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Dupilumab improved objective and patient-reported outcomes in patients with chronic rhinosinusitis with nasal polyps and complete nasal obstruction

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Abstract

Aim: The impact of complete bilateral nasal obstruction [nasal polyp score (NPS) = 8/8] on treatment outcomes in chronic rhinosinusitis with nasal polyps (CRSwNP) is unclear. This post hoc analysis assessed disease burden and dupilumab efficacy in patients with severe CRSwNP and baseline NPS = 8 in SINUS-24/-52 (NCT02912468/NCT02898454).

Methods: Efficacy outcomes assessed: NPS, peak nasal inspiratory flow (PNIF), Lund-Mackay computed tomography (LMK-CT), nasal congestion/obstruction (NC), loss of smell (LoS), rhinosinusitis visual analog scale (rhino-VAS), University of Pennsylvania Smell Identification Test (UPSIT), 22-item Sinonasal Outcome Test (SNOT-22) in patients receiving dupilumab 300 mg or placebo every 2 weeks. Responder analyses evaluated clinically meaningful improvements [≥ 1 (NPS, NC, LoS); ≥ 5 (LMK-CT); ≥ 8 (UPSIT); ≥ 8.9 (SNOT-22); ≥ 20 L/min (PNIF)].

Results: Ninety-eight patients were included [59% prior NP surgery, 84% systemic corticosteroids (SCS) use in the previous 2 years, 60% coexisting asthma, 91% anosmic, 97% impaired nasal airflow]. Least squares (LS) mean differences [dupilumab vs. placebo (95% CI)] in change from baseline at week (W) 24: NPS, −2.04 (−2.67, −1.40); PNIF, 65.9 (39.4, 92.4) L/min; LMK-CT, −4.97 (−6.50, −3.44); NC, −1.30 (−1.72, −0.89); LoS, −0.96 (−1.39, −0.54); Rhino-VAS, −3.37 (−4.67, −2.07); UPSIT, 8.55 (4.91, 12.20); SNOT-22, −25.3 (−34.1, −16.4) (all $P < 0.0001$). For all outcomes, significantly greater proportions of dupilumab vs. placebo patients achieved clinically meaningful improvements at W24. Fewer dupilumab vs. placebo

patients required SCS and/or surgery through W24 (11.8% vs. 36.7%; *P* = 0.0005). Efficacy outcomes were similar at W52 (SINUS-52; *n* = 39) with *P* values vs. placebo of < 0.0001 for NPS and NC; 0.0002 for LMK-CT; 0.0031 for LoS; 0.0014 for rhino-VAS; 0.0013 for UPSIT; 0.0012 for SNOT-22.

Conclusions: In patients with CRSwNP with complete bilateral nasal obstruction, dupilumab treatment resulted in clinically significant improvements in NPS, LMK-CT, PNIF, symptoms, and health-related quality of life.

Keywords

Type 2 inflammation, nasal polyposis, nasal inspiratory flow, nasal polyp score, biologics

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a predominantly type 2 inflammatory disease characterized by the presence of nasal polyps (NP) and symptoms of nasal obstruction, smell loss, and rhinorrhea [1]. The extent of nasal obstruction can be assessed using endoscopy and NP score (NPS; range 0–8), with bilateral NPS = 8 signifying complete obstruction [2]. Management of inadequately controlled CRSwNP, especially in patients with complete nasal obstruction, often requires sinonasal surgery followed by interventions including oral corticosteroids and biologics [3]. However, surgery does not control the underlying inflammation and carries a risk of complications, while recurrence is common [1]. There is therefore a need to assess the treatment algorithm for this group, including the potential earlier introduction of biologics to avoid or defer surgery.

Dupilumab blocks signaling by interleukin-4 and interleukin-13, key and central drivers of type 2 inflammation [4]. In the SINUS-24/-52 (NCT02912468/NCT02898454) trials in patients with severe CRSwNP, dupilumab significantly improved mean NPS [5] and increased the proportion of patients achieving clinically meaningful improvement in NPS [6]. Evidence is lacking on the impact of total nasal obstruction on treatment outcomes in CRSwNP. We conducted a post hoc analysis of the SINUS studies to assess dupilumab efficacy in this subgroup.

