Dupilumab in chronic rhinosinusitis without nasal polyps: randomized phase 2 trial (ORION)

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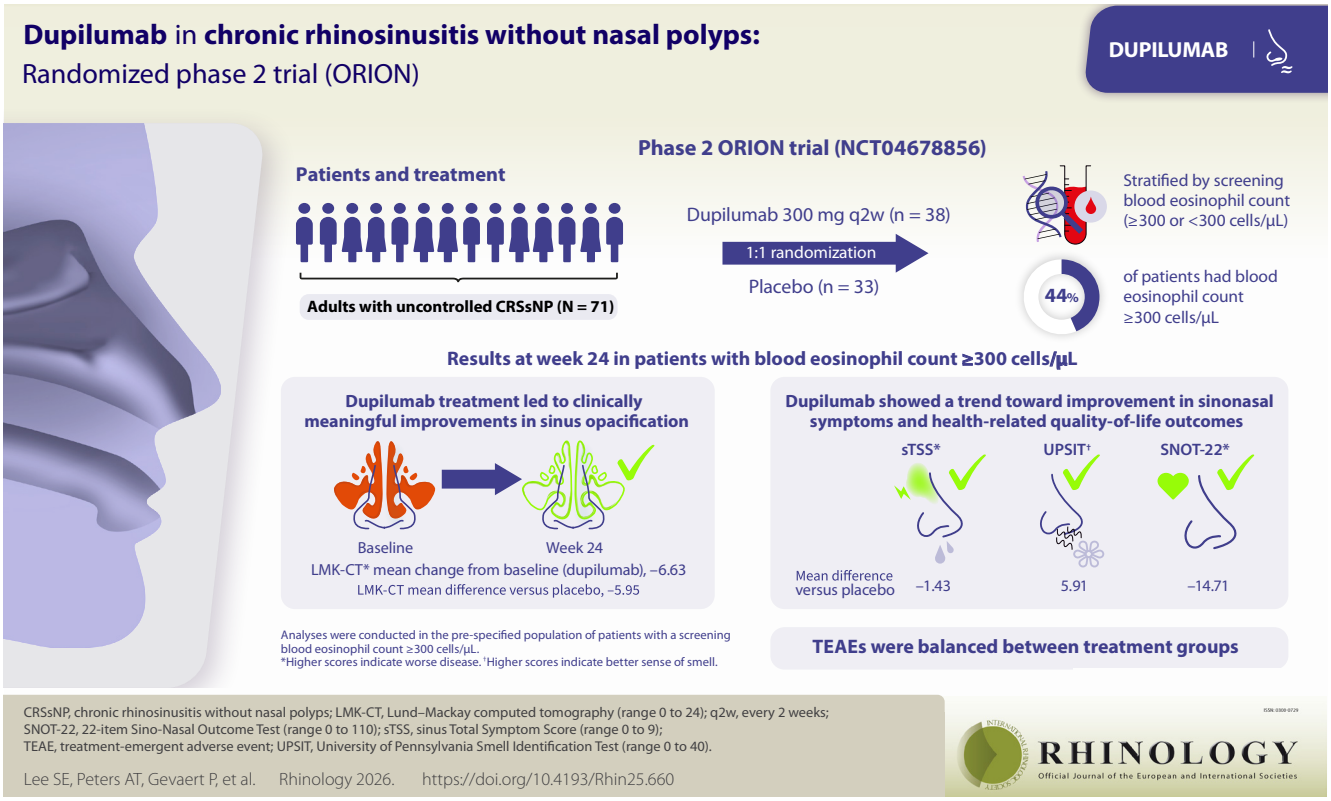

Abstract

Background: Chronic rhinosinusitis (CRS) is often driven by type 2 inflammation and is characterized by nasal obstruction/discharge, facial pain/pressure, and/or reduced smell, either with or without nasal polyps (CRSwNP or CRSsNP). **Objective**: To test whether dupilumab improves radiographic features in CRSsNP. **Methods**: ORION (NCT04678856), a phase 2, randomized, multicenter, double blind, placebo-controlled study, assessed dupilumab efficacy and safety in adults with uncontrolled CRSsNP. Patients were randomized 1:1 to dupilumab or placebo for 24 to 52 weeks. Endpoints included changes from baseline at week 24 in Lund–Mackay computed tomography (LMK-CT) score (dupilumab only [primary] and vs placebo [secondary]), sinus Total Symptom Score (sTSS), University of Pennsylvania Smell Identification Test (UPSIT) score, and 22-item Sino-Nasal Outcome Test (SNOT-22) score. Primary analysis was conducted in the intention-to-treat population with screening blood eosinophil count (sBEC) ≥300 cells/µL. Safety data were evaluated in all patients. **Results**: Seventy-one patients were randomized (dupilumab, n = 38; placebo, n = 33). In the dupilumab group with sBEC ≥300 cells/µL (n = 16), mean (95% CI) week 24 change from baseline in LMK-CT was -6.63 (-8.71 to -4.54); week 24 mean differences vs placebo (95% CI) for LMK-CT, sTSS, UPSIT, and SNOT-22 were -5.95 (-8.38 to -3.51), -1.43 (3.28 to 0.41), 5.91 (-1.56 to 13.38), and -14.71 (-34.35 to 4.94). Treatment-emergent adverse events were balanced between treatment groups. **Conclusion**: Dupilumab was associated with improvement in LMK-CT score and a trend toward improvement in sinonasal symptoms at week 24 in adults with severe, uncontrolled CRSsNP with sBEC ≥300 cells/µL.

Key words: chronic rhinosinusitis without nasal polyps, dupilumab, Lund–Mackay computed tomography, type 2 inflammation

Introduction

Chronic rhinosinusitis (CRS) without nasal polyps (CRSsNP) is a subtype of CRS [1] with a prevalence of 4 to 6% in adults [2,3] and an incidence in US children, adolescents, and adults of approximately 1048 cases per 100,000 person-years [4]. CRSsNP comprises approximately 80% of CRS cases, typically presenting with rhinorrhea and facial pain and/or pressure [1,5]. Around one-third of CRSsNP patients exhibits a predominantly type 2 (T2) inflammatory endotype [6,7] resembling CRS with nasal polyps (CRSwNP), with elevated levels of interleukin (IL)-4, IL-5, IL-13, and immunoglobulin E (IgE) [8-12]. These patients may have eosinophilic nasal mucosa and high blood eosinophil counts [13]. Patients with CRSsNP and tissue eosinophilia have greater disease severity and less improvement in quality-of-life following sinonasal surgery [14-16].

Approximately 25% of patients with CRSsNP undergo surgical intervention due to inadequately controlled symptoms, despite appropriate medical therapy including intranasal corticosteroids (INCS), systemic corticosteroids (SCS), and antibiotics [17,18]. Furthermore, 24 to 36% of patients with CRSsNP have coexisting asthma [5,13], which is known to increase the risk of recurrent sinonasal surgery [19]. The chronic, refractory nature of CRS contributes to its socioeconomic burden, including direct diagnostic and therapeutic costs, diminished productivity, and negative effects on physical and mental wellbeing [20-25].

Dupilumab, a fully human monoclonal antibody, inhibits both IL-4 and IL-13 signaling pathways, which are key and central drivers of T2 inflammation [26]. It is approved for nine indications, including as an add-on maintenance treatment in patients aged ≥12 years with inadequately controlled CRSwNP [27]. The ORION study aimed to assess dupilumab efficacy and safety in adult patients with uncontrolled CRSsNP, stratified by blood eosinophil count, as a systemic indicator of T2 inflammatory phenotype [28-32].

Materials and methods

Study design

Liberty ORION (NCT04678856) was a phase 2, multicenter, randomized, double blind, placebo-controlled study assessing the safety and efficacy of dupilumab in adults with uncontrolled CRSsNP. Following a 2- to 4-week screening period, patients were randomized 1:1 to dupilumab 300 mg every 2 weeks (q2w) or placebo for a treatment period of 24 to 52 weeks depending on the time of enrollment (Supplementary Material), and a post-treatment follow-up period of 12 weeks. Stratification factors included screening blood eosinophil count (sBEC; ≥300 cells/μL or <300 cells/μL), background INCS use, and global region.

Patients

Eligible patients were ≥18 years old with bilateral inflammation of the paranasal sinuses, Lund–Mackay computed tomography (LMK-CT) score ≥8, bilateral ethmoid opacification, and persistent symptoms of loss of smell and rhinorrhea, nasal congestion/obstruction, and facial pain/pressure. The LMK-CT score quantifies sinus opacification by grading the anterior ethmoid, posterior ethmoid, maxillary, frontal, and sphenoid sinuses, and each ostiomeatal complex; scores range from 0 to 24, with higher values indicating more extensive opacification [33]. Patients additionally had to have undergone prior sinonasal surgery for CRS, received SCS therapy for CRS within the prior 2 years, or have an intolerance/contraindication to SCS (Table S1).

Study endpoints

Endpoints were evaluated in the subgroup of patients with sBEC ≥300 cells/μL, those with sBEC <300 cells/μL, and the overall population. The primary endpoint was the change from baseline to week 24 in LMK-CT score in patients in the dupilumab arm with sBEC ≥300 cells/μL. In February 2023, the protocol was amended, changing the primary endpoint from sinus Total Symptom Score (sTSS) to the radiographic LMK-CT score, with sTSS reclassified as a secondary endpoint. The threshold LMK-CT minimal clinically important difference (MCID) score was defined as 4.95 points [34]. Secondary endpoints included change from baseline to week 24 in LMK-CT score in the dupilumab vs placebo arms, change from baseline to week 24 in sTSS, safety (treatment-emergent adverse events [TEAEs] and serious TEAEs), and pharmacokinetics (PK) (systemic concentration) and immunogenicity (formation of anti-drug antibodies [ADAs] and neutralizing antibodies) of dupilumab. sTSS is a composite score assessing nasal congestion (NC), anterior/posterior rhinorrhea, and facial pain/pressure, using a scale of 0 to 9, with a higher score indicating greater symptoms. Exploratory endpoints included change from baseline to week 24 in 22-item Sino Nasal Outcome Test (SNOT-22) score, University of Pennsylvania Smell Identification Test (UPSIT) score, three-dimensional computed tomography (CT) volumetric assessment of paranasal sinuses, NC symptom severity score, rhinorrhea severity score, facial pain/pressure severity score, loss of smell symptom severity score, rhinosinusitis severity visual analog scale (VAS), VAS for the European Quality of Life 5 Dimensions 5 Level Version (EQ-5D-5L), EQ-5D-5L single index score, Patient Global Impression of Change (PGIC), Patient Global Impression of Severity (PGIS), forced expiratory volume in 1 second (FEV_1), 6-item Asthma Control Questionnaire (ACQ-6) score, healthcare resource utilization, and analyses of biomarkers (serum total IgE, blood eosinophils, plasma eotaxin-3, serum periostin, and serum thymus and activation-regulated chemokine [TARC] levels) (Table S1) [35]. The MCID in SNOT-22 was defined as a decrease of ≥8.9 points [36], while the MCID in UPSIT was considered as a ≥4 points increase [37].

Changes in LMK-CT score, three-dimensional CT volumetric measurement of the sinuses, scores on sinonasal symptom measures, and UPSIT score were evaluated in the subgroup of

Table 1. Baseline characteristics—randomized population.

