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SHORT COMMUNICATION

Dupilumab provides early and durable improvement of symptoms in patients with chronic rhinosinusitis with nasal polyps

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Abstract

Objectives. To evaluate within-patient symptom improvement in the dupilumab SINUS-24/-52 studies in patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP) (NCT02912468/NCT02898454). **Methods.** Patients received dupilumab 300 mg or placebo every 2 weeks for 24 (SINUS-24) or 52 weeks (SINUS-52) on background intranasal corticosteroids. Patients daily reported symptoms of nasal congestion (NC), loss of smell (LoS) and rhinorrhoea on a scale of 0–3 (0 – no symptoms, 1 – mild, 2 – moderate, 3 – severe symptoms). The proportions of patients with moderate-to-severe symptoms (score ≥ 2) at baseline who improved to no-to-mild symptoms (score ≤ 1) were determined at Weeks 2, 24 (pooled studies) and 52 (SINUS-52). Subgroups with prior sinonasal surgery and coexisting asthma were analysed. **Results.** At baseline in the pooled intention-to-treat population (n = 724), the proportions of patients with scores ≥ 2 for NC, LoS and rhinorrhoea were 87, 94 and 64%, respectively. Significantly, more patients achieved scores ≤ 1 (no/mild symptoms) with dupilumab vs placebo for each symptom at each time point {Week 2 NC 12% vs 2% [odds ratio 8.9 (95% CI 3.0–26.3)], LoS 5% vs 1% [4.6 (1.3–16.8)], rhinorrhoea 9% vs 2% [4.8 (1.5–15.4)], all $P < 0.05$; Week 24 NC 54% vs 14% [8.7 (5.6–13.5)], LoS 43% vs 6% [14.4 (7.9–26.0)], rhinorrhoea 53% vs 16% [6.6 (4.1–10.9)], all $P < 0.0001$}. Results were similar in subgroups with prior surgery and coexisting asthma. **Conclusion.** Significantly, more patients achieved improvement from moderate-to-severe symptoms to no-to-mild symptoms with dupilumab than placebo, regardless of

prior surgery or coexisting asthma. Improvement was observed as early as Week 2 and continued through to Week 52.

Keywords: asthma, chronic inflammation, inflammation, interleukins

INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a highly symptomatic inflammatory disease of the upper airways, associated with a significant negative impact on health-related quality of life (HRQoL).[1] Patients with CRSwNP report nasal congestion (NC), loss of smell (LoS) and rhinorrhoea among their most troublesome and severe symptoms.[2] Disease burden can be more pronounced in patients with prior sinonasal surgery and in patients with coexisting inflammatory diseases such as asthma and nonsteroidal anti-inflammatory drug-exacerbated respiratory disease.[3] Despite standard-of-care treatment with intranasal corticosteroids (INCS) and systemic corticosteroids (SCS), the symptoms of CRSwNP often persist, and patients frequently experience recurrence of nasal polyps (NP) after sinonasal surgery.[4]

Chronic inflammation in CRSwNP is primarily driven by a type 2 immune response with the type 2 signature cytokines interleukin (IL)-4 and IL-13 as key and central components.[5,6] Dupilumab is a fully human VelocImmune®-derived monoclonal antibody that binds to IL-4Rα, the shared receptor component for IL-4 and IL-13, thereby blocking signalling by both cytokines.[5,6] Dupilumab is approved as add-on maintenance treatment for adult patients with inadequately controlled CRSwNP.[7] In the randomised, phase 3 SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454) studies in patients with severe CRSwNP, dupilumab added to INCS was generally well-tolerated and significantly improved NC, LoS and rhinorrhoea, disease-related and general HRQoL, and endoscopic and radiographic signs of CRSwNP.[8]

This *post hoc* analysis of the SINUS-24 and SINUS-52 studies assessed the early onset and durable long-term effects of dupilumab on patient-reported symptoms of NC, LoS and rhinorrhoea among patients with moderate-to-severe symptoms at baseline. We include outcomes for a stringent measure of symptom improvement, that is achievement of no or mild symptoms, for each of the key symptoms of CRSwNP in the overall study population and for subgroups with coexisting asthma or prior sinonasal surgery, who are often refractory to treatment.[4]

