and other from UCB Pharma, grants, and personal fees and other from Uriach Group, outside the submitted work.

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Author contributions

J. Mullol, C. Bachert, and L.P. Mannent conceived and designed the study, performed experiments, and analyzed data. T.M. Laidlaw, G.W. Canonica, J.K. Han, and J.F. Maspero performed experiments and analyzed data. N. Amin conceived and designed the study and analyzed data. C. Picado, N. Daizadeh, B. Ortiz, Y. Li, M. Ruddy, and E. Laws performed data analysis. All authors revised and approved the final version.

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TABLE 1 Baseline demographic and disease characteristics in patients with CRSwNP with and without NSAID-ERD.

Characteristics/Parameters	CRSwNP patients with NSAID-ERD (n = 204)	CRSwNP patients without NSAID-ERD (n = 520)	P-value NSAID-ERD vs non-NSAID-ERD [†]
Age, mean (SD), years	50.30 (12.87)	51.82 (12.79)	.1523
Female gender, n (%)	116 (56.9)	171 (32.9)	< .0001
Time since first NP diagnosis, mean (SD), years	12.85 (9.20)	10.28 (9.45)	.001
Patients with previous surgery for NP, n (%)	159 (77.9)	300 (57.7)	< .0001
Patients with SCS use during the previous 2 years, n (%)	148 (72.5)	390 (75.0)	.4971
Bilateral endoscopic NPS, [‡] mean (SD), range 0–8	5.92 (1.32)	5.98 (1.22)	.5405
Daily NC score, [‡] mean (SD), range 0–3	2.43 (0.58)	2.39 (0.58)	.3792
LMK-CT score, [‡] mean (SD), range 0–24	19.33 (3.83)	17.99 (4.09)	< .0001
SNOT-22 total score, [‡] mean (SD), range 0–110	52.86 (19.63)	50.19 (21.02)	.1208
Total symptom score (TSS), [‡] mean (SD), range 0–9	7.33 (1.35)	7.09 (1.45)	.0452
Rhinosinusitis severity (VAS), [‡] mean (SD), range 0–10	7.99 (2.09)	7.83 (2.07)	.3563
UPSIT score, [‡] mean (SD), range 0–40	11.88 (6.47)	14.81 (8.67)	< .0001

Anosmia (UPSIT score ≤ 18), n (%)	178 (88.6)	373 (73.3)	< .0001
Daily loss of smell score, [‡] mean (SD), range 0–3	2.83 (0.43)	2.70 (0.56)	.0009
SNOT-22 smell/taste item, [‡] mean (SD)	4.48 (1.04)	4.19 (1.20)	.0017
Patients with comorbid asthma, n (%)	181 (88.7)	247 (47.5)	< .0001
PNIF, L/min, mean (SD)	84.86 (54.75)	87.94 (56.62)	.5067
FEV ₁ , L, mean (SD) [§]	2.56 (0.86)	2.65 (0.90)	.2928
ACQ-6 score, mean (SD), [§] range 0–6	1.56 (1.12)	1.62 (1.10)	.6149
Total IgE, IU/mL, median (95% CI)	127.00 (108.00, 163.00)	115.50 (99.00, 133.00)	.1701
Serum TARC, pg/mL, median (95% CI)	280.00 (262.00, 299.00)	297.50 (277.00, 312.00)	.5541
Serum periostin, ng/mL, median (95% CI)	117.50 (110.00, 127.00)	99.00 (94.60, 104.00)	< .0001
Eotaxin-3, pg/mL, median (95% CI)	69.25 (62.70, 77.30)	57.30 (53.70, 60.80)	.0093

Blood eosinophils, Giga/L, median (95% CI)	0.36 (0.33, 0.43)	0.34 (0.31, 0.37)	.0277
Urinary LTE ₄ , pg/mL, median (95% CI)	218.00 (178.00, 286.00)	85.00 (70.40, 94.50)	< .0001
Nasal eotaxin-3, pg/mL, median (95% CI)	43.40 (13.70, 93.20)	16.50 (9.52, 22.80)	.0095
Nasal IgE, IU/mL, median (95% CI)	9.00 (5.00, 26.00)	5.00 (4.00, 8.00)	.0632
Nasal ECP, ng/mL, median (95% CI)	35.00 (24.00, 118.00)	25.00 (11.00, 40.00)	.0705

*Nominal *P*-values for comparing patients with and without NSAID-ERD based on t-test for equal variance for quantitative parameters (t-test for unequal variances in cases where homogeneity of variances was not met) and chi-square test for qualitative parameters. Wilcoxon rank sum test was used to compare non-parametric data for the biomarkers.

[‡]Higher mean scores indicate more severe disease, except for UPSIT score, where lower scores indicate more severe disease.

[§]Analyzed in patients with asthma with NSAID-ERD (n = 181) and without NSAID-ERD (n = 247).

^{||}Nasal secretion biomarkers were assessed only in patients from SINUS-52. CRSwNP with NSAID-ERD, n = 120; CRSwNP without NSAID-ERD, n = 328.