Characteristic	Screening blood eosinophil count ≥300 cells/μL			Screening blood eosinophil count <300 cells/μL			All patients		
	Placebo (n = 15)	Dupilumab 300 mg q2w (n = 16)	All (n = 31)	Placebo (n = 18)	Dupilumab 300 mg q2w (n = 22)	All (n = 40)	Placebo (n = 33)	Dupilumab 300 mg q2w (n = 38)	All (n = 71)
Age, years, mean (SD)	44.87 (18.07)	43.00 (12.32)	43.90 (15.14)	49.61 (17.15)	48.95 (12.47)	49.25 (14.56)	47.45 (17.46)	46.45 (12.60)	46.92 (14.95)
Sex, n (%)									
Female	8 (53.3)	11 (68.8)	19 (61.3)	8 (44.4)	14 (63.6)	22 (55.0)	16 (48.5)	25 (65.8)	41 (57.7)
Region*, n (%)									
Asia	1 (6.7)	1 (6.3)	2 (6.5)	2 (11.1)	4 (18.2)	6 (15.0)	3 (9.1)	5 (13.2)	8 (11.3)
Latin America	2 (13.3)	2 (12.5)	4 (12.9)	0	3 (13.6)	3 (7.5)	2 (6.1)	5 (13.2)	7 (9.9)
East Europe	3 (20.0)	5 (31.3)	8 (25.8)	5 (27.8)	6 (27.3)	11 (27.5)	8 (24.2)	11 (28.9)	19 (26.8)
Western countries	9 (60.0)	8 (50.0)	17 (54.8)	11 (61.1)	9 (40.9)	20 (50.0)	20 (60.6)	17 (44.7)	37 (52.1)
Race, n (%)									
White	14 (93.3)	13 (81.3)	27 (87.1)	16 (88.9)	18 (81.8)	34 (85.0)	30 (90.9)	31 (81.6)	61 (85.9)
Black or African American	0	1 (6.3)	1 (3.2)	0	0	0	0	1 (2.6)	1 (1.4)
Asian	1 (6.7)	1 (6.3)	2 (6.5)	2 (11.1)	4 (18.2)	6 (15.0)	3 (9.1)	5 (13.2)	8 (11.3)
Not reported	0	1 (6.3)	1 (3.2)	0	0	0	0	1 (2.6)	1 (1.4)
Ethnicity, n (%)									
Hispanic or Latino	1 (6.7)	1 (6.3)	2 (6.5)	1 (5.6)	4 (18.2)	5 (12.5)	2 (6.1)	5 (13.2)	7 (9.9)
Non-Hispanic or Latino	13 (86.7)	13 (81.3)	26 (83.9)	17 (94.4)	18 (81.8)	35 (87.5)	30 (90.9)	31 (81.6)	61 (85.9)
Baseline weight, kg, mean (SD)	80.31 (20.65)	73.26 (15.49)	76.67 (18.21)	76.07 (12.48)	70.69 (14.39)	73.11 (13.67)	77.99 (16.55)	71.77 (14.71)	74.66 (15.79)
Baseline BMI, kg/m^2, mean (SD)	28.52 (7.13)	26.42 (5.38)	27.44 (6.27)	27.56 (4.35)	26.09 (5.26)	26.75 (4.87)	28.00 (5.71)	26.23 (5.24)	27.05 (5.49)
Time since first diagnosis of CRSsNP, years, mean (SD)	7.41 (7.89)	7.32 (9.01)	7.37 (8.32)	11.53 (9.20)	10.15 (7.88)	10.77 (8.41)	9.66 (8.75)	9.00 (8.35)	9.31 (8.49)
Number of patients with comorbid asthma, n (%)	8 (53.3)	9 (56.3)	17 (54.8)	9 (50.0)	8 (36.4)	17 (42.5)	17 (51.5)	17 (44.7)	34 (47.9)
Number of prior sinonasal surgeries, mean (SD)	1.0 (0.0)	2.0 (1.7)	1.4 (1.2)	1.3 (0.7)	1.4 (0.8)	1.4 (0.7)	1.2 (0.5)	1.7 (1.2)	1.4 (0.9)
Time since most recent sinonasal surgery, years, mean (SD)	5.37 (5.81)	1.73 (1.07)	3.85 (4.73)	5.77 (6.38)	3.26 (2.25)	4.67 (5.04)	5.59 (5.94)	2.63 (1.95)	4.32 (4.83)
Background INCS use, n (%)	12 (80.0)	12 (75.0)	24 (77.4)	12 (66.7)	18 (81.8)	30 (75.0)	24 (72.7)	30 (78.9)	54 (76.1)
Baseline LMK-CT score, mean (SD)	11.73 (3.51)	11.28 (3.37)	11.50 (3.39)	11.31 (2.98)	11.50 (3.99)	11.41 (3.53)	11.50 (3.19)	11.41 (3.69)	11.45 (3.44)
Baseline sTSS, mean (SD)	7.45 (1.21)	7.74 (1.22)	7.60 (1.20)	7.20 (0.93)	7.36 (1.21)	7.29 (1.08)	7.31 (1.06)	7.52 (1.21)	7.42 (1.14)
Baseline nasal congestion/obstruction symptom severity score, mean (SD)	2.69 (0.42)	2.82 (0.29)	2.75 (0.36)	2.59 (0.44)	2.57 (0.43)	2.58 (0.43)	2.63 (0.43)	2.67 (0.40)	2.65 (0.41)
Baseline anterior/posterior rhinorrhea severity score †, mean (SD)	2.54 (0.45)	2.65 (0.36)	2.59 (0.40)	2.43 (0.43)	2.29 (0.53)	2.35 (0.49)	2.48 (0.44)	2.44 (0.49)	2.46 (0.46)
Baseline facial pain/pressure severity score, mean (SD)	2.22 (0.85)	2.27 (0.80)	2.25 (0.81)	2.19 (0.53)	2.50 (0.60)	2.36 (0.58)	2.20 (0.68)	2.41 (0.69)	2.31 (0.69)
Baseline UPSIT score, mean (SD)	24.87 (7.41)	25.69 (9.13)	25.29 (8.21)	20.06 (9.76)	22.73 (9.05)	21.53 (9.35)	22.24 (8.98)	23.97 (9.08)	23.17 (9.01)
Baseline SNOT-22 score, mean (SD)	75.17 (18.32)	79.86 (14.93)	77.69 (16.41)	68.71 (13.39)	69.19 (22.20)	68.97 (18.55)	71.38 (15.65)	73.46 (20.08)	72.52 (18.10)
Baseline 3D CT total volume occupied by disease in all sinuses (%), mean (SD)	55.95 (19.36)	52.63 (16.99)	54.24 (17.95)	52.70 (17.86)	49.71 (19.65)	51.06 (18.68)	54.18 (18.33)	50.94 (18.39)	52.44 (18.31)

patients with sBEC ≥300 cells/μL. Changes in LMK-CT score, scores on sinonasal symptom measures, and UPSIT score were also evaluated in the subgroup of patients with sBEC <300 cells/μL. PK, safety, and biomarkers were analyzed in the total patient population. FEV_1 and ACQ-6 scores were evaluated only in patients with coexisting asthma.

Statistical considerations and protocol modifications

In the initial study protocol (September 2020), the sample size was calculated at 140 patients, with ~100 patients with sBEC ≥300 cells/μL. However, due to difficulties in recruitment due to the COVID-19 pandemic and geopolitical conflicts, the protocol was amended in February 2023 to reduce the target patient population, modify endpoints, and amend the study from a two-part phase 2/3 study to a single-part phase 2 study. An alternative size calculation was conducted to ensure sufficient accuracy for estimating the primary endpoint in patients with sBEC ≥300 cells/μL. With a 1:1 randomization ratio, an assumed standard deviation (SD) of 5 and an estimated 10% dropout rate, approximately 15 patients per arm with sBEC ≥300 cells/μL were targeted to provide a two-sided 95% confidence interval (CI) with a half-width of <3 for the primary endpoint. An additional 20 patients per arm with sBEC <300 cells/μL were planned for inclusion, bringing the total sample size to approximately 35 patients per treatment arm. In the initial protocol, the primary endpoint of change from baseline at week 24 in LMK-CT score was intended to be compared between the dupilumab and placebo groups; however, following the amendment, the reduced sample size did not support adequate power for the placebo comparison. Therefore, no statistical hypotheses were tested. Efficacy analyses were conducted on the intention-to-treat (ITT) population in patients with sBEC ≥300 cells/μL and are shown; efficacy data for other populations are available in the Supplementary Material.

Data collected after sinonasal surgery or SCS treatment were excluded. The worst post baseline value on or before the time of surgery or SCS treatment was used to assign week 24 or week 52 value. Missing data were not imputed. Descriptive statistics along with the 95% CI of the mean for the dupilumab group are presented for the primary endpoint. Secondary and exploratory endpoints were analyzed using the same methodology. Mean treatment differences (95% CI) between dupilumab and placebo groups are presented. Safety analyses were conducted on all treated patients.

The full study protocol (number NCT04678856) is available at: https://cdn.clinicaltrials.gov/large-docs/56/NCT04678856/Prot_000.pdf.

Ethical approval

This study was conducted according to the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines for Good Clinical Practice, and all applicable laws, rules, and regulations. The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (e.g. advertisements) were submitted to an institutional review board/independent ethics committee by the Investigators and were reviewed and approved before study initiation. This includes Commissie voor Medische Ethiek-Universitair Ziekenhuis in Gent, Belgium (study's global principal investigator, Dr. Philippe Gevaert's ethics committee) and institutional review boards/independent ethics committees of study sites screening participants (Table S2). Signed informed consent was obtained from all patients taking part in the study.

Results

Baseline demographics and characteristics

From December 2, 2020, to May 22, 2023, 269 adult patients were screened, and 71 randomized (dupilumab: 38, placebo: 33) (Figure S1). Forty-one (57.7%) patients were female. Of the randomized patients, 31 (43.7%) had sBEC ≥300 cells/μL; 16 (22.5%) in the dupilumab group, 15 (21.1%) in the placebo group (Figure S1). Overall, 34 (89.5%) patients in dupilumab group completed the 52-week treatment period, compared with 24 (72.7%) patients in the placebo group. Baseline demographics and disease characteristics were balanced across treatment groups and consistent with a population of patients with inadequately controlled CRSsNP (Table 1; Table S3).

Endpoints in patients with screening blood eosinophil count ≥300 cells/μL

LMK-CT score

For patients with sBEC ≥300 cells/μL, treatment with dupilumab led to a clinically meaningful reduction in sinus opacification,

Table 1 *legend*. 3D, three-dimensional; BMI, body mass index; CRSsNP, chronic rhinosinusitis without nasal polyps; CT, computed tomography; INCS, intranasal corticosteroids; LMK-CT, Lund–Mackay computed tomography; q2w, every 2 weeks; SD, standard deviation; SNOT-22, 22-item Sino-Nasal Outcome Test; sTSS, sinus Total Symptom Score; UPSIT, University of Pennsylvania Smell Identification Test. *Asia: China, South Korea; Latin America: Argentina, Chile; East Europe: Hungary, Russia, Ukraine; Western countries: Belgium, Canada, Portugal, Spain, Sweden, United States. †Average of anterior and posterior rhinorrhea scores.