RESULTS

Demographics and baseline disease characteristics for the overall pooled population were balanced between treatment groups (Table 1). Mean duration of CRSwNP was 11 years, 63.4% of patients had prior sinonasal surgery and 59.1% had coexisting asthma. The proportions of patients reporting moderate-to-severe symptoms (scores ≥ 2) at baseline were 86.7% for NC, 94.1% for LoS and 64.1% for rhinorrhoea; 62.2% of patients reported severity as moderate-to-severe for all three symptoms at baseline.

Significantly, more patients achieved the stringent criterion of no or mild symptoms (scores ≤ 1) with dupilumab than placebo for each of the outcomes by Week 2, as well as at Week 24 and Week 52 (Figure 1). At Week 52, patients were almost seven times more likely to achieve no or mild NC symptoms with dupilumab compared with placebo [OR (95% CI) 6.9 (3.7–12.6), $P < 0.0001$]; over 17 times more likely to have no or mild LoS symptoms [OR 17.4 (6.9–43.8), $P < 0.0001$]; and almost six times more likely to have no or mild rhinorrhoea symptoms [OR 5.9 (3.0–11.9), $P < 0.0001$]. Among patients with available data who did not reach no or mild symptoms, dupilumab-treated patients consistently demonstrated greater improvement in reaching mild-to-moderate symptoms ($1 < \text{scores} \leq 2$) than placebo for all three outcomes at Weeks 2, 24 and 52 (data not shown).

For all three outcome measures, consistently fewer dupilumab- than placebo-treated patients were classified as nonresponders due to either rescue treatments or missing scores.

For the subgroups of patients with coexisting asthma or prior NP surgery, the results at Weeks 24 and 52 were consistent with those of the overall population, with significantly more patients in each subgroup achieving the stringent criterion of no or mild symptoms (scores ≤ 1) with

Table 1. Demographics and baseline disease characteristics (pooled SINUS-24 and SINUS-52)

	Placebo (*n* = 286)	Dupilumab 300 mg q2w (*n* = 438)	Overall (*n* = 724)
Age, years, mean (SD)	51.28 (12.90)	51.47 (12.79)	51.39 (12.83)
Female, *n/n* (%)	121/286 (42.3)	166/438 (37.9)	287/724 (39.6)
Time since first NP diagnosis, years, mean (SD)	10.83 (9.01)	11.12 (9.73)	11.01 (9.45)
Asthma, *n/n* (%)	170/286 (59.4)	258/438 (58.9)	428/724 (59.1)
≥1 prior sinus surgery, *n/n* (%)	187/286 (65.4)	272/438 (62.1)	459/724 (63.4)
SCS use in the previous 2 years, *n/n* (%)	209/286 (73.1)	329/438 (75.1)	538/724 (74.3)
Bilateral endoscopic NPS, range 0–8, mean (SD)	5.91 (1.26)	6.00 (1.24)	5.97 (1.25)
UPSIT score, range 0–40, mean (SD)[a]	14.09 (8.30)	13.90 (8.16)	13.98 (8.21)
NC score, range 0–3, mean (SD)[b]	2.41 (0.54)	2.39 (0.60)	2.40 (0.58)
Moderate-to-severe symptoms (score ≥ 2), *n/n* (%)	255/286 (89.2)	373/438 (85.2)	628/724 (86.7)
In patients with coexisting asthma, *n/n* (%)[c]	153/170 (90.0)	223/258 (86.4)	376/428 (87.9)
In patients with ≥ 1 prior sinus surgery, *n/n* (%)[d]	169/187 (90.4)	238/272 (87.5)	407/459 (88.7)
LoS score, range 0–3, mean (SD)[b]	2.72 (0.52)	2.74 (0.54)	2.74 (0.53)
Moderate-to-severe symptoms (score ≥ 2), *n/n* (%)	271/286 (94.8)	410/438 (93.6)	681/724 (94.1)
In patients with coexisting asthma, *n/n* (%)[c]	163/170 (95.9)	250/258 (96.9)	413/428 (96.5)
In patients with ≥ 1 prior sinus surgery, *n/n* (%)[d]	178/187 (95.2)	256/272 (94.1)	434/459 (94.6)
Rhinorrhoea score, range 0–3, mean (SD)[b,e]	2.04 (0.70)	2.00 (0.71)	2.02 (0.70)
Moderate-to-severe symptoms (score ≥ 2), *n/n* (%)	186/286 (65.0)	278/438 (63.5)	464/724 (64.1)
In patients with coexisting asthma, *n/n* (%)[c]	114/170 (67.1)	172/258 (66.7)	286/428 (66.8)
In patients with ≥ 1 prior sinus surgery, *n/n* (%)[d]	130/187 (69.5)	176/272 (64.7)	306/459 (66.7)