ACQ-6, 6-item Asthma Control Questionnaire; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; ECP, eosinophil cationic protein; FEV₁, forced expiratory volume in 1 second; IgE, immunoglobulin E; LMK-CT, Lund–Mackay computed tomography; NC, nasal congestion; NP, nasal polyp; NPS, nasal polyp score; NSAID-ERD, non-

steroidal anti-inflammatory drug-exacerbated disease; PNIF, peak nasal inspiratory flow; SCS, systemic corticosteroids; SD, standard deviation; SNOT-22, 22-item Sinonasal Outcome Test; TARC, thymus and activation-regulated chemokine; TSS, Total Symptom Score; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog scale.

TABLE 2 Treatment effect comparisons on CRSwNP disease control, airway function, and sense of smell at Week 24 in patients with CRSwNP with and without NSAID-ERD (SINUS-24 and SINUS-52 pooled).

Characteristics/ Parameters	CRSwNP patients with NSAID-ERD	CRSwNP patients without NSAID-ERD	Overall interaction <i>P</i> -value in CRSwNP patients with/without NSAID-ERD [‡]
	LS mean difference vs placebo (95% CI), <i>P</i> -value vs placebo ⁺	LS mean difference vs placebo (95% CI), <i>P</i> -value vs placebo ⁺	
NPS score, range 0–8	–1.89 (–2.30, –1.49) < .0001	–1.92 (–2.20, –1.64) < .0001	.9786
NC score, range 0–3	–1.17 (–1.39, –0.95) < .0001	–0.77 (–0.92, –0.63) < .0001	.0044
LMK-CT score, range 0–24	–6.33 (–7.39, –5.27) < .0001	–6.04 (–6.69, –5.40) < .0001	.5637
SNOT-22 score, range 0–110	–24.35 (–29.54, –19.17) < .0001	–16.80 (–19.91, –13.69) < .0001	.0313
TSS, range 0–9	–3.01 (–3.53, –2.49) < .0001	–2.32 (–2.70, –1.95) < .0001	.0425

Rhinosinusitis (VAS), range 0–10	–3.59 (–4.30, –2.87) < .0001	–2.84 (–3.32, –2.37) < .0001	.2354
UPSIT score, range 0–40	10.17 (7.95, 12.39) < .0001	10.69 (9.32, 12.07) < .0001	.8548
Daily loss of smell score, range 0–3	–1.01 (–1.23, –0.79) < .0001	–1.05 (–1.20, –0.89) < .0001	.9338
SNOT-22 decreased smell/taste score	–2.12 (–2.54, –1.70) < .0001	–1.92 (–2.18, –1.66) < .0001	.5352
FEV ₁ , [§] L	0.26 (0.15, 0.36) < .0001	0.19 (0.08, 0.30) 0.001	.3434
ACQ-6 score, [§] range 0–6	–0.97 (–1.22, –0.72) < .0001	–0.72 (–0.92, –0.52) < .0001	.1630
PNIF, L/min	52.05 (39.71, 64.40) < .0001	33.11 (25.48, 40.74) < .0001	.0123

[†]Each of the imputed complete data was analyzed by fitting an ANCOVA model with change from baseline at the corresponding visit as the response variable, and the corresponding baseline value, treatment group, prior surgery history, region, and study indicator (SINUS-52 = 0 and SINUS-24 = 1) as covariates. Analysis was based on the same imputed dataset using WOCF/MI from primary analysis of the endpoint in each of the 2 studies (SINUS-52 and SINUS-24).

[‡]Each of the imputed complete data was analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, NSAID-ERD status, prior surgery history, region, NSAID-ERD status-by-treatment interaction, and study indicator (SINUS-52 = 0 and SINUS-24 = 1) as covariates.

[§]Analyzed in patients with asthma only.

ACQ-6, 6-item Asthma Control Questionnaire; ANCOVA, analysis of covariance; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; FEV₁, forced expiratory volume in 1 second; LMK-CT, Lund–Mackay computed tomography; LS, least square; MI, multiple imputation; NC, nasal congestion; NPS, nasal polyp score; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated disease; PNIF, peak nasal inspiratory flow; SNOT-22, 22-item Sinonasal Outcome Test; TSS, Total Symptom Score; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog scale; WOCF, worst observation carried forward.

TABLE 3 Summary of safety over 24 weeks among patients with CRSwNP with and without NSAID-ERD.

	CRSwNP patients with NSAID-ERD [†]		CRSwNP patients without NSAID-ERD [†]	
	Placebo	Dupilumab 300 mg q2w	Placebo	Dupilumab 300 mg q2w
Patients, n (%)	(n = 82)	(n = 121)	(n = 200)	(n = 319)
Any TEAE	65 (79.3)	85 (70.2)	143 (71.5)	220 (69.0)
Any serious TEAE	5 (6.1)	6 (5.0)	11 (5.5)	9 (2.8)
Any TEAE leading to death	0	0	0	0
Any TEAE leading to permanent treatment discontinuation	4 (4.9)	4 (3.3)	11 (5.5)	7 (2.2)
TEAEs occurring in ≥ 5% of patients (MedDRA PT), n (%)				
Nasopharyngitis	12 (14.6)	19 (15.7)	29 (14.5)	36 (11.3)
Upper respiratory tract infection	5 (6.1)	2 (1.7)	NA	NA
Headache	10 (12.2)	8 (6.6)	14 (7.0)	24 (7.5)
Asthma	10 (12.2)	5 (4.1)	10 (5.0)	2 (0.6)
Nasal polyps	12 (14.6)	4 (3.3)	21 (10.5)	8 (2.5)

Arthralgia	0	8 (6.6)	NA	NA
Acute sinusitis	NA	NA	11 (5.5)	5 (1.6)
Epistaxis	NA	NA	16 (8.0)	21 (6.6)
Injection-site erythema	9 (11.0)	13 (10.7)	13 (6.5)	15 (4.7)

[†]One patient in each patient group (with NSAID-ERD, without NSAID-ERD) was randomized but not treated.