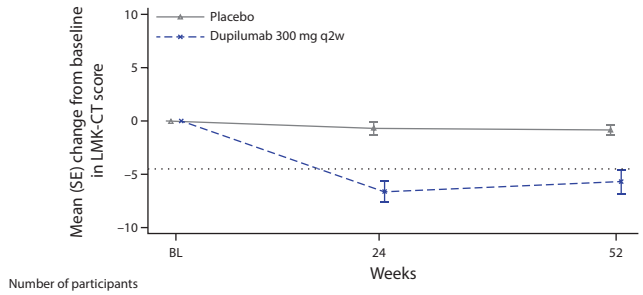

Figure 1. Mean change from baseline in LMK-CT score over time in the ITT population with screening blood eosinophil count ≥300 cells/μL. LMK-CT score range 0 to 24; higher scores indicate greater sinus opacification. The threshold for the MCID in LMK-CT score was defined as 4.95 points [34]. The dotted line indicates the LMK-CT MCID. The number and percentage of patients achieving MCID threshold for LMK-CT are displayed in Table S4. BL, baseline; ITT, intention-to-treat; LMK-CT, Lund–Mackay computed tomography; MCID, minimal clinically important difference; q2w, every 2 weeks; SE, standard error.

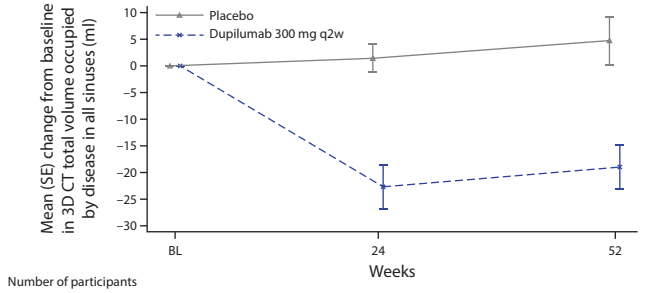

Figure 2. Mean change from baseline in 3D CT total volume occupied by disease in all sinuses over time—ITT population with screening blood eosinophil count ≥300 cells/μL. 3D, three-dimensional; BL, baseline; CT, computed tomography; ITT, intention-to-treat; q2w, every 2 weeks; SE, standard error.

with a mean (SD) change from baseline in LMK-CT score of -6.63 (3.91) (95% CI: -8.71 to -4.54) at week 24 (primary endpoint and -5.71 (3.94) (95% CI: -8.21 to -3.21) at week 52. Following 24 weeks of dupilumab treatment, the mean difference in LMK-CT score vs placebo was -5.95 (95% CI: -8.38 to -3.51) (Figure 1). Baseline and week 24 sinus CT scan images from a patient with sBEC ≥300 cells/μL who responded to dupilumab treatment are shown (Figure S2). The proportion of patients who achieved the MCID in outcomes, where applicable, are given (Table S4).

Three-dimensional volumetric measurement of the sinuses

In patients with sBEC ≥300 cells/μL, treatment with dupilumab led to a reduction in mean three-dimensional CT total volume occupied by disease at week 24 (mean difference vs placebo -24.13 [95% CI: -34.58 to -13.68]), which was sustained through week 52 (mean difference vs placebo -23.68 [95% CI: -36.46 to -10.91]) (Figure 2).

Sinonasal symptom measures

In patients with sBEC ≥300 cells/μL, improvement in sTSS with dupilumab vs placebo was observed as early as week 8, with a mean difference vs placebo of -1.43 (95% CI: -3.28 to 0.41) at week 24 and a mean difference vs placebo of -2.40 (95% CI: -4.65 to -0.15) at week 52 (Figure 3A). Week 24 mean difference vs placebo in NC, facial pain/pressure, and anterior/posterior rhinorrhea (components of sTSS) were -0.64 (95% CI: -1.24 to -0.03), -0.24 (-0.91 to 0.44), and -0.57 (-1.20 to 0.07), respectively (Figure S3).

Among patients with sBEC ≥300 cells/μL, those who received dupilumab had a mean difference vs placebo in SNOT-22 total score of -14.71 (95% CI: -34.35 to 4.94) at week 24 and -25.46 (-47.42 to -3.49) at week 52 (Figure 3B). At week 24, 86.7% of dupilumab-treated patients vs 53.8% in the placebo group had a clinically meaningful improvement in SNOT-22.

Dupilumab treatment was associated with a mean difference vs placebo in UPSIT score of 5.91 (95% CI: -1.56 to 13.38) at week 24 and 3.64 (-5.66 to 12.95) at week 52 (Figure 3C) in patients with sBEC ≥300 cells/μL.

Additional efficacy endpoints

In patients with sBEC ≥300 cells/μL receiving dupilumab, improvements were seen in rhinosinusitis VAS and ACQ-6 scores, with some improvements in other measures (Figure S4, Table S5).

Endpoints in other patient populations

Additional results in patients with sBEC <300 cells/μL, and regardless of sBEC, can be found in the Supplementary Material. Improvements in LMK-CT score and sinonasal symptom measures were observed in patients receiving dupilumab with sBEC <300 cells/μL (Table S6), and improvements in LMK-CT score and sTSS were observed irrespective of sBEC (Table S7).

Biomarkers

In the dupilumab group of the safety population, serum total IgE, periostin, and serum TARC levels decreased at week 24, while blood eosinophils and plasma eotaxin-3 levels remained stable. At week 52, however, all these biomarkers displayed a reduction (Table S8).

PK and immunogenicity

Mean trough dupilumab concentrations increased over time to week 12, reached steady state by week 24, and were sustained at steady-state level throughout week 52 (Figure S5). Immunogenicity results are given (Tables S9 and S10).

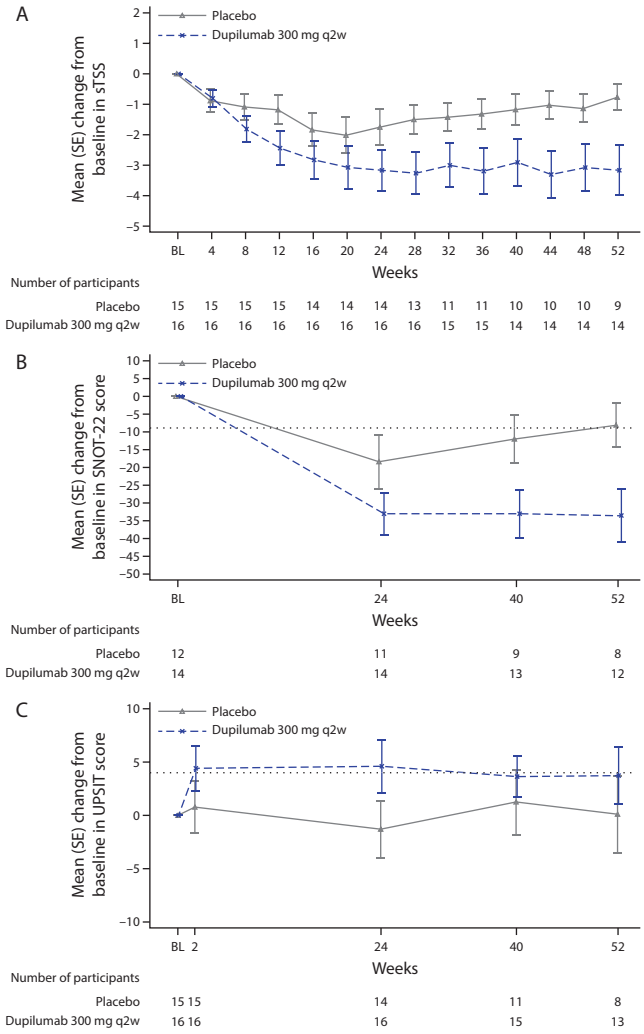

Figure 3. Mean change from baseline in (A) sTSS, (B) SNOT-22 score, and (C) UPSIT score over time in the ITT population with screening blood eosinophil count ≥300 cells/μL. sTSS score range 0 to 9; higher scores indicate greater symptom severity. sTSS is a composite score combining NC, facial pain/pressure, and anterior/posterior rhinorrhea (all range 0 to 3). SNOT-22 score range 0 to 110; higher scores indicate greater rhinosinusitis-related health burden. The clinically meaningful improvement in SNOT-22 was defined as a decrease of ≥8.9 points [36], while for UPSIT was considered as an increase of ≥4 [37]. The dotted lines indicate outcome MCID. The number and percentage of patients achieving MCID threshold for SNOT-22 and for UPSIT are displayed in Table S4. UPSIT score range 0 to 40; lower scores indicate decreased olfaction. BL, baseline; ITT, intention-to-treat; MCID, minimal clinically important difference; NC, nasal congestion; q2w, every 2 weeks; SE, standard error; SNOT-22, 22-item Sino-Nasal Outcome Test; sTSS, sinus Total Symptom Score; UPSIT, University of Pennsylvania Smell Identification Test.

Safety

The incidence of TEAEs was similar between groups. In the dupilumab group, 29 (76.3%) patients had ≥1 TEAE, compared with 27 (81.8%) patients in the placebo group (Table 2). Serious TEAEs were reported in 7.9% of the dupilumab group and 18.2% of the placebo group, none of which were deemed related to the investigational medicinal product by the Investigator (Supplementary Results). The most commonly reported TEAEs occurring in >5% of patients were COVID-19, nasopharyngitis, upper respiratory tract infection, headache, injection-site erythema, injection-site reaction, and accidental overdose (Table 2). There were no TEAEs leading to death, no cases of clinically symptomatic eosinophilia, eosinophilic pneumonia or eosinophilic granulomatosis with polyangiitis, and one case of systemic hypersensitivity (urticaria) in the placebo group. One patient (2.6%) who received dupilumab permanently discontinued treatment due to a TEAE (COVID-19 infection). No TEAEs of special interest were reported in dupilumab recipients.

Discussion

In the phase 2 ORION study, treatment with dupilumab was associated with improved radiographic findings (LMK-CT) and trends toward improvement in sinonasal symptoms and health-related quality of life vs placebo, with effects most evident in patients with T2 inflammatory phenotypes (i.e. sBEC ≥300 cells/μL). Dupilumab met the amended primary endpoint of reducing sinus opacification and was generally well tolerated, with no new safety concerns identified in the study population. Similarly to the efficacy outcomes noticed in patients with sBEC ≥300 cells/μL, amelioration of LMK-CT, sTSS, SNOT-22, and UPSIT scores were observed in participants with sBEC <300 cells/μL at screening treated with dupilumab [38]. LMK-CT score was selected as the primary endpoint because it provides an objective, reproducible measure of sinus opacification, which reflects underlying inflammation [39].

Evidence suggests that patients with CRSsNP and T2 inflammation are more likely to have reduced sense of smell and taste, headache and/or migraine, and coexisting asthma [6, 13, 40]. Current medical therapies commonly prescribed for CRSsNP include INCS, SCS, and antibiotics, but are insufficient, with around 27% of patients requiring surgery and 18% continuing to have symptoms [17]. Even with surgery, patients with CRSsNP and other coexisting T2 inflammatory conditions such as asthma may require additional future surgeries [19]. Thus, there is a need for novel therapies [41]. In the phase 2 ORION study, improvement in CRSsNP symptomatology may have resulted from the reduction of sinus inflammation observed radiographically by LMK-CT [39, 42] in both the full dupilumab-treated ITT population and in patients with/without screening blood eosinophils ≥300 cells/μL treated with dupilumab. Radiographic improvements only assess one domain of disease; improvements in other parameters such as sTSS, UPSIT, and SNOT-22, were only seen in the subset of patients with sBEC ≥300 cells/μL.