LoS, loss of smell; NC, nasal congestion; NP, nasal polyps; NPS, nasal polyp score; q2w, every 2 weeks; SCS, systemic corticosteroids; SD, standard deviation; UPSIT, University of Pennsylvania Smell Identification Test.

[a]Lower scores indicate worse sense of smell.

[b]Higher scores indicate more severe disease.

[c]Analysed in patients with coexisting asthma.

[d]Analysed in patients with prior sinus surgery.

[e]Average of scores for anterior and posterior rhinorrhoea.

dupilumab than placebo for each of the outcomes at Week 24 and Week 52 (Figures 2 and 3). At Week 52, patients with coexisting asthma were about 13 times more likely to achieve no or mild NC symptoms with dupilumab compared with placebo [OR (95% CI) 13.3 (5.5–32.2), $P < 0.0001$]; over 140 times more likely to have no or mild LoS symptoms [OR 141.8 (11.8–1709.4), $P < 0.0001$]; and almost 11 times more likely to have no or mild rhinorrhoea symptoms [OR 10.7 (3.8–29.7), $P < 0.0001$]. At Week 52, patients who had a history of prior NP surgery were over 11 times more likely to achieve no or mild NC symptoms with dupilumab compared with placebo [OR (95% CI) 11.5 (4.6–28.8), $P < 0.0001$]; over 70 times more likely to have no or mild LoS symptoms [OR 72.4 (8.6–612.8), $P < 0.0001$]; and almost six times more likely to have no or mild rhinorrhoea symptoms [OR 5.9 (2.5–13.9), $P < 0.0001$].

DISCUSSION

This *post hoc* analysis of data from the SINUS-24 and SINUS-52 studies was conducted in a population with severe CRSwNP, based on the majority having moderate-to-severe symptoms of NC, LoS or rhinorrhoea at baseline. This analysis demonstrated that among patients with moderate-to-severe baseline sinonasal symptoms, those who received dupilumab 300 mg q2w were significantly more likely to achieve improvement to no or mild symptoms compared with placebo (i.e. INCS alone). A statistically significant effect of dupilumab on symptom improvement was observed as early as Week 2, using data pooled from both SINUS-24 and SINUS-52 studies, and was continued to Week 52 of SINUS-52, indicating a rapid onset and durable effect of dupilumab. Furthermore, these effects were observed in subgroups with coexisting asthma or with prior NP surgery, both of which are associated with more refractory disease.[4] Our findings are consistent with those reported in the overall SINUS-24/SINUS-52 studies[8] and provide additional insights into when patients with CRSwNP receiving dupilumab might expect to achieve meaningful improvement in their symptom burden,[9] which may help facilitate meaningful