Materials and methods

Study design and patients

Details of the SINUS-24/-52 studies are published [5]. Briefly, eligible patients were 18 years or older with bilateral CRSwNP and symptoms despite the use of intranasal corticosteroids (INCS) and had received systemic corticosteroids (SCS) in the previous 2 years or had undergone prior sinonasal surgery. Patients had to have bilateral NPS ≥ 5 (≥ 2 each nostril) at screening and at least two of the following symptoms: nasal congestion/obstruction (NC) and either loss of smell (LoS) or nasal discharge (anterior or posterior). Patients received mometasone furoate nasal spray 100 mg in each nostril twice daily during the 28-day run-in before randomization and throughout the treatment period. Patients on background INCS were randomized to dupilumab (Regeneron Pharmaceuticals Inc./Sanofi) 300 mg or placebo every 2 weeks (q2w) for 24 weeks (SINUS-24) or to dupilumab 300 mg or placebo q2w for 52 weeks or dupilumab 300 mg q2w for 24 weeks, then every 4 weeks for 28 weeks (SINUS-52). This analysis included patients in the pooled intention-to-treat (ITT) population with NPS = 8 at randomization and compared patients who received placebo or dupilumab 300 mg q2w. NPS scores were averaged from two independent masked viewers of the endoscopy video.

Outcomes and statistical analyses

Outcomes assessed were NPS, peak nasal inspiratory flow (PNIF), Lund-Mackay computed tomography (LMK-CT; range 0–24), NC (0–3), LoS (0–3), rhinosinusitis visual analog scale (rhino-VAS; 0–10), University of Pennsylvania Smell Identification Test (UPSIT; 0–40), and 22-item Sinonasal Outcome Test (SNOT-22; 0–110).

Least squares (LS) mean changes from baseline for patients treated with dupilumab 300 mg q2w or placebo were assessed at week (W) 24 (pooled SINUS-24/-52) and W52 (SINUS-52). Each of the imputed complete data was analyzed by fitting an analysis of covariance model with the corresponding baseline value, treatment group, asthma/nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD) status, prior NP surgery, regions, and the study (for the pooled SINUS-24/-52) as covariates. Analysis was based on the same imputed dataset using worst observation carried forward (WOCF)/multiple imputation (MI) from the primary analysis of the coprimary endpoints NPS and NC [5].

Responder analyses evaluated the proportion of patients with clinically meaningful improvements in each outcome [7–9]. Odds ratios (ORs) with 95% confidence intervals (CIs) for the comparison of the dupilumab and placebo groups were derived from the Mantel-Haenszel estimator; the treatment groups were compared via a Cochran-Mantel-Haenszel test performed on the association between the responder status and treatment group, stratified by asthma/NSAID-ERD status, prior NP surgery, regions, and study (for the pooled SINUS-24/-52).

Comparisons of the time to NP surgery and/or SCS during treatment were performed using a Cox proportional hazard model, with treatment, asthma/NSAID-ERD status, prior NP surgery, regions, and study (for the pooled SINUS-24/-52) as covariates.

For all analyses, statistical significance was attributed at *P*-values < 0.05; all reported *P*-values are nominal.

Results

Baseline characteristics

Of the pooled ITT population (*n* = 724), 98 patients (13.5%) had NPS = 8 at randomization [30/286 placebo (10.5%); 68/438 dupilumab (15.5%)]. Approximately 59% of patients with NPS = 8 had prior NP surgery (of whom 24% had ≥ 3 previous surgeries), 84% had used SCS in the previous 2 years, and 60% had coexisting asthma (Table 1). Patients had a high symptom burden (mean [standard deviation (SD)] NC score 2.7 [0.4]/3.0 and LoS 2.9 [0.3]/3.0) and 91% were anosmic. Nasal airflow was severely impaired [mean (SD) PNIF 33.8 (45.1) L/min and 97% of patients below the normative value of 138.4 L/min [10]]. In SINUS-52 (*n* = 303), 17/153 (11.1%) placebo patients and 22/150 (14.7%) dupilumab patients had NPS = 8 at baseline.