CRSwNP, chronic rhinosinusitis with nasal polyps; MedDRA, Medical Dictionary for Regulatory Activities; NA, not available; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated disease; PT, Preferred Term; TEAE, treatment-emergent adverse event.

FIGURE 1 Changes from baseline to Week 24 in CRSwNP disease control and symptom burden in patients with CRSwNP with and without NSAID-ERD, as assessed by (A) nasal polyp score (NPS), (B) patient-assessed symptom severity score for nasal congestion or obstruction (NC), (C) Lund–Mackay computed tomography (LMK-CT) score, (D) 22-item Sinonasal Outcome Test (SNOT-22) score, (E) patient-reported Total Symptom Score (TSS), (F) visual analog scale (VAS) for rhinosinusitis, (G) University of Pennsylvania Smell Identification Test (UPSIT) score, (H) loss of smell score, and (I) 22-item Sinonasal Outcome Test (SNOT-22) smell/taste item score.

***Nominal $P < .0001$ vs placebo.

BL, baseline; CRSwNP, chronic rhinosinusitis with nasal polyps; LS, least square; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated disease; q2w, every 2 weeks; SE, standard error.

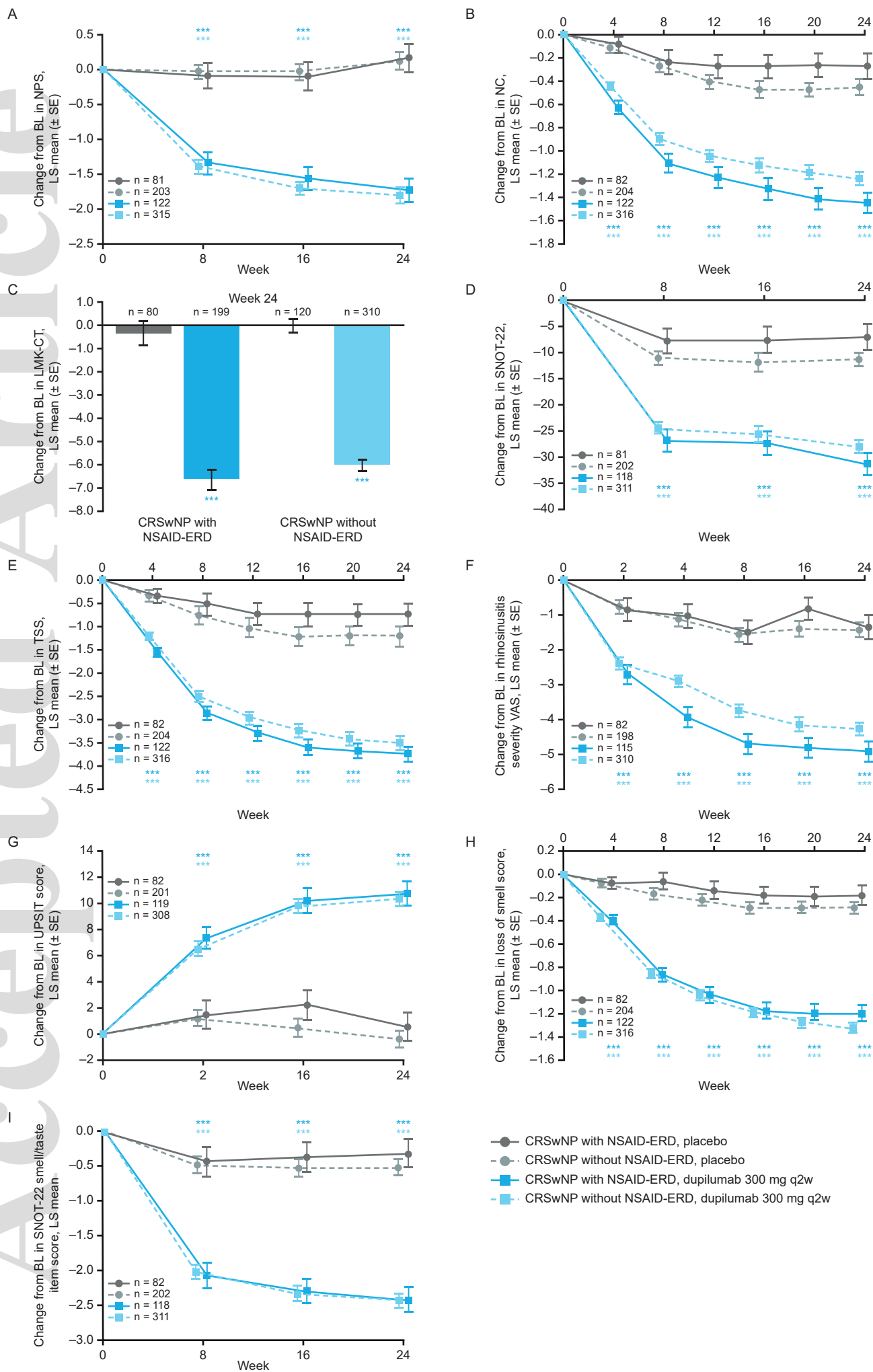
FIGURE 2 Kaplan–Meier analysis of time to first (A) systemic corticosteroids (SCS) use and (B) nasal polyp (NP) surgery in patients with CRSwNP with and without NSAID-ERD.

CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; HR, hazard ratio; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated disease; q2w, every 2 weeks.

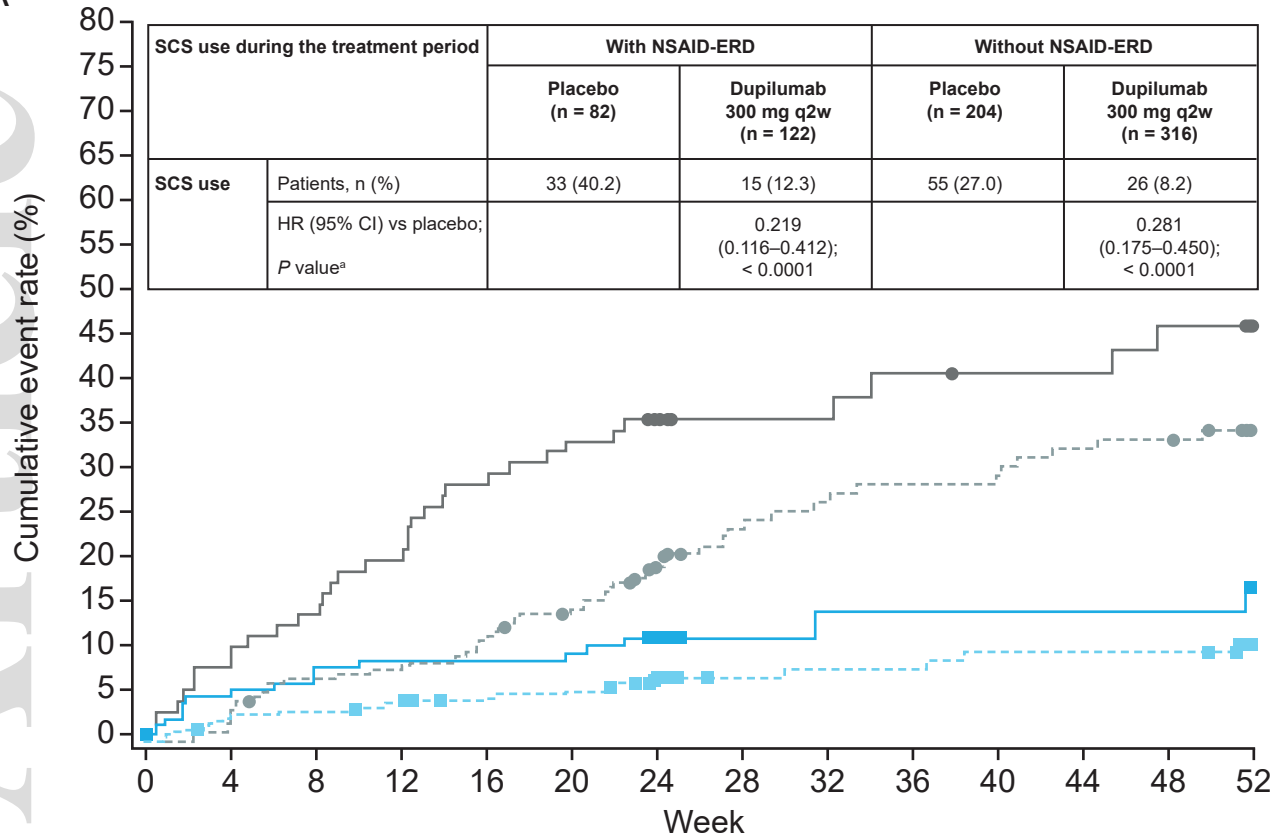
FIGURE 3 Changes from baseline to Week 24 in airway function and asthma control in patients with CRSwNP with and without NSAID-ERD, as assessed by (A) peak nasal inspiratory flow (PNIF), (B) forced expiratory volume in 1 second (FEV_1), and (C) 6-item Asthma Control Questionnaire (ACQ-6) score. Asthma-specific endpoints (FEV_1 and ACQ-6) were measured only in patients with a recorded history of asthma.

Nominal $P = .001$, *Nominal $P < .0001$ vs placebo.