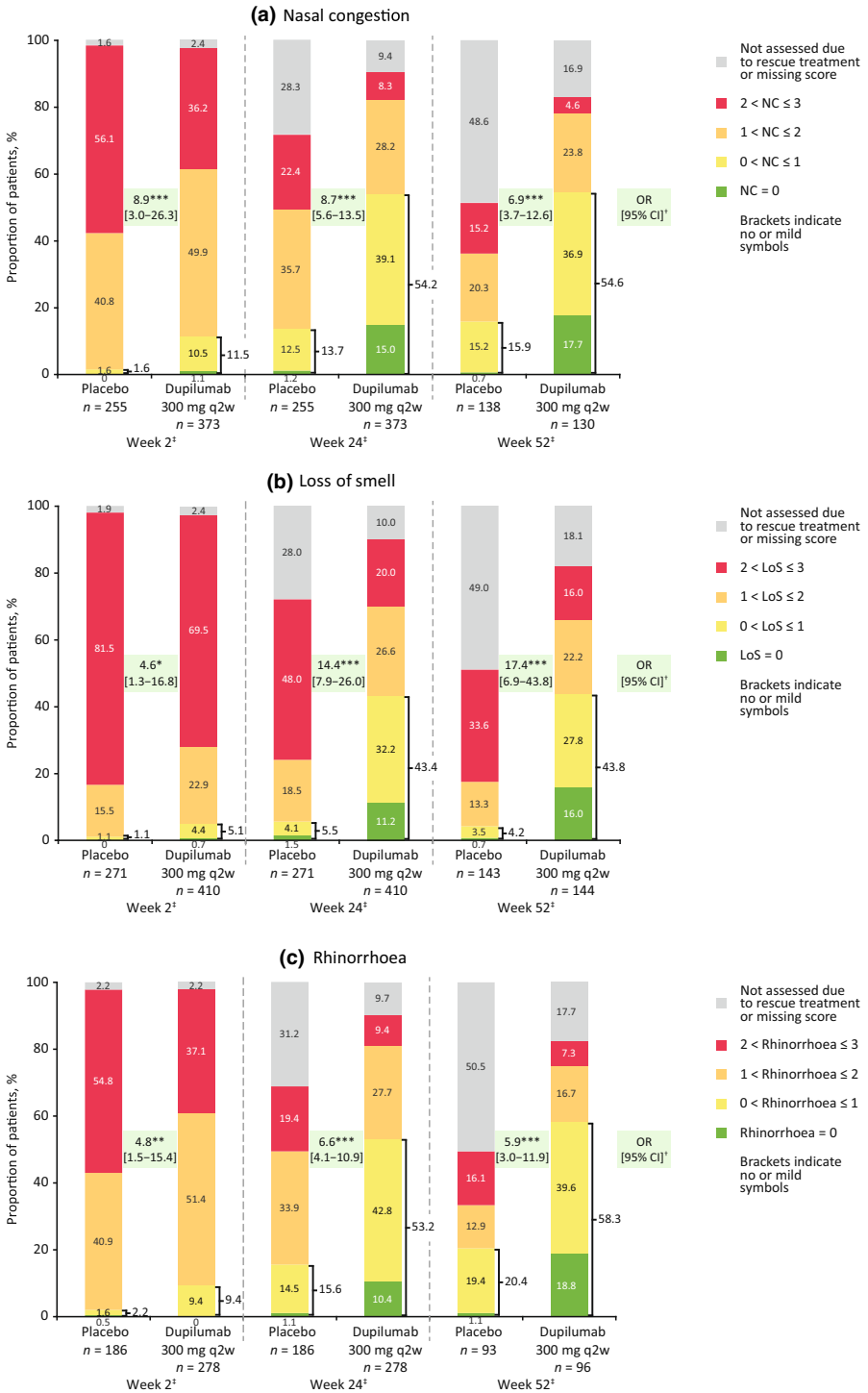

Figure 1. Proportion of patients with moderate-to-severe symptoms of CRSwNP at baseline (score ≥ 2) who achieved symptom scores of 0, > 0 to ≤ 1, > 1 to ≤ 2 or > 2 to ≤ 3 for **(a)** NC, **(b)** LoS or **(c)** rhinorrhoea at Weeks 2 and 24 (pooled SINUS-24 and SINUS-52), and 52 (SINUS-52). †OR [95% CI] presented for dupilumab vs. placebo for the outcome measure of symptom score ≤ 1 (no or mild symptoms). ‡Data are weekly averages for Week 2 and monthly averages for Weeks 24 (pooled SINUS-24 and SINUS-52) and 52 (SINUS-52). *Nominal $P < 0.05$, **$P < 0.01$, ***$P < 0.0001$ vs. placebo. CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; LoS, loss of smell; NC, nasal congestion; OR, odds ratio; q2w, every 2 weeks.