CRSsNP and CRSwNP differ in histologic, inflammatory, and clinical features. Patients with CRSwNP show a more consistent

Table 2. Overview of adverse event profile: TEAEs—safety population.

Adverse events, n (%)	Placebo (n = 33)	Dupilumab 300 mg q2w (n = 38)
Patients with any TEAE	27 (81.8)	29 (76.3)
Patients with any serious TEAE	6 (18.2)	3 (7.9)
Patients with any TEAE leading to death	0	0
Patients with any TEAE leading to permanent study intervention discontinuation	0	1 (2.6)
TEAEs occurring in ≥5% of patients in any treatment group		
Infections and infestations	17 (51.5)	21 (55.3)
COVID-19	7 (21.2)	8 (21.1)
Bronchitis	0	2 (5.3)
Gastroenteritis	0	2 (5.3)
Nasopharyngitis	2 (6.1)	2 (5.3)
Otitis media	1 (3.0)	2 (5.3)
Viral upper respiratory tract infection	2 (6.1)	2 (5.3)
Upper respiratory tract infection	3 (9.1)	0
Nervous system disorders	6 (18.2)	3 (7.9)
Headache	2 (6.1)	2 (5.3)
Respiratory, thoracic, and mediastinal disorders	4 (12.1)	2 (5.3)
Asthma	2 (6.1)	1 (2.6)
Gastrointestinal disorders	5 (15.2)	7 (18.4)
Chronic gastritis	0	2 (5.3)
Gastroesophageal reflux disease	0	2 (5.3)
Musculoskeletal and connective tissue disorders	6 (18.2)	6 (15.8)
Arthralgia	1 (3.0)	2 (5.3)
Back pain	0	2 (5.3)
General disorders and administration-site conditions	2 (6.1)	8 (21.1)
Injection-site erythema	1 (3.0)	4 (10.5)
Injection-site reaction	1 (3.0)	3 (7.9)
Fatigue	0	2 (5.3)
Injection-site swelling	2 (6.1)	0
Injury, poisoning, and procedural complications	7 (21.2)	7 (18.4)
Accidental overdose	3 (9.1)	2 (5.3)
Fall	2 (6.1)	1 (2.6)

n (%) = number and percentage of patients with at least one adverse event during the treatment-emergent period. q2w, every 2 weeks; TEAE, treatment-emergent adverse event.

T2 phenotype [43]. Although there is a subgroup of patients with CRSsNP with a similar T2 phenotype [6, 7], identification of patients more likely to respond to T2-targeted therapy is not well defined. There is currently no established biomarker or biomarker threshold for identifying T2 inflammation in CRSsNP, and a knowledge gap remains on how best to distinguish patients with CRSsNP who may benefit from treatments targeting T2 inflammation. The ORION study sought to address this knowledge gap by investigating the efficacy of dupilumab in patients with CRSsNP with sBEC ≥300 cells/μL, because this threshold indicates T2 inflammation in other inflammatory airway diseases such as asthma, and is predictive of response to biologic therapies [44]. These data suggest that blood eosinophil count may be a useful biomarker to identify patients with CRSsNP who may benefit from treatments that target T2 inflammation; however, further validation is required.

Indeed, T2 inflammation in CRSsNP is associated with elevated blood and sinus eosinophil counts [13], and a blood eosinophil count of ≥300 cells/μL has predictive value for identifying eosinophilic CRSsNP [45]. Because blood eosinophil count may

be used to guide treatment decisions in patients with asthma [46], clinical research to develop a similar approach for patients with CRSsNP would be valuable in identifying patients who may derive greater benefit from treatments targeting T2 inflammation. However, phenotypic and endotypic classification can be challenging due to inter-observer variability [47, 48]. Immune markers of T2 inflammation often do not map to polyp status in patients, so intra-operative tissue evaluation can help demonstrate T2 inflammation missed by endoscopy [49]. As such, tissue histopathology may better distinguish active T2 inflammation than blood eosinophil counts alone.

This study had several limitations, including that the study was originally designed with a primary clinical endpoint of sTSS; however, recruitment challenges necessitated a protocol amendment, changing the primary endpoint to a radiographic one, and moving the original clinical primary endpoint to a secondary endpoint. This radiographic endpoint may not fully correlate with clinical symptoms or disease burden [39, 50]. Due to the small sample size, only descriptive statistical analyses could be performed without multiplicity control, restricting the ability to make strong efficacy conclusions. For particular SNOT-22 outcomes, we acknowledge that interpretation by eosinophil subgroup is limited by the relatively small sample size. As this is a Phase 2 study, these findings are intended to inform the design and powering of future Phase 3 trials, where more robust subgroup analyses will be feasible. In smaller patient cohorts, the known heterogeneity of CRSsNP symptoms may impact changes observed in the placebo group. Further, the study inclusion criteria targeted a specific population of patients, leading to a high screen failure rate, particularly for the criterion requiring bilateral inflammation of paranasal sinuses (LMK-CT score ≥8) and bilateral ethmoid opacification, and enrollment of a population that was predominantly white and from Western countries. Future studies are needed to confirm the efficacy observed in this clinical trial and to better elucidate the impact of dupilumab on CRSsNP.

Conclusion

In patients with inadequately controlled CRSsNP and sBEC ≥300 cells/μL, treatment with dupilumab led to clinically meaningful improvements in sinus opacification assessed by LMK-CT score; additionally, patients had a trend toward improvement in multiple other parameters, including clinical symptoms, sense of smell, and health-related quality of life. Dupilumab was well tolerated, with no new safety concerns identified.

Abbreviations

3D: Three-dimensional: ACQ-6: 6-item Asthma Control Questionnaire; ADA: Anti-drug antibody; BL: Baseline; BMI: Body mass index; CI: Confidence interval; CRS: Chronic rhinosinusitis; CRSsNP: Chronic rhinosinusitis without nasal polyps; CRSwNP: Chronic rhinosinusitis with nasal polyps; CT: Computed tomography; EQ-5D-5L: European Quality of Life 5 Dimensions 5 Level Version; FEV_1: Forced expiratory volume in 1 second; IgE: Immunoglobulin E; IL: Interleukin; INCS: Intranasal corticosteroids; ITT: Intention-to-treat; LMK-CT: Lund–Mackay computed tomography; MCID: Minimal clinically important difference; NC: Nasal congestion; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PK: Pharmacokinetics; q2w: Every 2 weeks; sBEC: Screening blood eosinophil count; SCS: Systemic corticosteroids; SD: Standard deviation; SE: Standard error; SNOT-22: 22-item Sino-Nasal Outcome Test; sTSS: Sinus Total Symptom Score; TARC: Thymus and activation-regulated chemokine; TEAE: Treatment-emergent adverse event; T2: Type 2; UPSIT: University of Pennsylvania Smell Identification Test; VAS: Visual analog scale.

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Author contributions

SEL, ATP, JKH, CB, FMdS, and AR performed the study investigation and wrote, reviewed, and edited the manuscript. PG conceptualized the study and contributed to the methodology set up, performed the study investigation, and wrote, reviewed, and edited the manuscript. C-CH performed the formal result analysis, contributed to the methodology visualization and set up, and wrote, reviewed, and edited the manuscript. PC conceptualized the study and contributed to the methodology set up, wrote the original manuscript draft, and reviewed and edited the manuscript. JM, AM, APF, LBR, and NAP conceptualized the study, contributed to the methodology set up, and wrote, reviewed, and edited the manuscript.

Conflict of interest

This work was funded by Sanofi and Regeneron Pharmaceuticals Inc. Disclosure of potential conflict of interest: SEL is an advisory board member for and reports clinical trial funding from AstraZeneca, Genentech, GSK, Regeneron Pharmaceuticals Inc., and Sanofi, and reports publication support from AstraZeneca, GSK, Regeneron Pharmaceuticals Inc., and Sanofi. ATP has received research support from AstraZeneca, Insmed, Regeneron Pharmaceuticals Inc., and Sanofi, and is an advisory board member for AstraZeneca, Chiesi, Eli Lilly, GSK, Regeneron Pharmaceuti-

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPLEMENTARY MATERIAL

Methods

Key inclusion and exclusion criteria

Key inclusion criteria for enrollment in the Liberty ORION study were:

- At least 18 years of age at the time of signing the informed consent form
- Bilateral inflammation of the paranasal sinuses on computed tomography scan with a Lund–Mackay (LMK) computed tomography score ≥8 and bilateral ethmoid opacification before randomization
- The following symptoms ongoing for at least 12 consecutive weeks before Visit 1
  - Loss of smell and rhinorrhea (anterior/posterior) of any severity, with or without facial pain/pressure
  - Nasal congestion, with a score of ≥2 at Visit 1 (day score) and Visit 2 (weekly average score)
- Sinus Total Symptom Score ≥5 at Visit 1 (day score) and Visit 2 (weekly average score)
- At least one of:
  - Prior sinonasal surgery for chronic rhinosinusitis (CRS)
  - Treatment with systemic corticosteroid therapy for CRS, as defined by any dose and duration within the prior 2 years before screening (Visit 1) or intolerance/contraindication to systemic corticosteroids (SCS)

Key exclusion criteria were:

- Conditions or concomitant diseases making the patient non-evaluable at Visit 1 or for the primary efficacy endpoint, including:
  - Nasal polyposis observed during nasal endoscopy at Visit 1, or history of nasal polyposis
  - Nasal septal deviation causing complete occlusion of at least one nostril
  - Acute sinusitis, purulent drainage, nasal infection, or upper respiratory tract infection at Visit 1 or 2
  - Ongoing rhinitis medicamentosa
  - Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome), granulomatosis with polyangiitis (Wegener's granulomatosis), microscopic polyangiitis, Young's syndrome, Kartagener's syndrome or other dyskinetic ciliary syndromes, cystic fibrosis
- Nasal cavity malignant tumor and benign tumors (e.g. papilloma, hemangioma)
- Forced expiratory volume in 1 second (FEV_1) ≤50% of predicted normal at Visit 1
- Radiologic suspicion or confirmed invasive or expansive fungal rhinosinusitis
- Dupilumab treatment within the last 12 months or discontinuation of dupilumab due to adverse event (AE)
- Sinus surgery within the 6 months before Visit 1, or sinonasal surgery changing the structure of the nose such that evaluation of LMK is not possible
- Unstable dose of intranasal corticosteroid spray 4 weeks before Visit 1 and during screening, or use of intranasal corticosteroid drops, intranasal corticosteroid-emitting devices/stents, or nasal spray using exhalation delivery system during the screening period
- Use of SCS during the screening period
- Biologic therapy/systemic immunosuppressant treatment 4 weeks or five half-lives before Visit 1, whichever is longer

Settings and locations

The study was conducted at 58 sites in 13 countries (Argentina, Belgium, Canada, Chile, China, Hungary, Portugal, Russia, South Korea, Spain, Sweden, Ukraine, United States). The full list of study sites is available at: https://clinicaltrials.gov/study/NCT04678856#contacts-and-locations.