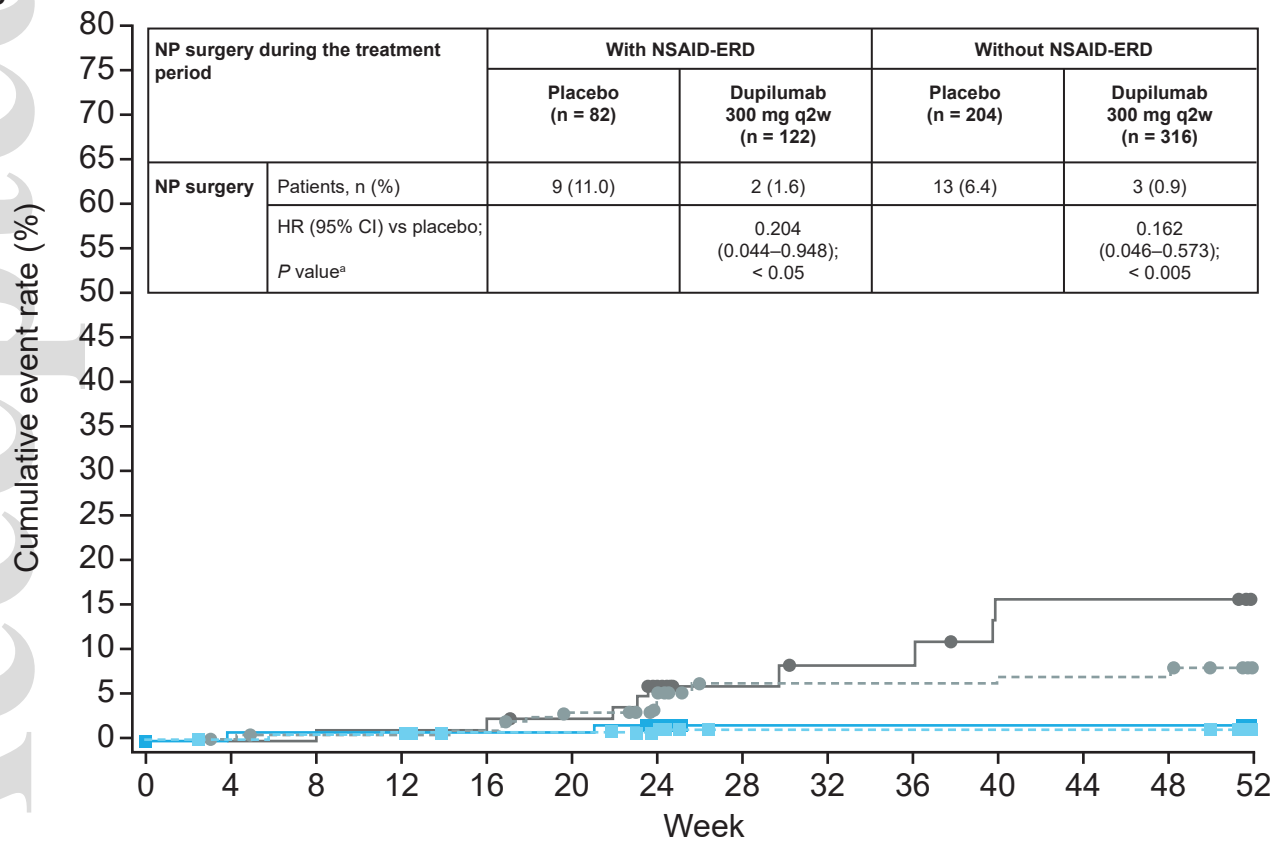
BL, baseline; CRSwNP, chronic rhinosinusitis with nasal polyps; LS, least square; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated disease; q2w, every 2 weeks; SE, standard error.