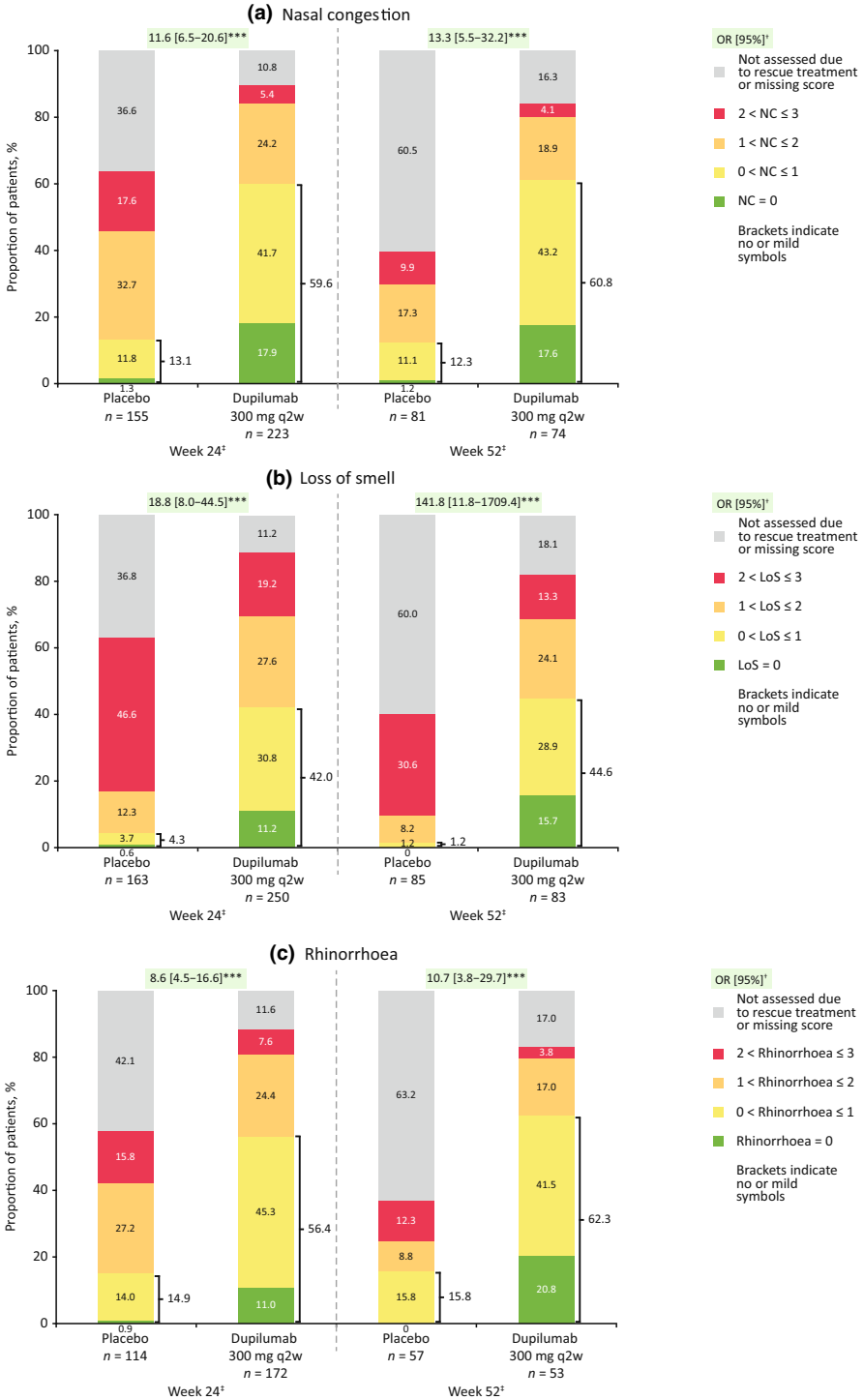

Figure 2. Proportion of patients, among those with coexisting asthma and moderate-to-severe symptoms of CRSwNP at baseline (score ≥ 2), who achieved scores of 0, > 0 to ≤ 1, > 1 to ≤ 2 or > 2 to ≤ 3 for **(a)** NC, **(b)** LoS or **(c)** rhinorrhoea at Weeks 24 (pooled SINUS-24 and SINUS-52) and 52 (SINUS-52). †OR [95% CI] presented for dupilumab vs. placebo for the outcome measure of symptom score ≤ 1 (no or mild symptoms). ‡Data are monthly averages for Weeks 24 (pooled SINUS-24 and SINUS-52) and 52 (SINUS-52). ***Nominal $P < 0.0001$ vs. placebo. CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; LoS, loss of smell; NC, nasal congestion; OR, odds ratio; q2w, every 2 weeks.