Efficacy

At W24, 38/273 placebo patients (13.9%) and 16/420 dupilumab patients (3.8%) had NPS = 8 (Figure 1). In patients with NPS = 8 at baseline, 16.7% of placebo patients and 78.1% of dupilumab patients had NPS < 8 at W24, and all outcomes significantly improved with dupilumab vs. placebo (*P* < 0.0001; Figure 2). Similar statistically significant improvements were observed at W52 in SINUS-52 [*P* < 0.0001 for NPS and NC; *P* = 0.0002 for LMK-CT; *P* = 0.0031 for LoS; *P* = 0.0014 for rhino-VAS; *P* = 0.0013 for UPSIT; and *P* = 0.0012 for SNOT-22 (Figure S1)].

At W24 in the pooled population with NPS = 8 at baseline, 69.1% of dupilumab patients had achieved a clinically meaningful improvement in NPS vs. 10.0% of placebo patients [OR (95% CI) 25.1 (4.3, 145.5), *P* < 0.0001; Figure 3]. Over half (55.9%) of dupilumab-treated patients achieved an NPS response at the first post-baseline assessment (W4). The proportions of patients with clinically meaningful improvements in the other outcomes were also significantly greater with dupilumab vs. placebo at W24 [*P* < 0.0001 for NPS, LMK-CT, NC, and LoS; *P* = 0.0002 for PNIF; *P* = 0.0005 for UPSIT; and *P* = 0.0010 for SNOT-22 (Figure 3)]. Similar results were seen at W52 (Figure S2), statistically significant for all outcomes (*P* = 0.0013 for NPS; *P* = 0.0018 for LMK-CT; *P* = 0.0034 for NC; *P* = 0.0013 for LoS; and *P* = 0.0089 for UPSIT) except SNOT-22 (*P* = 0.2569).

Among patients with baseline PNIF < 138.4 L/min, 23/66 (34.8%) dupilumab vs. 0/29 (0%) placebo patients achieved PNIF ≥ 138.4 L/min at W24 (*P* = 0.004).

Table 1. Demographics and baseline characteristics [pooled SINUS-24/-52 studies, subgroup of patients with nasal polyp score (NPS) = 8 and intention-to-treat (ITT) population]

Characteristic	Patients with NPS = 8 (*n* = 98)	ITT population (*n* = 724)
Age, years	53.8 (13.2)	51.4 (12.8)
Male sex, *n* (%)	55 (56)	437 (60)
Region, *n* (%)		
Asia	8 (8)	49 (7)
Latin America	29 (30)	137 (19)
East Europe	22 (22)	216 (30)
Western countries	39 (40)	322 (44)
Time since first NP diagnosis, years	13.5 (10.9)	11.0 (9.5)
Prior NP surgery, *n* (%)	58 (59)	459 (63)
Time since most recent surgery, years	10.1 (6.9)	7.2 (6.4)
Number of previous surgeries, *n* (%)*		
1	36 (62)	254 (55)
2	8 (14)	94 (20)
≥ 3	14 (24)	111 (24)
SCS use in past 2 years, *n* (%)	82 (84)	538 (74)
Asthma, *n* (%)	59 (60)	428 (59)
NSAID-ERD, *n* (%)	32 (33)	204 (28)
NPS (0–8)	8.0 (0.0)	6.0 (1.3)
NC score (0–3)	2.7 (0.4)	2.4 (0.6)
LMK-CT total score (0–24)	18.9 (3.9)	18.4 (4.1)
LoS score (0–3)	2.9 (0.3)	2.7 (0.5)
Anterior rhinorrhea (0–3)	2.4 (0.6)	2.1 (0.7)
Posterior rhinorrhea (0–3)	2.3 (0.8)	2.0 (0.8)
TSS (0–9)	8.0 (1.2)	7.2 (1.4)
Rhinosinusitis VAS (0–10)	8.3 (2.2)	7.9 (2.1)
UPSIT score (0–40)	11.5 (6.3)	14.0 (8.2)
UPSIT anosmia†, *n* (%)	88 (91)‡	551 (78)‡
SNOT-22 total score (0–110)	56.9 (21.6)	50.9 (20.7)
PNIF (L/min)	33.8 (45.1)	87.1 (56.1)
PNIF group (L/min), *n* (%)		
< 97.5	93 (94.9)	453 (62.6)
≥ 97.5–< 138.4	2 (2.0)	150 (20.7)
≥ 138.4	3 (3.1)	121 (16.7)