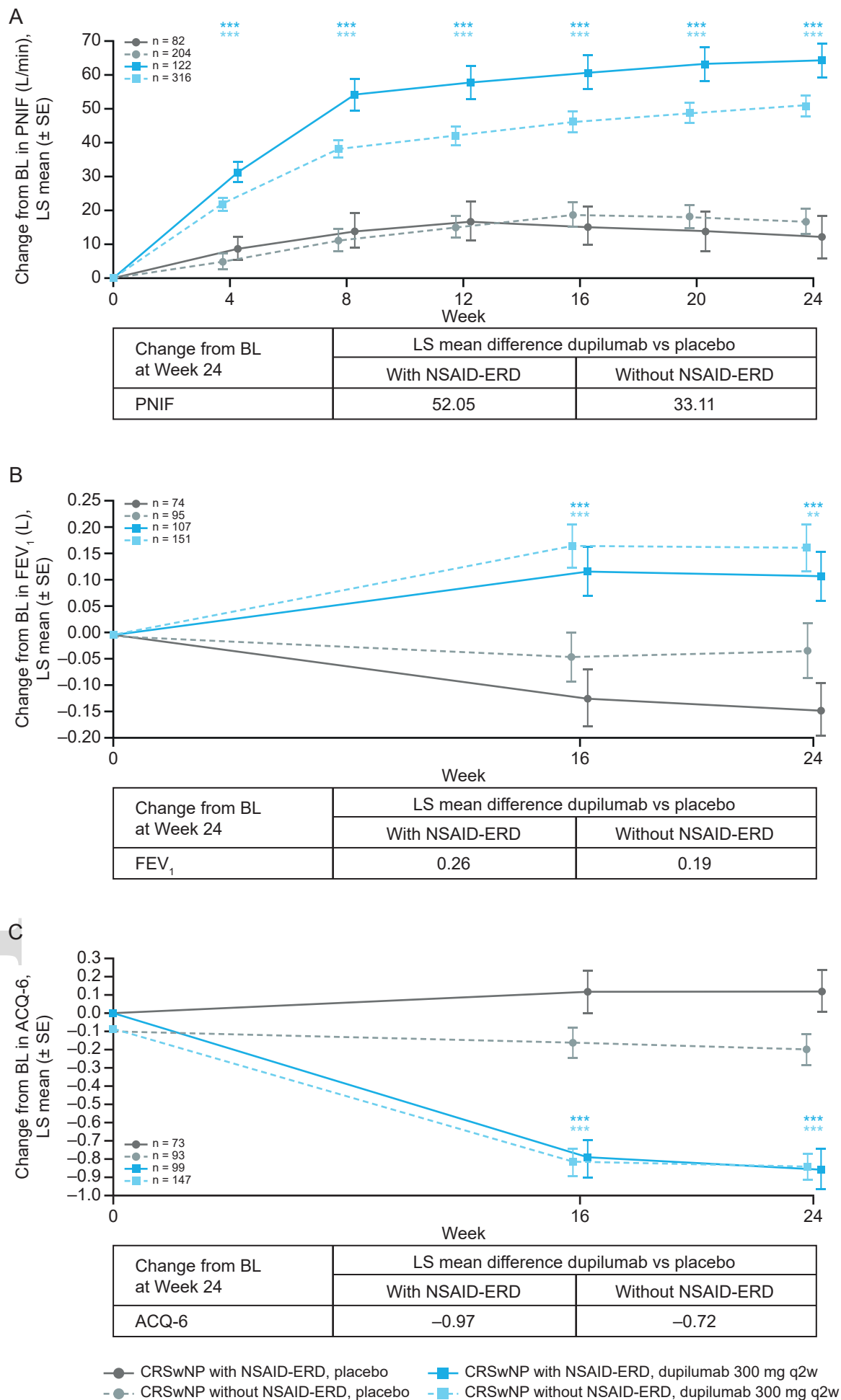
A



B



- CRSwNP with NSAID-ERD, placebo
- CRSwNP without NSAID-ERD, placebo
- CRSwNP with NSAID-ERD, dupilumab 300 mg q2w
- CRSwNP without NSAID-ERD, dupilumab 300 mg q2w



SUPPLEMENTARY MATERIALS

SUPPLEMENTARY METHODS

Statistical methods

For this subgroup analysis, data in the intent-to-treat (ITT; all patients randomly assigned to treatment) populations from SINUS-24 and SINUS-52 were pooled. Imputed complete data were analyzed by fitting an analysis of covariance (ANCOVA) model, with the change from baseline as the response, and corresponding baseline value, treatment group, prior surgery history, region, study indicator, NSAID-ERD history, and NSAID-ERD history-by-treatment interaction as covariates. The results from models of all imputed data were combined using Rubin's rule, and a *P*-value for the test of interaction was provided based on the combined inference. For the Kaplan–Meier estimates of time to SCS use and NP surgery, hazard ratios (HRs) were derived from a Cox proportional-hazard model, with the event of first NP surgery (actual or planned, whichever was earlier) as the response variable, and treatment, prior surgery history, region (pooled by country), and study indicator as covariates. For all endpoints, *P*-values presented in this paper are nominal and not adjusted for multiplicity. The chi-square test was used for treatment effect comparisons (dupilumab vs placebo) on improvement in anosmia (UPSIT ≤ 18) at Week 24. Percentage change from baseline at Week 24 in biomarkers was compared using the Wilcoxon rank sum test.

SUPPLEMENTARY TABLE 1 Patient eligibility criteria for SINUS-24 and SINUS-52 (adapted from the primary publication.¹

Key inclusion criteria:
• ≥18 years of age
• CRSwNP
• Prior treatment with systemic glucocorticoids within the last 2 years (or a medical contraindication or intolerance to systemic glucocorticoids), prior surgery for nasal polyps, or both
• Endoscopic bilateral nasal polyp score of ≥5 (out of 8), with a score of ≥2 in each nasal cavity
• Ongoing symptoms for ≥8 weeks prior to study entry, including: – Nasal congestion, blockage, or obstruction with moderate or severe symptom severity (score 2 or 3) and a weekly average severity score of ≥1 (range 0 to 3) at randomization – At least one other symptom, such as partial loss of smell (hyposmia), total loss of smell (anosmia), or anterior or posterior rhinorrhea
• Patients with concomitant asthma had to be stable in the previous 6 weeks using their regular asthma treatment
Key exclusion criteria:
• Previous participation in a dupilumab study
• Received biologic therapy/systemic immunosuppressant to treat inflammatory or autoimmune disease within 2 months of study entry or 5 half-lives, whichever is longer
• Received experimental monoclonal antibody treatment within 5 half-lives or 6 months of study entry
• Received anti-IgE therapy within 130 days prior to study entry
• Received leukotriene antagonist/modifier treatment unless continuous treatment was received ≥30 days prior to study entry
• Any sinus intranasal surgery (including nasal polypectomy) within 6 months before Visit 1
• Patients with FEV₁ ≤50% of predicted normal (comorbid asthma patients)
• Presence of antrochoanal nasal polyps; acute rhinosinusitis; upper respiratory infection; allergic granulomatous angiitis/eosinophilic granulomatosis with polyangiitis; granulomatosis with polyangiitis; cystic fibrosis; fungal rhinosinusitis; Young syndrome; Kartagener syndrome; or dyskinetic cilia syndrome

CRSwNP, chronic rhinosinusitis with nasal polyps; FEV₁, forced expiratory volume in 1 second; IgE, immunoglobulin E.