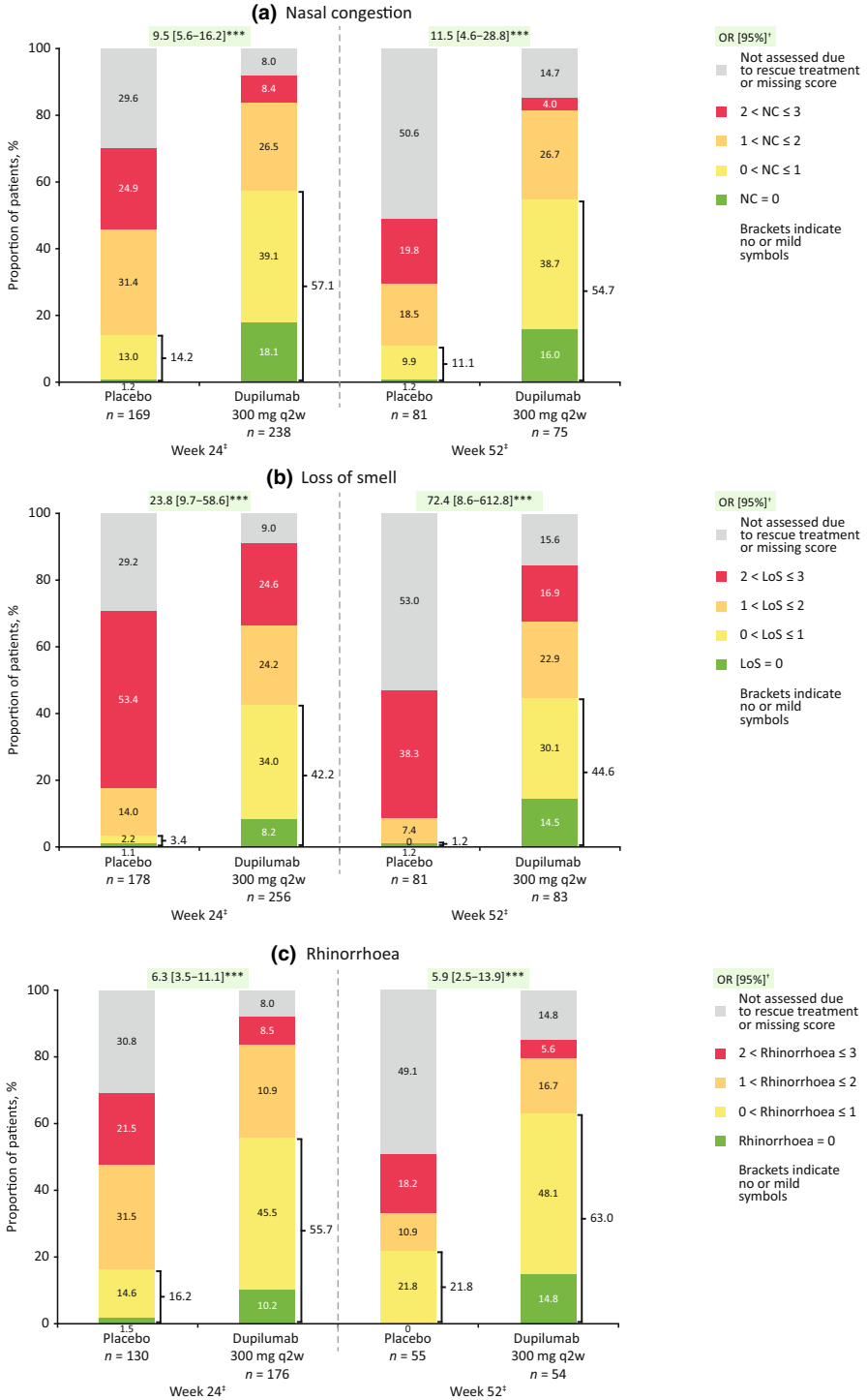

Figure 3. Proportion of patients, among those with prior sinonasal surgery and moderate-to-severe symptoms of CRSwNP at baseline (score ≥ 2), who achieved scores of 0, > 0 to ≤ 1, > 1 to ≤ 2 or > 2 to ≤ 3 for **(a)** NC, **(b)** LoS or **(c)** rhinorrhoea at Weeks 24 (pooled SINUS-24 and SINUS-52) and 52 (SINUS-52). †OR [95% CI] presented for dupilumab vs. placebo for the outcome measure of symptom score ≤ 1 (no or mild symptoms). ‡Data are monthly averages for Weeks 24 (pooled SINUS-24 and SINUS-52) and 52 (SINUS-52). ***Nominal $P < 0.0001$ vs. placebo. CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; LoS, loss of smell; NC, nasal congestion; OR, odds ratio; q2w, every 2 weeks.

physician–patient dialogues on optimal disease management plans.

A limitation of this analysis is its *post hoc* nature and the lack of data beyond 1 year to further the understanding of the long-term dupilumab treatment effects on symptom improvement. It would be interesting to assess whether the reduction in symptom severity experienced by dupilumab-treated patients continued beyond 1 year.