Randomization and blinding

The randomization process was managed centrally by the sponsor, with investigational medicinal products packaged accordingly. This included generation of the randomization list and allocation of intervention numbers by the Interactive Response Technology (IRT) system. Before study commencement, each site received login credentials and guidance for IRT usage. Randomization was stratified by screening blood eosinophil count (sBEC; ≥300 cells/μL or <300 cells/μL), background intranasal corticosteroid use (yes or no), and region. Furthermore, alerts were implemented to ensure an adequate representation of patients with coexisting asthma, restricting those without to no more than 70% of the randomized population. Upon screening, the Investigator or designee obtained the patient number from the IRT. If rescreening was required, a new informed consent form needed to be signed, resulting in the assignment of a new patient number. Once randomized, patients could not be rerandomized within the study. Dupilumab 300 mg and placebo were provided in visually indistinguishable 2 mL pre-filled syringes, each labeled with a treatment kit number for identification. The sponsor was blinded until after the final database lock.

Statistical consideration

In efficacy analyses, data following surgery or SCS administration were excluded, and the worst post baseline value before these events was assigned using a "worst observation carried forward" approach. Baseline values were used for patients with no post baseline data. Data collected after discontinuing the study intervention were included in the analysis. No imputation

was performed for missing data.
Safety assessments were conducted on the safety population, comprising all patients who received at least one dose of study medication. The incidence of AEs, including treatment-emergent AEs (TEAEs), serious AEs, and AEs leading to discontinuation, was tabulated by system organ class and preferred term. AEs were further categorized by severity, relationship to treatment, and endpoint. Laboratory and vital signs data were summarized using descriptive statistics, with clinically significant abnormalities flagged based on pre-defined criteria. Final analyses were conducted following the database lock, which occurred after all patients completed the end-of-study visit.

Treatment duration

Treatment was stopped for all patients when the last patient had completed 24 weeks of treatment. Therefore, all patients following Amendment 02 were treated for at least 24 weeks, and the other patients (enrolled before Amendment 02) had a variable treatment period of up to 52 weeks.

Results

Additional results for patients with sBEC ≥300 cells/µL

Healthcare resource utilization and productivity

Summary of healthcare resource utilization

Both dupilumab 300 mg every 2 weeks (q2w) and placebo treatments resulted in a comparable number of visits to general practitioners and specialists. However, dupilumab treatment led to a lower number of unscheduled visits compared with placebo (Table S5).

Summary of missed days at work/missed days at school

Patients treated with dupilumab 300 mg q2w reported a higher mean (standard deviation [SD]) number of missed workdays compared with those receiving placebo (17.20 [63.90] vs 7.89 [14.43]). No patients in either treatment group reported missing school days (Table S5).

Patient Global Impression of Severity (PGIS) of CRS without nasal polyps (CRSsNP)

The PGIS assesses CRSsNP severity on a 4-point scale ranging from "None" to "Severe." At baseline, no patients in the dupilumab or placebo groups rated their CRSsNP severity as "None" or "Mild" (Table S3). By week 24, dupilumab treatment improved patient-reported CRSsNP severity, with 40.0% of patients rating their symptom severity as "None" or "Mild" compared with 23.1% in the placebo group. This improvement continued through week 52 (Table S5).

Patient Global Impression of Change (PGIC) of CRSsNP

The PGIC evaluates the change in CRSsNP symptoms on a 7-point scale from "Very much better" to "Very much worse." Patients treated with dupilumab reported greater improvements, with 53.3% rating their symptoms as "Very much better" or "Moderately better" compared with 23.1% in the placebo group at week 24. This improvement was maintained through week 52 (Table S5).

Visual analog scale (VAS) for the European Quality of Life 5 Dimensions 5 Level Version (EQ-5D-5L)

The VAS for EQ-5D-5L measures self-rated health on a scale from 0 (worst imaginable health) to 100 (best imaginable health). The baseline mean (SD) VAS scores were higher in the dupilumab group compared with the placebo group (58.21 [30.03] vs 49.75 [32.90]), indicating better health-related quality of life (Table S3). Both treatment groups showed improvement at week 24, with mean difference vs placebo of -3.01 (95% confidence interval [CI]: -30.89 to 24.86). This improvement continued through week 52 (Table S5).

6-item Asthma Control Questionnaire (ACQ-6) in patients with coexisting asthma

Among patients with sBEC ≥300 cells/µL, there were 8 patients with coexisting asthma in the placebo group and 9 patients in the dupilumab group. At baseline, asthma was uncontrolled with a mean (SD) ACQ-6 score of 2.25 (0.94) in the placebo group and 2.44 (1.16) in the dupilumab group (Table S3). Dupilumab treatment resulted in a substantial decrease in ACQ-6 score at week 24 (mean difference vs placebo -1.03 [95% CI: -2.40 to 0.34]), with improvements observed as early as week 12 and sustained through week 52 (mean difference vs placebo -1.89 [95% CI: -3.67 to -0.12]) (Table S5, Figure S5).

Spirometry in patients with coexisting asthma

In the dupilumab group, mean (SD) baseline FEV_1 for patients with coexisting asthma was 2.76 (0.87) L in the placebo group and 2.62 (0.78) L in the dupilumab group, with a baseline percent predicted FEV_1 of 88.78% (13.85) (Table S3). Dupilumab treatment improved FEV_1 at week 24 (mean difference vs placebo 0.42 L [95% CI: -0.09 to 0.94]) and maintained its value at week 52 (mean difference vs placebo 0.42 L [95% CI: -0.15 to 0.98]), indicating improved lung function (Table S5).

Safety results

Serious TEAEs in the dupilumab group included cholecystitis acute and biloma, chronic gastritis, and myocardial bridging, whereas in the placebo group serious TEAEs included CRS, diabetic neuropathy, peripheral arterial occlusive disease, syncope, asthma, foot deformity, and spinal osteoarthritis.

Table S1. Study objectives and selected endpoints.

Objectives	Endpoints
Primary	
To evaluate the efficacy of dupilumab as assessed by the reduction at week 24 in sinus opacification on CT scan in the dupilumab group only	Change from baseline to week 24 in opacification of sinuses assessed by CT scan using the LMK score in the dupilumab group
Secondary	
To evaluate the efficacy of dupilumab as assessed by the reduction at week 24 in sinus opacification on CT scan and sTSS vs placebo	Change from baseline to week 24 in opacification of sinuses assessed by CT scan using the LMK score Change from baseline to week 24 in sTSS*
To evaluate the safety and tolerability of dupilumab in patients with CRSsNP vs placebo	Incidence of TEAEs, serious TEAEs, and TEAEs leading to treatment discontinuation
Exploratory	
To evaluate the effect of dupilumab on overall health status, global impression of disease severity/change, and HCRU/productivity vs placebo	Change from baseline to week 24 in the EQ 5D-5L Cumulative amount of HCRU Cumulative number of missed days of school/work Change from baseline to week 24 in PGIS of CRSsNP PGIC in CRSsNP at week 24 Change from baseline to week 24 in headache severity score using the symptom diary
To characterize the effect of dupilumab in patients with CRSsNP by evaluating blood biomarkers vs placebo	Pharmacodynamic biomarker levels in blood (IgE, eotaxin-3, periostin, and TARC)
To explore the effect of dupilumab as assessed by three-dimensional CT volumetric measurement of the paranasal sinuses	Change from baseline to week 24 in three-dimensional CT volumetric measurement of the paranasal sinuses
To evaluate the efficacy of dupilumab in improving CRSsNP symptoms at week 24 vs placebo	Change from baseline to week 24 in: • NC symptom severity score using the daily CRSsNP sinonasal symptom e-diary • Anterior/posterior rhinorrhea severity score using the daily CRSsNP sinonasal symptom e-diary • Facial pain/pressure severity score using the daily CRSsNP sinonasal symptom e-diary • Loss of smell symptom severity score using the daily CRSsNP sinonasal symptom e-diary • UPSIT score
To evaluate the effect of dupilumab on CRSsNP overall disease severity at week 24 vs placebo	Change from baseline to week 24 in rhinosinusitis severity VAS
To evaluate the effect of dupilumab at week 24 in the subgroups of patients with comorbid asthma in the dupilumab group	Change from baseline to week 24 in the dupilumab group in: • FEV1 in the CRSsNP with asthma population • ACQ-6 score in the CRSsNP with asthma population
To evaluate the effect of dupilumab in patients regardless of screening blood eosinophil count in the dupilumab group	Change from baseline to week 24 in opacification of sinuses assessed by CT scan using LMK score regardless of screening blood eosinophil count in the dupilumab group Change from baseline to week 24 in sTSS regardless of the screening blood eosinophil count in the dupilumab group
To evaluate the effect of dupilumab on HRQoL at week 24 vs placebo	Change from baseline to week 24 in SNOT-22 score

ACQ-6, 6-item Asthma Control Questionnaire; CRSsNP, chronic rhinosinusitis without nasal polyps; CT, computerized tomography; EQ-5D-5L, European Quality of Life 5 Dimensions 5 Level Version; FEV_1, forced expiratory volume in 1 second; HCRU, healthcare resource utilization; HRQoL, health related quality of life; IgE, immunoglobulin E; LMK, Lund–Mackay; NC, nasal congestion; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; SNOT-22, 22-item Sino-Nasal Outcome Test; sTSS, sinus Total Symptom Score; TARC, thymus and activation-regulated chemokine; TEAE, treatment-emergent adverse event; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog scale.
*Composite severity score consisting of the NC, anterior/posterior rhinorrhea, and facial pain/pressure items of the CRSsNP sinonasal symptom e-diary.

Table S2. Institutional Review Board and Independent Ethics Committees study approval references.