SUPPLEMENTARY TABLE 2 Counts for each response to the two questions of the NSAID-ERD diagnosis questionnaire in the randomized population of the pooled SINUS-24 and SINUS-52 studies.

Patient response	Placebo q2w (n = 286)	Dupilumab 300 mg q2w/q2w–q4w (n = 438)	All (n = 724)
Question 1: <i>Have you ever had respiratory, nasal and/or bronchial symptoms following the intake of aspirin or/and NSAID?</i>			
No symptoms from aspirin or NSAID	144 (50.3%)	211 (48.2%)	355 (49.0%)
Does not take aspirin or NSAID	61 (21.3%)	105 (24.0%)	166 (22.9%)
Yes; only to one drug	30 (10.5%)	46 (10.5%)	76 (10.5%)
Yes; to 2 or more drugs	51 (17.8%)	76 (17.4%)	127 (17.5%)
Question 2: <i>While having a positive clinical history of NSAID-ERD, have you ever undergone an aspirin provocation test, either nasal, bronchial, or oral?</i>			
No test	135 (47.2%)	179 (40.9%)	314 (43.4%)
Yes; negative result	1 (0.3%)	3 (0.7%)	4 (0.6%)
Yes; positive result	9 (3.1%)	17 (3.9%)	26 (3.6%)
NSAID-ERD status			
Q1 Yes or Q2 Positive	82 (28.7%)	122 (27.9%)	204 (28.2%)

SUPPLEMENTARY TABLE 3 Treatment effect comparisons for improvement in anosmia (UPSIT $\leq$ 18) at Week 24 in patients with CRSwNP with and without NSAID-ERD (SINUS-24 and SINUS-52 pooled).

Anosmia category	CRSwNP patients with NSAID-ERD		CRSwNP patients without NSAID-ERD	
	Placebo (n = 82)	Dupilumab 300 mg q2w (n = 122)	Placebo (n = 204)	Dupilumab 300 mg q2w (n = 316)
Baseline				
Number	82	119	201	308
UPSIT ≤ 18, n (%)	74 (90.2)	104 (87.4)	145 (72.1)	228 (74.0)
UPSIT > 18, n (%)	8 (9.8)	15 (12.6)	56 (27.9)	80 (26.0)
P-value [†]	.5329		.6382	
Week 24				
Number	82	118	193	300
UPSIT ≤ 18, n (%)	73 (89.0)	47 (39.8)	139 (72.0)	70 (23.3)
UPSIT > 18, n (%)	9 (11.0)	71 (60.2)	54 (28.0)	230 (76.7)
P-value [†]	< .0001		< .0001	

[†]Dupilumab vs placebo using chi-square test.

CRSwNP, chronic rhinosinusitis with nasal polyps; NSAID-ERD, non-steroidal anti-inflammatory

drug-exacerbated disease; q2w, every 2 weeks; UPSIT, University of Pennsylvania Smell Identification Test.

SUPPLEMENTARY TABLE 4 Proportion of patients with UPSIT > 18 at Week 24 in patients with CRSwNP with and without NSAID-ERD and UPSIT ≤ 18 at baseline (SINUS-24 and SINUS-52 pooled).

	CRSwNP patients with NSAID-ERD and UPSIT ≤ 18 at baseline (n = 178)	CRSwNP patients without NSAID-ERD and UPSIT ≤ 18 at baseline (n = 373)
UPSIT > 18 at Week 24, n (%)	63 (35.4)	164 (44.0)
UPSIT ≤ 18 at Week 24, n (%)	115 (64.6)	209 (56.0)
<i>P</i> -value [†]	.1133	

[†]Cochran–Mantel–Haenszel test was performed on the association between the responder status and comparing group (without NSAID-ERD vs with NSAID-ERD), stratified by prior surgery history, region, and study indicator (SINUS-52 = 0 and SINUS-24 = 1).

CRSwNP, chronic rhinosinusitis with nasal polyps; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated disease; UPSIT, University of Pennsylvania Smell Identification Test.

SUPPLEMENTARY TABLE 5 Change from baseline to Week 24 in biomarkers in patients with CRSwNP and with and without NSAID-ERD (evaluated in SINUS-52 only).