Dual inhibition of IL-4/IL-13 with dupilumab significantly improved patient-reported symptoms of NC, LoS and rhinorrhoea compared with placebo, including in subgroups with prior sinus surgery and coexisting asthma. Symptom improvement was observed as early as Week 2 and continued through to Week 52 of treatment, suggesting a rapid, durable and sustained treatment effect of dupilumab in reducing patient symptom burden.

METHODS

This analysis used data from the phase 3, randomised, double-blind, placebo-controlled, parallel-group SINUS-24 and SINUS-52 studies.[8] Eligible patients in both studies were ≥ 18 years of age, had bilateral NP (bilateral NP score ≥ 5 of maximum score of 8) and had symptoms of CRSwNP despite INCS, SCS within 2 years and/or surgery for NP. Patients were required to have symptoms of NC, LoS or rhinorrhoea, and all patients provided written informed consent. Patients in the SINUS-24 study (n = 276) were randomised 1:1 to dupilumab 300 mg subcutaneous (SC) every 2 weeks (q2w) or matching placebo for 24 weeks. Patients in the SINUS-52 study (n = 448) were randomised 1:1:1 to dupilumab 300 mg SC q2w for 52 weeks, or dupilumab 300 mg SC q2w to Week 24 and then 300 mg SC every 4 weeks to Week 52, or matching placebo for 52 weeks. All patients in both studies received daily background therapy with a stable dose of intranasal mometasone furoate nasal spray.