Country	IRB/IEC	Related clinical site number(s)	IRB/IEC decision(s) number(s)/reference(s)
Argentina	Comite de Etica en Investigacion INAER	0320001	Registration code: 5995
	Fundacion Cidea	0320002	Registration code: 6281
	Comite de Etica en Investigacion INAER	0320003	Registration code: 6325
Belgium	Commissie voor Medische Ethiek-Universitair Ziekenhuis Gent	0560001; 0560002	BC 09202
Canada	Comité d'éthique de la recherche du CHUM	1240001; 1240012	20.283
	Comité d'éthique de la recherche du CHUM	1200005	MP-02-2021-9387, 20.283
	Advarra	1240002	SSU00131586
	Advarra	1240003	SSU00135281
	Queen 's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB)	1240007	TRAQ #: 6034785
	Hamilton Integrated Research Ethics Board (HiREB)	1240010	12856
	UBC – Providence Health Care Research	1240013	H21-03195
	Western University Health Sciences Research	1240016	121280
Chile	Comite de Etica de la Investigacion S.S.M Sur Oriente	1520001	Approval received on 23 September 2021*
China	Beijing Tongren Hospital, Capital Medical	1560001	TREC2021-04
	IEC of First Hospital, Jilin University	1560005	21Y341-001
	Shanghai Tongji Hospital	1560006	2021-105
	Medical Clinical Trial Ethics Committee of Yantai Yuhuangding Hospital	1560008	[2021] No. 83
	IEC of The First Affiliated Hospital of Chongqing Medical University	1560010	CY202115001
	The Third Xiangya Hospital Of Central South University	1560013	21261
Hungary	Egészségügyi Tudományos Tanács	3480001; 3480004	OGYI/50751-5/2021
Portugal	CEIC – Comissão de Ética para a Investigação Clínica	6200001; 6200002; 6200003	MAP / MAP / OF / 2021 / 6080 / 20201092
Russia	Ethics Board at Ministry of Health of the Russian Federation	6430001; 6430002; 6430003; 6430005	Protocol № 264
	Ethics Board at Ministry of Health of the Russian Federation	6430002	Protocol № 245
	Ethics Board at Ministry of Health of the Russian Federation	6430003	Protocol № 248
	Ethics Board at Ministry of Health of the Russian Federation	6430005	Protocol № 04
	The Independent Interdisciplinary Ethics Committee	6430001	Protocol № 15
South Korea	Samsung Medical Center	4100002	2022-08-085-002
	SMG Seoul National University Boramae Medical Center	4100003	20-2022-104
Spain	CEIm Corporació Sanitaria Parc Taulí	7240001; 7240002; 7240004; 7240005; 7240007; 7240008; 7240009	Act nº 534
Sweden	Etikprovningsmyndigheten	7520001	Dnr 2021-04691
Ukraine	LEC of the Central City Clinical Hospital	8040001	Protocol № 51
	LEC of the Institute of otolaryngology n.a. prof.O.S. Kolom	8040002	Protocol № 2/21
	LEC of Regional Clinical Specialized Dispensary for Radiation Protection of Citizenry	8040004	Protocol № 3
	LEC of Municipal Non-Commercial Enterprise Clinical Hospital of Emergency Medical Care	8040005	Protocol № 3
	LEC of the Medical Center of the LLC "Medical Center" Consilium Medical	8040007	Protocol № 2021/3/3
	LEC of the Treatment and diagnostic center "Healthy and Happy"	8040008	Protocol № 29

Table S2 *continued*. Institutional Review Board and Independent Ethics Committees study approval references.

Country	IRB/IEC	Related clinical site number(s)	IRB/IEC decision(s) number(s)/reference(s)
United States	Eastern Virginia Medical School	8400009	21-04-FB-0097
	WCG IRB	8400003; 8400004; 8400006; 8400007; 8400010; 8400014; 8400015; 8400016; 8400017; 8400021	20203050

Clinical sites shown screened at least 1 participant. Clinical site names can be found at: ClinicalTrials.gov. IEC, independent ethics committee; IRB, institutional review board. *No specific decision number/reference was given.

Table S3. Additional baseline disease characteristics—randomized population.

Characteristic	Screening blood eosinophil count ≥300 cells/μL			Screening blood eosinophil count <300 cells/μL			All patients		
	Placebo (n = 15)	Dupilumab 300 mg q2w (n = 16)	All (n = 31)	Placebo (n = 18)	Dupilumab 300 mg q2w (n = 22)	All (n = 40)	Placebo (n = 33)	Dupilumab 300 mg q2w (n = 38)	All (n = 71)
Loss of smell symptom severity score	2.62 (0.62)	2.61 (0.43)	2.61 (0.52)	2.45 (0.67)	2.48 (0.67)	2.47 (0.66)	2.53 (0.64)	2.53 (0.58)	2.53 (0.60)
Headache severity score	2.01 (0.98)	2.33 (0.77)	2.17 (0.88)	2.23 (0.51)	2.24 (0.88)	2.24 (0.73)	2.13 (0.75)	2.28 (0.83)	2.21 (0.79)
Rhinosinusitis severity VAS score	8.85 (1.23)	9.18 (0.97)	9.03 (1.09)	8.74 (1.06)	8.94 (1.12)	8.85 (1.08)	8.78 (1.11)	9.03 (1.05)	8.92 (1.08)
EQ-VAS score	49.75 (32.90)	58.21 (30.03)	54.31 (31.04)	51.59 (23.51)	54.00 (29.91)	52.92 (26.91)	50.83 (27.24)	55.69 (29.59)	53.48 (28.43)
EQ-5D-5L single index score	0.64 (0.32)	0.48 (0.36)	0.55 (0.35)	0.62 (0.27)	0.59 (0.27)	0.61 (0.27)	0.63 (0.29)	0.54 (0.31)	0.58 (0.30)
PGIS categorical score, n (%)	(n = 12)	(n = 14)	(n = 26)	(n = 17)	(n = 21)	(n = 38)	(n = 29)	(n = 35)	(n = 64)
None	0	0	0	0	0	0	0	0	0
Mild	0	0	0	0	0	0	0	0	0
Moderate	3 (25.0)	3 (21.4)	6 (23.1)	7 (41.2)	3 (14.3)	10 (26.3)	10 (34.5)	6 (17.1)	16 (25.0)
Severe	9 (75.0)	11 (78.6)	20 (76.9)	10 (58.8)	18 (85.7)	28 (73.7)	19 (65.5)	29 (82.9)	48 (75.0)
Coexisting asthma, n (%)	8 (53.3)	9 (56.3)	17 (54.8)	9 (50.0)	8 (36.4)	17 (42.5)	—	—	34 (47.9)
FEV_1, L*	2.76 (0.87)	2.62 (0.78)	2.69 (0.80)	2.78 (0.99)	2.27 (0.63)	2.54 (0.85)	2.77 (0.91)	2.46 (0.71)	2.61 (0.82)
FEV_1, % predicted*	82.86 (11.94)	88.78 (13.85)	86.00 (12.95)	82.73 (7.61)	81.45 (14.52)	82.13 (11.03)	82.79 (9.55)	85.33 (14.23)	84.06 (12.00)
ACQ-6 score*	2.25 (0.94)	2.44 (1.16)	2.37 (1.05)	2.19 (1.43)	2.52 (1.20)	2.34 (1.30)	2.21 (1.22)	2.48 (1.14)	2.35 (1.17)

Data are shown as mean (SD), unless otherwise stated. ACQ-6, 6-item Asthma Control Questionnaire; EQ-5D-5L, European Quality of Life 5 Dimensions 5 Level Version; EQ-VAS, EuroQol visual analog scale; FEV_1, forced expiratory volume in 1 second; PGIS, Patient Global Impression of Severity; q2w, every 2 weeks; SD, standard deviation; SNOT-22, 22-item Sino-Nasal Outcome Test; sTSS, sinus Total Symptom Score; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog scale. *Assessed only in patients with coexisting asthma.

Table S4. Proportion of patients with sBEC ≥300 cells/μL who achieved the MCID in LMK-CT, SNOT-22, and UPSIT, at 24 weeks.

Outcome	MCID threshold	Number of patients per treatment group*	Number (%) of participants with sBEC ≥300 cells/μL achieving MCID at week 24
LMK-CT	≥4.95-point decrease	Dupilumab (16)	11 (68.8)
		Placebo (14)	1 (7.1)
SNOT-22	≥8.9-point decrease	Dupilumab (15)	13 (86.7)
		Placebo (13)	7 (53.8)
UPSIT	≥4-point increase	Dupilumab (16)	5 (31.3)
		Placebo (14)	2 (14.3)

LMK-CT, Lund–Mackay computed tomography; MCID, minimal clinically important difference; sBEC, screening blood eosinophil count; SNOT-22, 22-item Sino-Nasal Outcome Test; UPSIT, University of Pennsylvania Smell Identification Test. *Dupilumab, n = 16; placebo, n = 15. Missing data were not imputed.

Table S5. Exploratory endpoints in patients with screening blood eosinophil count ≥300 cells/μL.

	Placebo (n = 15)	Dupilumab 300 mg q2w (n = 16)
Change from baseline in rhinosinusitis severity VAS		
Week 24	-1.27 (2.66)	-2.66 (2.20)
Week 52	-0.49 (1.24)	-3.82 (3.54)
Change from baseline in EQ-5D-5L single index score		
Week 24	0.07 (0.17)	0.25 (0.27)
Week 52	-0.11 (0.42)	0.28 (0.28)
Change from baseline in nasal congestion/obstruction score		
Week 24	-0.50 (0.70)	-1.14 (0.90)
Week 52	-0.25 (0.43)	-1.05 (1.03)
Change from baseline in anterior/posterior rhinorrhea severity score		
Week 24	-0.56 (0.84)	-1.12 (0.86)
Week 52	-0.18 (0.38)	-1.19 (1.09)
Change from baseline in facial pain/pressure severity score		
Week 24	-0.69 (0.76)	-0.92 (1.00)
Week 52	-0.33 (0.54)	-0.94 (1.10)
Change from baseline in loss of smell symptom severity score		
Week 24	-0.36 (0.64)	-1.09 (0.96)
Week 52	-0.54 (0.78)	-1.15 (1.03)
Change from baseline in headache severity score		
Week 24	-0.61 (0.87)	-0.98 (1.01)
Week 52	-0.16 (0.59)	-1.03 (1.02)
Cumulative post-baseline healthcare resource utilization and productivity		
Number of visits to general practitioner	0.57 (1.60)	0.63 (1.20)
Number of visits to specialist	0.93 (1.69)	0.81 (2.07)
Number of unscheduled visits	0.50 (0.94)	0.13 (0.34)
Days missing from work	7.89 (14.43)	17.20 (63.90)

	Placebo (n = 15)	Dupilumab 300 mg q2w (n = 16)
Patient Global Impression of Severity of CRSsNP, n (%)		
Week 24		
Number	13	15
None	1 (7.7)	1 (6.7)
Mild	2 (15.4)	5 (33.3)
Moderate	4 (30.8)	5 (33.3)
Severe	6 (46.2)	4 (26.7)
Week 52		
Number	9	12
None	0	3 (25.0)
Mild	0	4 (33.3)
Moderate	4 (44.4)	1 (8.3)
Severe	5 (55.6)	4 (33.3)
Patient Global Impression of Change of CRSsNP, n (%)		
Week 24 *		
Number	13	15
Very much better	2 (15.4)	4 (26.7)
Moderately better	1 (7.7)	4 (26.7)
A little better	3 (23.1)	5 (33.3)
No change	7 (53.8)	2 (13.3)
A little worse	0	0
Week 52 †		
Number	8	12
Very much better	1 (12.5)	4 (33.3)
Moderately better	1 (12.5)	1 (8.3)
A little better	1 (12.5)	5 (41.7)
No change	4 (50.0)	2 (16.7)
A little worse	1 (12.5)	0
Change from baseline in ACQ-6 score		
Week 24	-0.19 (1.59)	-1.22 (0.88)
Week 52	0.70 (0.82)	-1.19 (1.58)
Change from baseline in FEV1, L		
Week 24	-0.34 (0.64)	0.08 (0.23)
Week 52	-0.44 (0.67)	-0.02 (0.27)

Data are shown as mean (SD), unless otherwise stated. ACQ-6, 6-item Asthma Control Questionnaire; CRSsNP, chronic rhinosinusitis without nasal polyps; EQ-5D-5L, European Quality of Life 5 Dimensions 5 Level Version; FEV1, forced expiratory volume in 1 second; q2w, every 2 weeks; SD, standard deviation; VAS, visual analog scale. * No patients reported "A little worse," "Moderately worse," or "Very much worse." † No patients reported "Moderately worse" or "Very much worse."