All data are mean (standard deviation) unless otherwise stated. * Percentages calculated using number of patients with surgery as denominator; † UPSIT < 18; ‡ *n* = 97 (NPS = 8 population), *n* = 710 (ITT population). SCS: systemic corticosteroids; NSAID-ERD: nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; NC: nasal congestion/obstruction; LMK-CT: Lund-Mackay computed tomography; LoS: loss of smell; TSS: total symptom score; VAS: visual analog scale; UPSIT: University of Pennsylvania Smell Identification Test; SNOT-22: 22-item Sinonasal Outcome Test; PNIF: peak nasal inspiratory flow

Fewer dupilumab than placebo patients required SCS and/or NP surgery during the treatment period to W24 (11.8% vs. 36.7%; Cox proportional hazard model $P = 0.0005$); 0/68 dupilumab vs. 2/30 placebo patients had NP surgery. SCS were used by 8/68 (11.8%) dupilumab and 11/30 (36.7%) placebo patients.

Discussion

This analysis focused on patients with severe CRSwNP and complete nasal obstruction despite ongoing standard treatment with INCS and, in most cases, previous surgery. Alongside complete nasal obstruction, patients had high symptom burden at baseline (severe nasal congestion, smell loss, severely reduced nasal airflow) and reduced health-related quality of life (HRQoL). An NPS = 8 would also likely prohibit adequate dispersion of INCS. These characteristics emphasize the need for effective treatment in this subgroup. A