This *post hoc* analysis included patients with moderate-to-severe symptoms (i.e. scores ≥ 2) at baseline who received dupilumab 300 mg q2w or placebo to Week 24 (pooled SINUS-24 and SINUS-52) and Week 52 (SINUS-52). Data from SINUS-52 were used to assess symptom improvement at Week 52 to understand the dupilumab treatment effect beyond Week 24.

Patients recorded symptom scores daily for NC, LoS and rhinorrhoea (average of scores for anterior and posterior rhinorrhoea) on a scale of 0–3, where 0 – none, 1 – mild, 2 – moderate and 3 – severe. Outcomes assessed were the proportion of patients who achieved symptom improvement, defined as reduction to no or mild symptoms (scores ≤ 1) for NC, LoS or rhinorrhoea at Weeks 2, 24 and 52, and the distribution of patients with scores = 0, > 0 and ≤ 1, > 1 and ≤ 2 and > 2 and ≤ 3 at Weeks 2, 24 and 52. Daily symptom scores were averaged for responder analyses using weekly averages until Week 4 to capture the onset of effect, and monthly averages for Weeks 24 and 52 (as prespecified in the studies).

In addition to the overall population, outcomes were reported for subgroups with coexisting asthma or with prior sinonasal surgery.

Odds ratios (ORs) with 95% confidence intervals (CIs) for the outcome of symptom score ≤ 1 were derived from the Mantel–Haenszel estimator; the Cochran–Mantel–Haenszel test was performed on the association between the outcome and treatment group (dupilumab vs. placebo), stratified by asthma/nonsteroidal anti-inflammatory drug-exacerbated respiratory disease status, prior surgery history, region and, for the analyses on the pooled SINUS studies, by study. Patients with missing scores or with rescue treatment were counted as nonresponders. All P-values are nominal. Descriptive statistics were used to describe the proportions of patients achieving each score reported.

AUTHOR CONTRIBUTIONS

Philippe Gevaert, Stella E Lee, Russell A Settipane and Martin Wagenmann: Performed experiments. Jérôme Msihid, Shahid Siddiqui, Scott Nash, Juby A Jacob-Nara, Asif H Khan, Siddhesh Kamat and Chien-Chia Chuang: Conceived & designed the study. All authors performed data analysis, and all authors read and approved the final manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the Open Science Framework (OSF) repository at https://osf.io/y6atx/, reference number: DOI 10.17605/OSF.IO/Y6ATX

CONFLICT OF INTEREST

PG receives clinical trial funding and is an advisory board member for 3NT, Argenx, Genentech, Novartis, Regeneron Pharmaceuticals Inc., Roche, Sanofi and Stallergenes Greer. SEL receives clinical trial funding and is an advisory board member for GlaxoSmithKline and Sanofi, receives clinical trial funding from AstraZeneca and Genentech, and is an advisory board member for Novartis and Regeneron Pharmaceuticals Inc. RAS receives research grants, fees for lectures and is an advisory board member for AstraZeneca, GlaxoSmithKline and Regeneron Pharmaceuticals Inc., receives fees for lectures and is an advisory board member for Grifols, Pharming and Sanofi, receives research grants and fees for lectures from Genentech, receives fees for lectures from Boehringer Ingelheim, OptiNose and Takeda, is an advisory board member for Aimmune Therapeutics, ALK, BioCryst, DBV Technologies and Pfizer, and receives research grants from Chiesi, Merck, Novartis and Stallergenes Greer. MW is a member of national and international scientific

advisory boards (consulting), receives fees for lectures and research grants from ALK-Abelló, Allakos, AstraZeneca, GlaxoSmithKline, HAL, Meda Pharmaceuticals, Novartis, Otonomy, Roche, Sanofi-Aventis, Stallergenes Greer, Strekin and Teva. C-CC, JAJ-N, AHK and JM are employees and may hold stock and/or stock options in Sanofi. SK and SN are employees and shareholders of Regeneron Pharmaceuticals Inc. SS is a former employee and may hold stock and/or stock options in Regeneron Pharmaceuticals Inc.

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