Table S6. Results for patients with screening blood eosinophil count <300 cells/μL.

	Placebo (n = 18)	Dupilumab 300 mg q2w (n = 22)
LMK-CT, mean (SD) change from baseline		
Week 24	0.72 (4.21)	-5.61 (5.12)
Week 52	-1.18 (5.17)	-6.27 (5.21)
LMK-CT, mean difference vs placebo (95% CI)		
Week 24	—	-6.33 (-9.51 to -3.16)
Week 52	—	-5.09 (-9.04 to -1.13)
sTSS, mean (SD) change from baseline		
Week 24	-1.79 (1.48)	-1.80 (2.05)
Week 52	-2.06 (1.99)	-3.00 (2.44)
sTSS, mean difference vs placebo (95% CI)		
Week 24	—	-0.01 (-1.18 to 1.16)
Week 52	—	-0.94 (-2.66 to 0.79)
SNOT-22, mean (SD) change from baseline		
Week 24	-19.00 (15.87)	-21.71 (27.93)
Week 52	-22.58 (20.99)	-36.83 (30.94)
SNOT-22, mean difference vs placebo (95% CI)		
Week 24	—	-2.71 (-19.01 to 13.58)
Week 52	—	-14.25 (-36.63 to 8.13)
UPSIT, mean (SD) change from baseline		
Week 24	-0.06 (6.89)	2.45 (6.77)
Week 52	-2.33 (9.65)	-0.43 (6.03)
UPSIT, mean difference vs placebo (95% CI)		
Week 24	—	2.52 (-2.03 to 7.06)
Week 52	—	1.90 (-4.51 to 8.32)

CI, confidence interval; LMK-CT, Lund–Mackay computed tomography; q2w, every 2 weeks; SD, standard deviation; SNOT-22, 22-item Sino-Nasal Outcome Test; sTSS, sinus Total Symptom Score; UPSIT, University of Pennsylvania Smell Identification Test.

Table S7. LMK-CT and sTSS scores at week 24, regardless of screening blood eosinophil count.

	Placebo (n = 33)	Dupilumab 300 mg q2w (n = 38)
LMK-CT, mean (SD) change from baseline		
Week 24	0.07 (3.46)	-6.04 (4.62)
Week 52	-1.04 (4.00)	-6.02 (4.61)
sTSS, mean (SD) change from baseline		
Week 24	-1.77 (1.79)	-2.38 (2.40)
Week 52	-1.54 (1.82)	-3.08 (2.70)

LMK-CT, Lund–Mackay computed tomography; q2w, every 2 weeks; SD, standard deviation; sTSS, sinus Total Symptom Score.

Table S8. Biomarker response—safety population.

Biomarkers	Placebo (n = 33)	Dupilumab 300 mg q2w (n = 38)
Total serum IgE, IU/mL		
Baseline	259.23 (442.00)	448.41 (1832.52)
Week 24 change from baseline	-29.92 (127.96)	-314.66 (1459.57)
Week 52 change from baseline	70.62 (266.09)	-103.51 (235.90)
Eotaxin-3 in plasma, pg/mL		
Baseline	210.00 (219.48)	187.35 (163.12)
Week 24 change from baseline	-5.19 (179.94)	94.68 (1029.07)
Week 52 change from baseline	37.17 (71.68)	-35.33 (183.57)
Periostin in serum, ng/mL		
Baseline	78.73 (25.79)	69.04 (27.05)
Week 24 change from baseline	6.96 (25.79)	-15.88 (20.73)
Week 52 change from baseline	-0.18 (28.59)	-17.71 (23.12)
TARC in serum, pg/mL		
Baseline	409.17 (525.87)	281.30 (145.35)
Week 24 change from baseline	-3.06 (256.60)	-42.13 (115.94)
Week 52 change from baseline	-35.64 (236.78)	-60.85 (57.00)
Blood eosinophils, 10^9 cells/L		
Baseline	0.300 (0.201)	0.264 (0.171)
Week 24 change from baseline	0.034 (0.257)	0.018 (0.192)
Week 52 change from baseline	0.041 (0.205)	-0.010 (0.277)

Data are shown as mean (SD). IgE, immunoglobulin E; q2w, every 2 weeks; SD, standard deviation; TARC, thymus and activation-regulated chemokine.

Table S9. Summary of ADA incidence during the on-treatment period—ADA population.

	Placebo (n = 33)	Dupilumab 300 mg q2w (n = 38)
Pre-existing immunoreactivity, n (%)	1 (3.0)	0
Treatment-emergent response	1 (3.0)	1 (2.6)
Persistent response, n (%)	1 (3.0)	1 (2.6)
Transient response, n (%)	0	0
Indeterminate response, n (%)	0	0
Peak post-baseline titer		
Number	1	1
Median	960	480
Q1, Q3	960, 960	480, 480
Min, Max	960, 960	480, 480
Low (<1000), n (%)	1 (3.0)	1 (2.6)
Moderate (1000 to 10,000), n (%)	0	0
High (>10,000), n (%)	0	0
Patients with treatment-boosted response, n (%)	1 (3.0)	0
Peak post-baseline titer		
Number	1	0
Median	1920	—
Q1, Q3	1920, 1920	—
Min, Max	1920, 1920	—

	Placebo (n = 33)	Dupilumab 300 mg q2w (n = 38)
Low (<1000), n (%)	0	0
Moderate (1000 to 10,000), n (%)	1 (3.0)	0
High (>10,000), n (%)	0	0
Ratio of peak post-baseline to baseline titer		
Number	1	0
Mean (SD)	64.00 (VNC)	—
Median	64	—
Q1, Q3	64, 64	—
Min, Max	64, 64	—
ADA-positive (treatment-emergent or treatment-boosted), n (%)	2 (6.1)	1 (2.6)
Peak post-baseline titer		
Number	2	1
Median	1440	480
Q1, Q3	960, 1920	480, 480
Min, Max	960, 1920	480, 480
Low (<1000), n (%)	1 (3.0)	1 (2.6)
Moderate (1000 to 10,000), n (%)	1 (3.0)	0
High (>10,000), n (%)	0	0
ADA-negative (neither treatment-emergent nor treatment-boosted), n (%)	31 (93.9)	37 (97.4)
Peak post-baseline titer		
Number	1	0
Median	30	—
Q1, Q3	30, 30	—
Min, Max	30, 30	—
Low (<1000), n (%)	1 (3.0)	0
Moderate (1000 to 10,000), n (%)	0	0
High (>10,000), n (%)	0	0

ADA, anti-drug antibody; Max, maximum; Min, minimum; Q, quartile; q2w, every 2 weeks; SD, standard deviation; VNC, value not calculated.

Table S10. NAb status during the on-treatment period—ADA population.

	Placebo (n = 33)	Dupilumab 300 mg q2w (n = 38)
Patients with positive NAb*	3 (9.1)	1 (2.6)
Patients with pre-existing immunoreactivity	1 (3.0)	0
Patients with treatment-emergent response	1 (3.0)	1 (2.6)
Persistent response	1 (3.0)	1 (2.6)
Transient response	0	0
Indeterminate response	0	0
Patients with treatment-boosted response	1 (3.0)	0
Peak post-baseline ADA titer		
Number, n	3	1
Low (<1000)	2 (6.1)	1 (2.6)
Moderate (1000 to 10,000)	1 (3.0)	0
High (>10,000)	0	0

Data are shown as n (%). ADA, anti-drug antibody; NAb, neutralizing antibody; q2w, every 2 weeks. *NAb-positive patients were defined as those with at least one post-baseline ADA classified as neutralizing-positive.

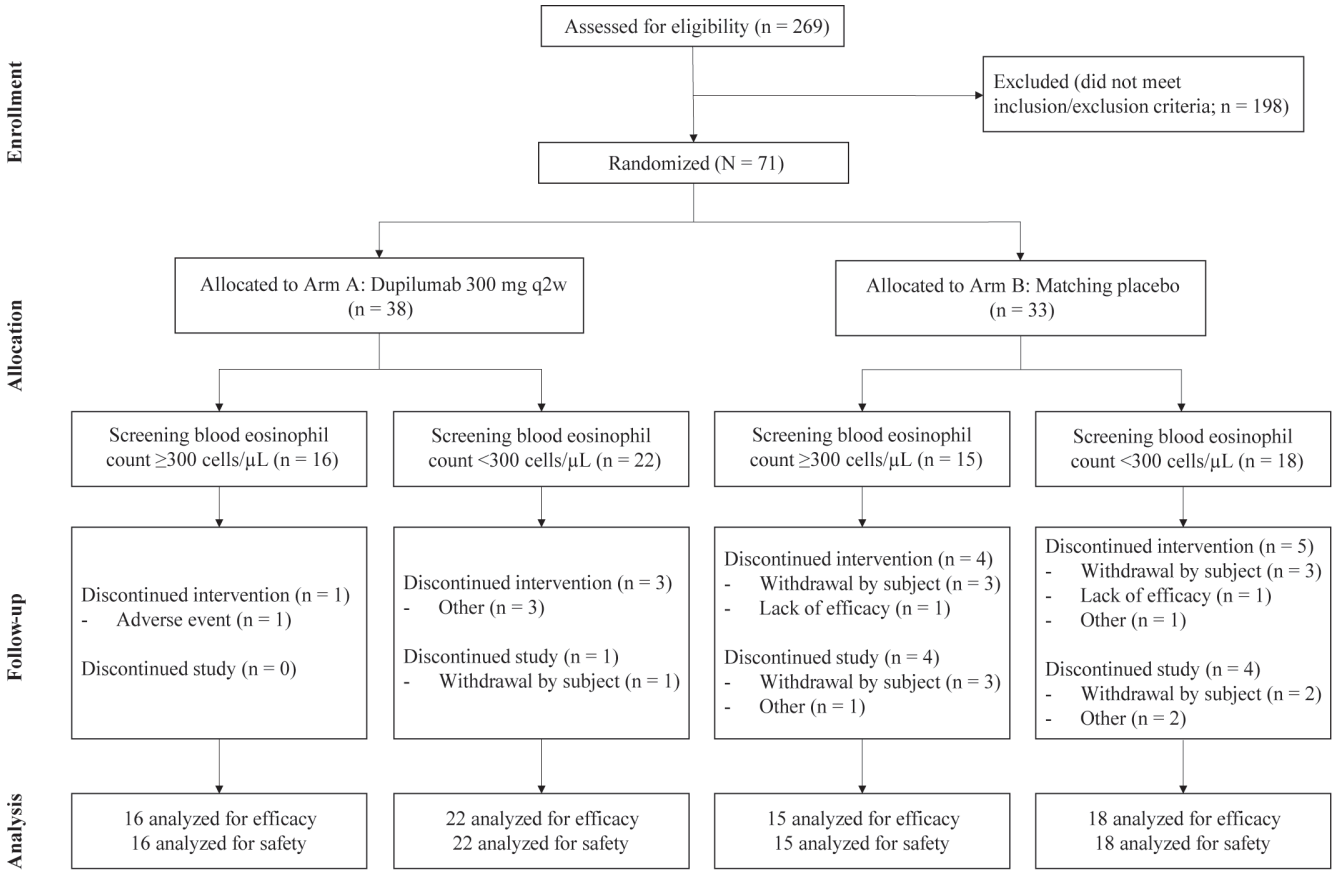


Figure S1. Patient disposition and trial profile. q2w, every 2 weeks.