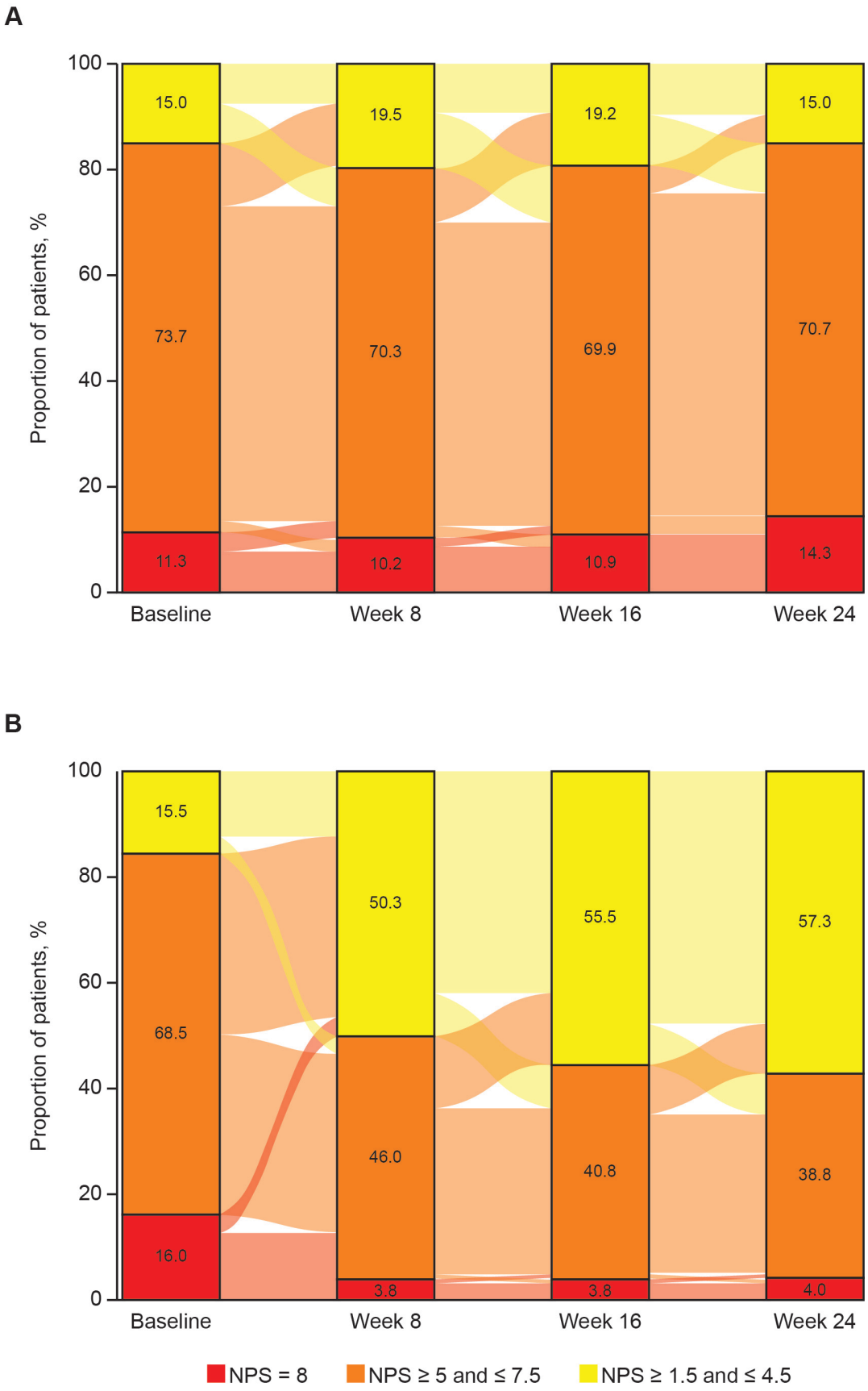

Figure 1. Sankey plots showing the distribution of nasal polyp score (NPS) categories from baseline to week 24 in patients treated with (A) placebo or (B) dupilumab 300 mg every 2 weeks (q2w; pooled SINUS-24/-52 studies)*. Although the eligibility criteria for the SINUS-24 and SINUS-52 studies included a requirement for NPS > 5 at the screening visit, some patients (15.0% and 15.5% of those randomized to placebo and dupilumab 300 mg q2w, respectively) had an NPS below this value (NPS ≥ 1.5 and ≤ 4.5; shown in yellow) at baseline, following the 28-day run-in period when all patients received mometasone furoate nasal spray 100 mg in each nostril twice daily. * Percentages were computed based on the total numbers of patients with a value at each visit. The percentages may not sum to 100.0 due to rounding