	CRSwNP patients with NSAID-ERD		CRSwNP patients without NSAID-ERD	
	Placebo (n = 44)	Dupilumab 300 mg q2w (n = 76)	Placebo (n = 106)	Dupilumab 300 mg q2w (n = 221)
Plasma eotaxin-3, pg/mL				
BL, median (95% CI)	72.65 (51.30, 85.60)	76.20 (64.40, 88.40)	59.40 (51.00, 66.60)	59.40 (53.80, 66.80)
% change from BL at Week 24, median (95% CI)	−1.68 (−16.58, 27.24)	−58.67 (−64.11, −51.45)	−6.51 (−14.93, 11.81)	−46.60 (−50.86, −41.70)
<i>P</i> -value vs placebo [†]	< .0001		< .0001	
Serum periostin, ng/mL				
BL, median (95% CI)	124.00 (99.60, 139.00)	112.00 (99.60, 136.00)	99.90 (86.70, 110.00)	96.20 (86.30, 102.00)
% change from BL at Week 24, median (95% CI)	4.93 (−5.56, 15.05)	−38.36 (−44.36, −30.32)	−0.40 (−6.13, 4.58)	−27.11 (−31.58, −20.75)
<i>P</i> -value vs placebo [†]	< .0001		< .0001	
Serum TARC, pg/mL				
BL, median (95% CI)	285.00 (227.00, 368.00)	282.00 (255.00, 326.00)	310.00 (262.00, 366.00)	305.00 (268.00, 328.00)
% change from BL at Week 24, median (95% CI)	−2.29 (−10.96, 7.96)	−41.50 (−44.36, −33.33)	−0.84 (−5.43, 5.93)	−38.52 (−41.44, −34.95)
<i>P</i> -value vs placebo [†]	< .0001		< .0001	
Nasal secretion eotaxin-3, pg/mL				
BL, median (95% CI)	14.80 (6.35, 349.00)	51.60 (16.70, 113.00)	10.40 (7.90, 24.90)	19.40 (8.27, 35.40)
% change from BL	−65.84	−95.26	0.00	−93.72

at Week 24, median (95% CI)	(−79.08, 159.86)	(−98.37, −88.04)	(−48.15, 79.26)	(−95.69, −83.62)
<i>P</i> -value vs placebo [†]	.0012		< .0001	
Nasal secretion total IgE, IU/mL				
BL, median (95% CI)	6.00 (4.00, 34.00)	17.00 (5.00, 47.00)	4.00 (4.00, 23.00)	5.00 (4.00, 9.00)
% change from BL at Week 24, median (95% CI)	−20.00 (−50.00, 25.00)	−70.83 (−92.31, −16.67)	0.00 (−25.00, 66.67)	−18.33 (−50.00, 0.00)
<i>P</i> -value vs placebo [†]	.0609		.0176	
Nasal ECP, ng/mL				
BL, median (95% CI)	26.5 (11.0, 200.0)	36.5 (24.0, 83.0)	24.0 (10.0, 47.0)	25.0 (9.0, 43.0)
% change from BL at Week 24, median (95% CI)	0.00 (−79.66, 200.00)	−70.59 (−83.33, −5.26)	−16.67 (−50.00, 62.50)	−35.29 (−73.00, 0.00)
<i>P</i> -value vs placebo [†]	.1655		.2057	

[†]Wilcoxon rank sum test comparing dupilumab vs placebo.

BL, baseline; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; ECP, eosinophil cationic protein; IgE, immunoglobulin E; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated disease; q2w, every 2 weeks; TARC, thymus and activation-regulated chemokine.

SUPPLEMENTARY TABLE 6 Change from baseline to Week 24 in biomarkers in patients with CRSwNP with and without NSAID-ERD (SINUS-24 and SINUS-52 pooled).

	CRSwNP patients with NSAID-ERD		CRSwNP patients without NSAID-ERD	
	Placebo (n = 82)	Dupilumab 300 mg q2w (n = 121)	Placebo (n = 200)	Dupilumab 300 mg q2w (n = 319)
Serum total IgE, IU/mL				
BL, median (95% CI)	153.00 (115.00, 210.00)	120.00 (98.00, 160.00)	120.00 (96.00, 150.00)	113.50 (95.00, 133.00)
% change from BL at Week 24, median (95% CI)	−1.22 (−8.82, 3.03)	−59.60 (−63.64, −56.20)	0.00 (−5.88, 4.57)	−54.96 (−57.78, −52.82)
<i>P</i> -value vs placebo [†]	< .0001		< .0001	
Blood eosinophils, Giga/L				
BL, median (95% CI)	0.39 (0.34, 0.44)	0.34 (0.31, 0.44)	0.34 (0.30, 0.39)	0.34 (0.29, 0.37)
% change from BL at Week 24, median (95% CI)	16.11 (0.00, 30.30)	40.00 (11.11, 66.67)	6.35 (−2.17, 20.00)	−3.92 (−13.12, 10.71)
<i>P</i> -value vs placebo [†]	.1116		.3181	
Urinary LTE ₄ , pg/mL				
BL, median (95% CI)	182.00 (117.00, 286.00)	242.00 (180.00, 364.00)	76.80 (66.00, 95.10)	88.90 (71.20, 99.50)
% change from BL at Week 24, median (95% CI)	−3.54 (−29.98, 9.35)	−76.18 (−80.83, −67.52)	8.18 (−10.04, 27.98)	−37.19 (−43.73, −25.60)
<i>P</i> -value vs placebo [†]	< .0001		< .0001	

[†]Wilcoxon rank sum test comparing dupilumab vs placebo.

BL, baseline; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; IgE, immunoglobulin E; LTE₄, leukotriene E₄; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated disease; q2w, every 2 weeks.

SUPPLEMENTARY MATERIALS – REFERENCES

1. Bachert C, Han JK, Desrosiers M, et al. 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. *Lancet*. 2019;394(10209):1638–1650