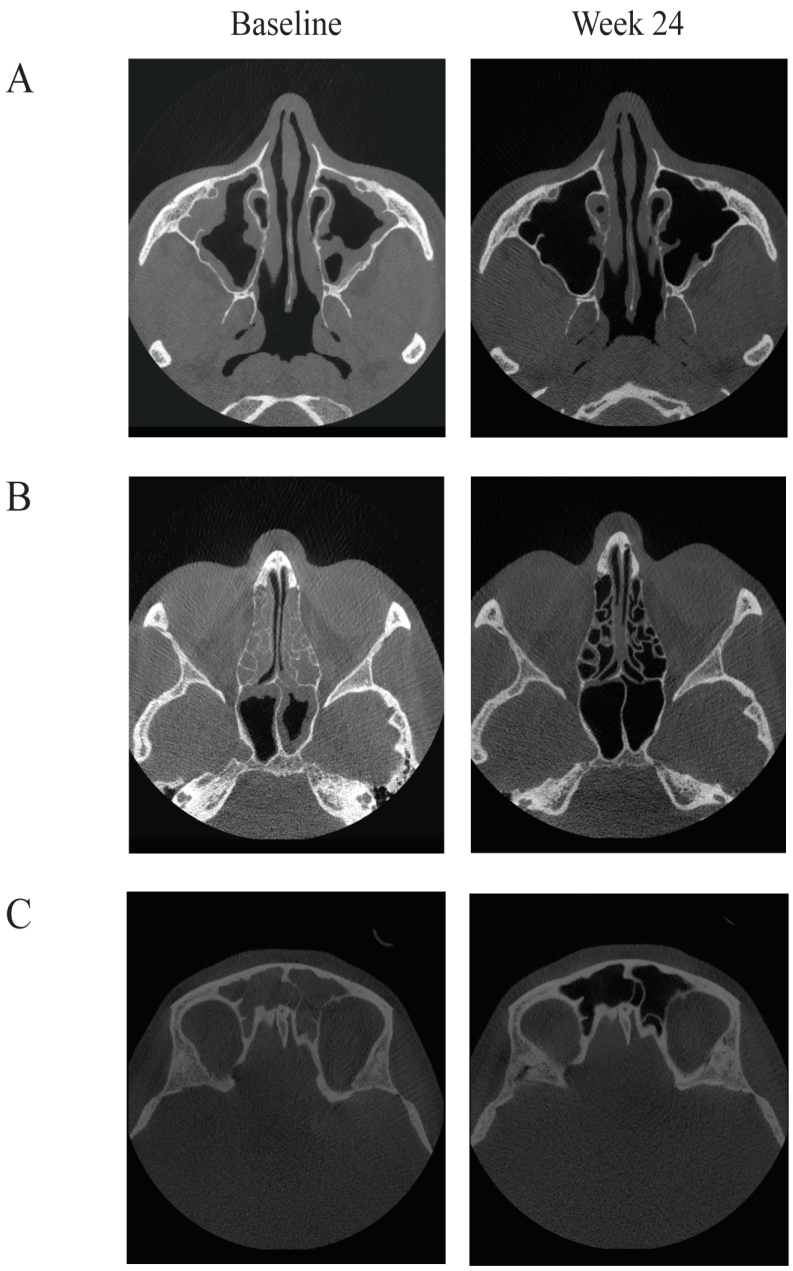


Figure S2. Baseline and week 24 sinus CT scans of a patient with sBEC ≥300 cells/μL treated with dupilumab, showing near complete resolution of opacification in (A) the bilateral maxillary sinuses, (B) the bilateral ethmoid and sphenoid sinuses, and (C) the bilateral frontal sinuses. CT, computed tomography; sBEC, screening blood eosinophil count.

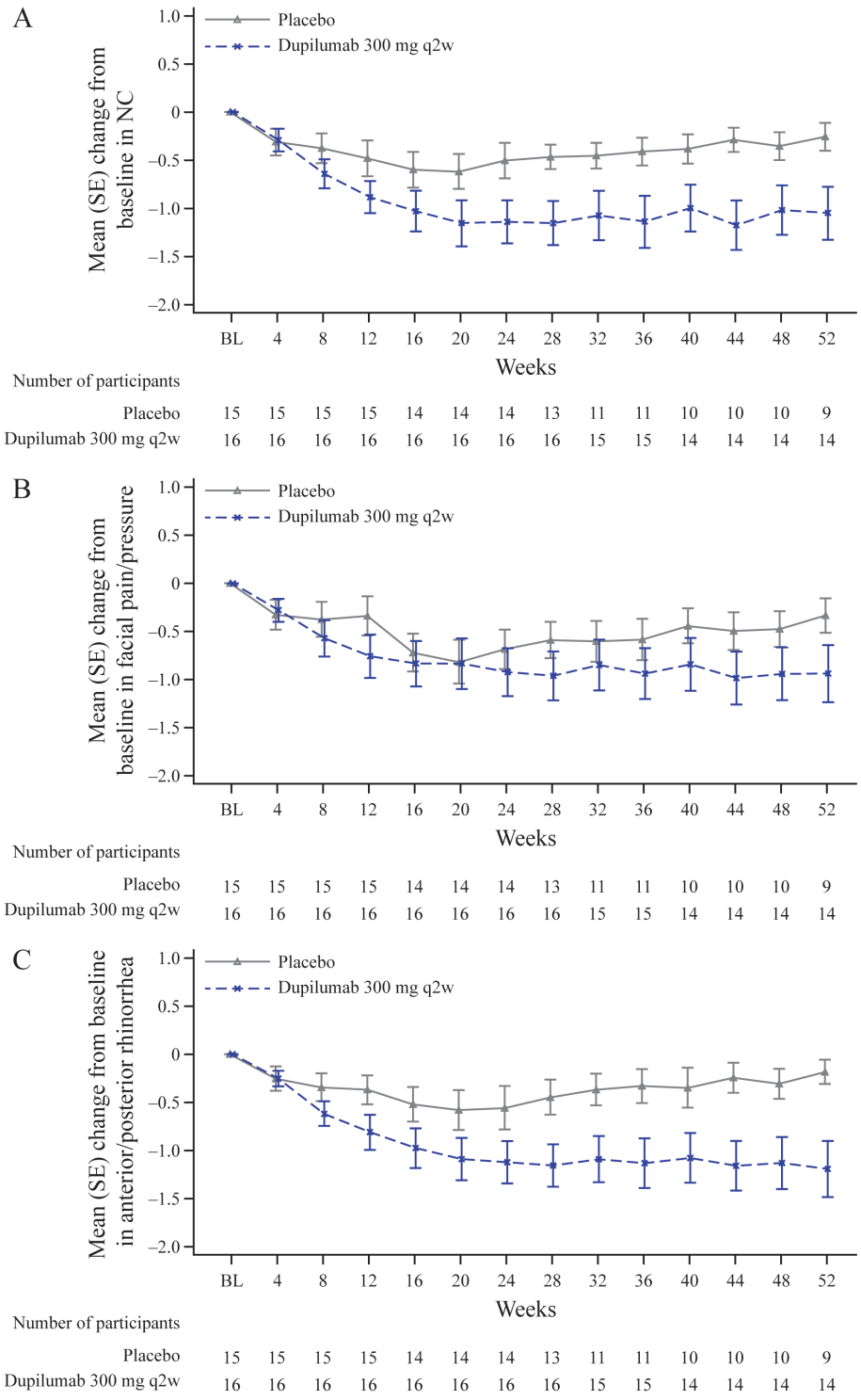
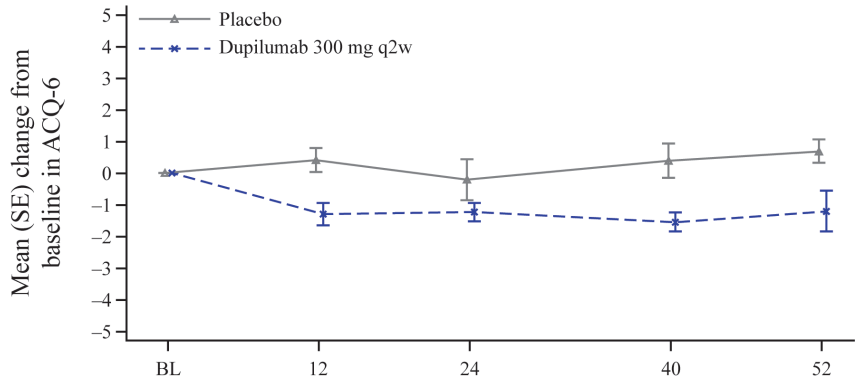
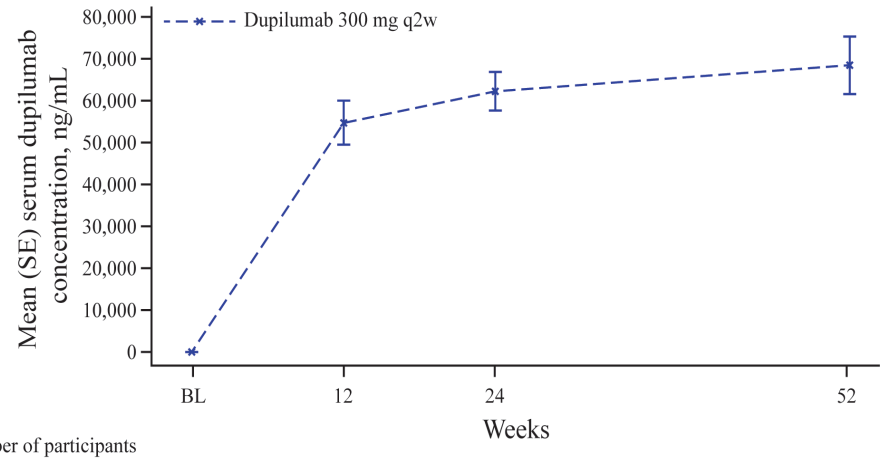


Figure S3. Mean change from baseline in sTSS components over time—ITT population with screening blood eosinophil count ≥300 cells/μL. (A) NC, (B) facial pain/pressure, (C) anterior/posterior rhinorrhea. NC, facial pain/pressure, and anterior/posterior rhinorrhea each have a range of 0 to 3; higher scores indicate greater symptom severity. BL, baseline; ITT, intention-to-treat; NC, nasal congestion; q2w, every 2 weeks; SE, standard error; sTSS, sinus Total Symptom Score.



Number of participants					
Placebo	6	5	6	5	5
Dupilumab 300 mg q2w	9	9	9	8	6

Figure S4. Mean change from baseline in ACQ-6 over time—ITT population with screening blood eosinophil count ≥300 cells/μL and coexisting asthma. ACQ-6 score range 0 to 6; higher scores indicate poorer asthma control. ACQ-6, 6-item Asthma Control Questionnaire; BL, baseline; ITT, intention-to-treat; q2w, every 2 weeks; SE, standard error.



Number of participants				
Dupilumab 300 mg q2w	22	25	28	20

Figure S5. Serum dupilumab concentrations—pharmacokinetic population. BL, baseline; q2w, every 2 weeks; SE, standard error.