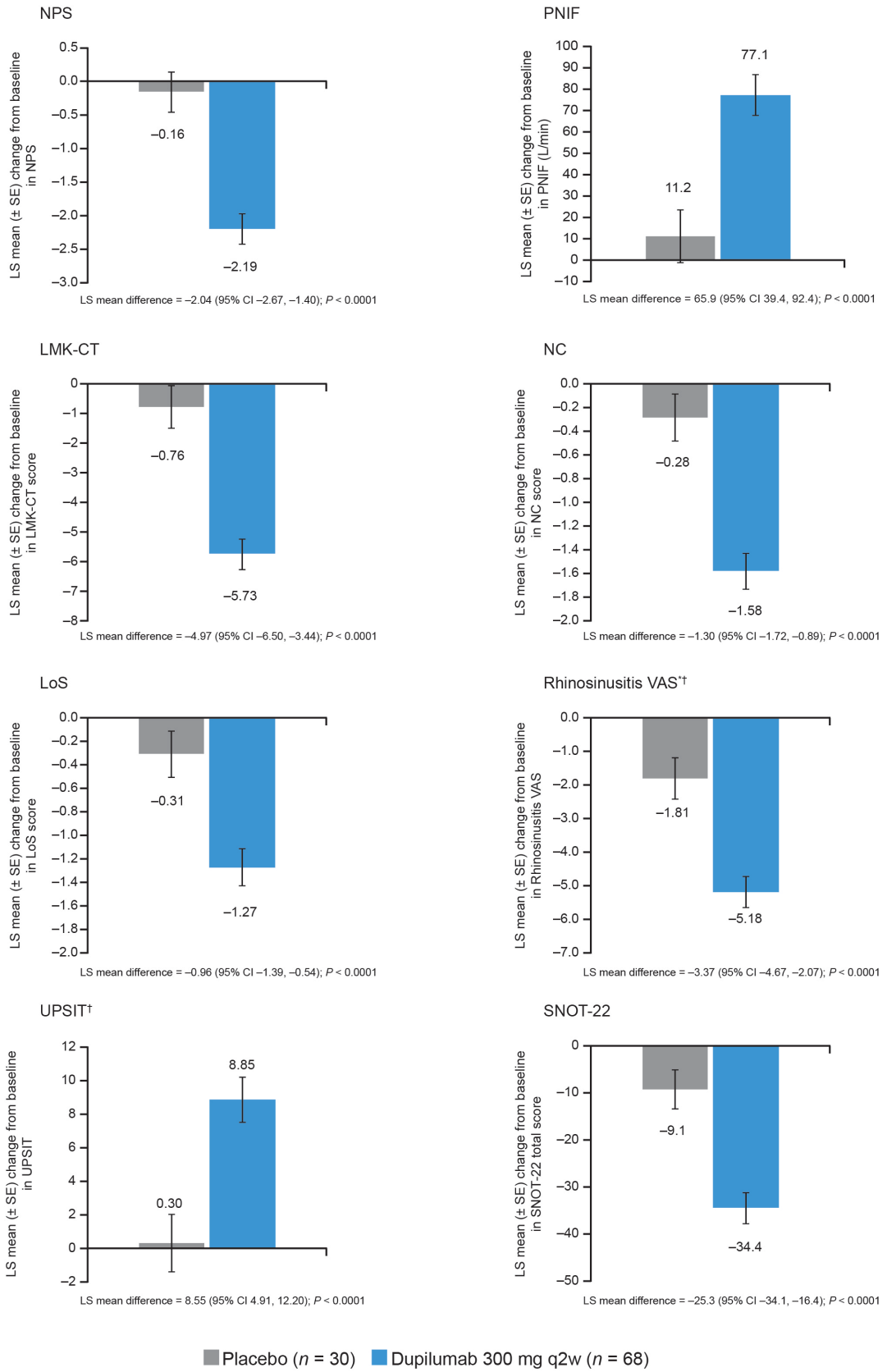

Figure 2. Least squares (LS) mean change from baseline in chronic rhinosinusitis with nasal polyps (CRSwNP) outcomes for placebo and dupilumab 300 mg every 2 weeks (q2w) at week 24 [pooled SINUS-24/-52 studies, subgroup of patients with nasal polyp score (NPS) = 8]. Each of the imputed complete data was analyzed by fitting an analysis of covariance (ANCOVA) model with the corresponding baseline value, treatment group, asthma/nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD) status, prior NP surgery, regions, and the study as covariates. Analysis was based on the same imputed dataset using worst observation carried forward (WOCF)/multiple imputation (MI) from primary analysis of the coprimary endpoints. * Placebo *n* = 29; † dupilumab *n* = 67. SE: standard error; CI: confidence interval; PNIF: peak nasal inspiratory flow; LMK-CT: Lund-Mackay computed tomography; NC: nasal congestion/obstruction; LoS: loss of smell; VAS: visual analog scale; UPSIT: University of Pennsylvania Smell Identification Test; SNOT-22: 22-item Sinonasal Outcome Test

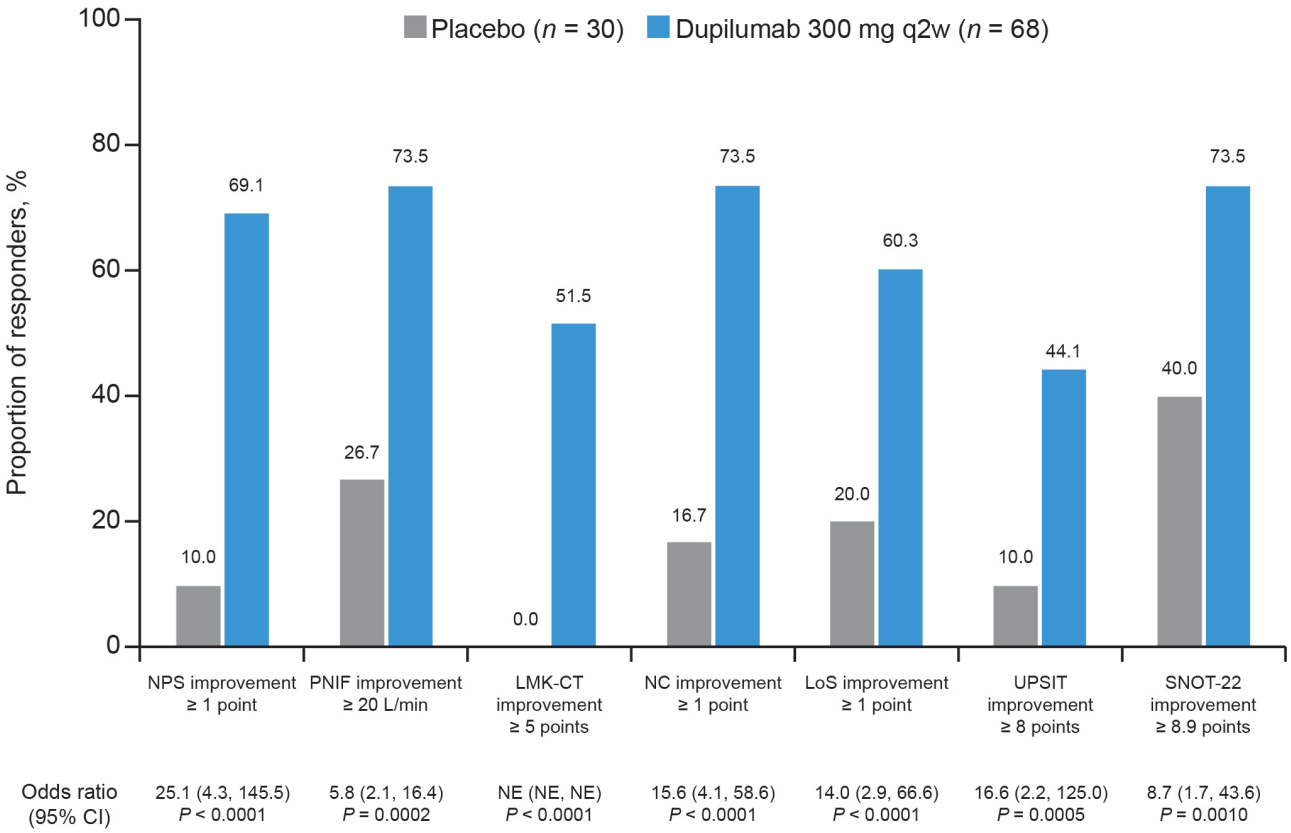

Figure 3. Proportion of responders for placebo and dupilumab 300 mg every 2 weeks (q2w) at week 24 [pooled SINUS-24/-52 studies, subgroup of patients with nasal polyp score (NPS) = 8]. Odds ratios (OR) were derived from the Mantel-Haenszel estimator, with Cochran-Mantel-Haenszel test performed on the association between the responder status and treatment group (dupilumab vs. placebo), stratified by asthma/nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD) status, prior surgery history, study identifier, and region. PNIF: peak nasal inspiratory flow; LMK-CT: Lund-Mackay computed tomography; NC: nasal congestion/obstruction; LoS: loss of smell; UPSIT: University of Pennsylvania Smell Identification Test; SNOT-22: 22-item Sinonasal Outcome Test; CI: confidence interval; NE: not evaluable

standard treatment option for these patients is sinonasal surgery, although we are unaware of any study that has examined the benefit of surgery specifically in patients with NPS = 8. While surgery can provide disease control for extended periods, it does not control the underlying inflammation and polyps may recur. The results of the current analysis suggest that targeting type 2 inflammation with dupilumab may provide a viable alternative to surgery in patients with complete nasal obstruction. These results do not allow comparison of biologic therapy with surgery in this group of patients but future studies addressing this question, or addressing the possibility of a combination of biologic with surgery, may be informative. The relatively small sample size precluded stratification of patients according to surgical status, as it might have been informative to compare outcomes between surgery-naive patients and those with prior surgery. Another important point to consider is the relative public health impact of conventional treatments vs. newer approaches such as biologic therapy. While the evidence is limited, recent studies suggest that patients receiving biologics use more drug-related services but have a reduced need for procedures including nasal endoscopy and sinus CT scans compared with those receiving conventional treatments, and require fewer outpatient visits compared with patients who underwent surgery alone [11, 12]. However, we are unaware of any such data for patients with NPS = 8.

The rapidity of the dupilumab response, with over half of patients responding by W4, is important as the rapid benefit is considered an advantage of surgery. The magnitude of efficacy improvements was similar to those previously reported for the ITT population [5, 6]. The results also add to existing evidence of dupilumab efficacy in patients with multiple prior surgeries [13]. Dupilumab treatment significantly reduced the requirement for SCS, thus lowering the risk of steroid-associated adverse effects [14].

Limitations of this analysis include its post hoc nature, the relatively small sample size, the lack of data on long-term outcomes beyond 52 weeks, and questions regarding generalizability to the wider population

of patients with CRSwNP. The relatively small sample size also precluded subdividing the groups according to surgical status.

In patients with CRSwNP with complete bilateral nasal obstruction, dupilumab treatment resulted in clinically significant improvements in NPS, LMK-CT, nasal inspiratory flow, symptoms, and HRQoL.

Abbreviations

CI: confidence interval

CRSwNP: chronic rhinosinusitis with nasal polyps

INCS: intranasal corticosteroids

ITT: intention-to-treat

LMK-CT: Lund-Mackay computed tomography

LoS: loss of smell

NC: nasal congestion/obstruction

NP: nasal polyps

NPS: nasal polyp score

NSAID-ERD: nonsteroidal anti-inflammatory drug-exacerbated respiratory disease

PNIF: peak nasal inspiratory flow

q2w: every 2 weeks

rhino-VAS: rhinosinusitis visual analog scale

SCS: systemic corticosteroids

SNOT-22: 22-item Sinonasal Outcome Test

UPSIT: University of Pennsylvania Smell Identification Test

W: week

Supplementary materials

The supplementary material for this article is available at: https://www.explorationpub.com/uploads/Article/file/100951_sup_1.pdf.

Declarations

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Author contributions

MW, CB, CH, MC, JM, SN, YD, PJR, HS, and JAJN: Conceptualization, Writing—original draft, Writing—review & editing. JM: Formal analysis. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflicts of interest

MW: ALK-Abelló, AstraZeneca, GlaxoSmithKline, Novartis, Sanofi, Stallergenes Greer, Takeda—advisory board member, lecture fees, and research grants. MC, JM, PJR, and JAJN: Sanofi—employees, may hold stock and/or stock options in the company. CB: ALK, AstraZeneca, GlaxoSmithKline, Mylan, Novartis, Sanofi,

Stallergenes Greer—advisory board member and speakers' fees. CH: AstraZeneca, Dianosic, GlaxoSmithKline, Sanofi—advisory board member. SN, YD, and HS: Regeneron Pharmaceuticals Inc.—employees, may hold stock and/or stock options in the company.

Ethical approval

The SINUS-24 and SINUS-52 studies were conducted according to the principles laid down in the Declaration of Helsinki. Institutional review boards and independent ethics committees reviewed and approved the protocols, informed consent forms, and patient information before study initiation. A full list of institutional review boards and independent ethics committees is shown in Table S1.

Consent to participate

All patients provided signed written informed consent prior to study participation.

Consent to publication

Not applicable.

Availability of data and materials

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.vivli.org/.

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