Original Article

Olfactory Outcomes With Dupilumab in Chronic Rhinosinusitis With Nasal Polyps

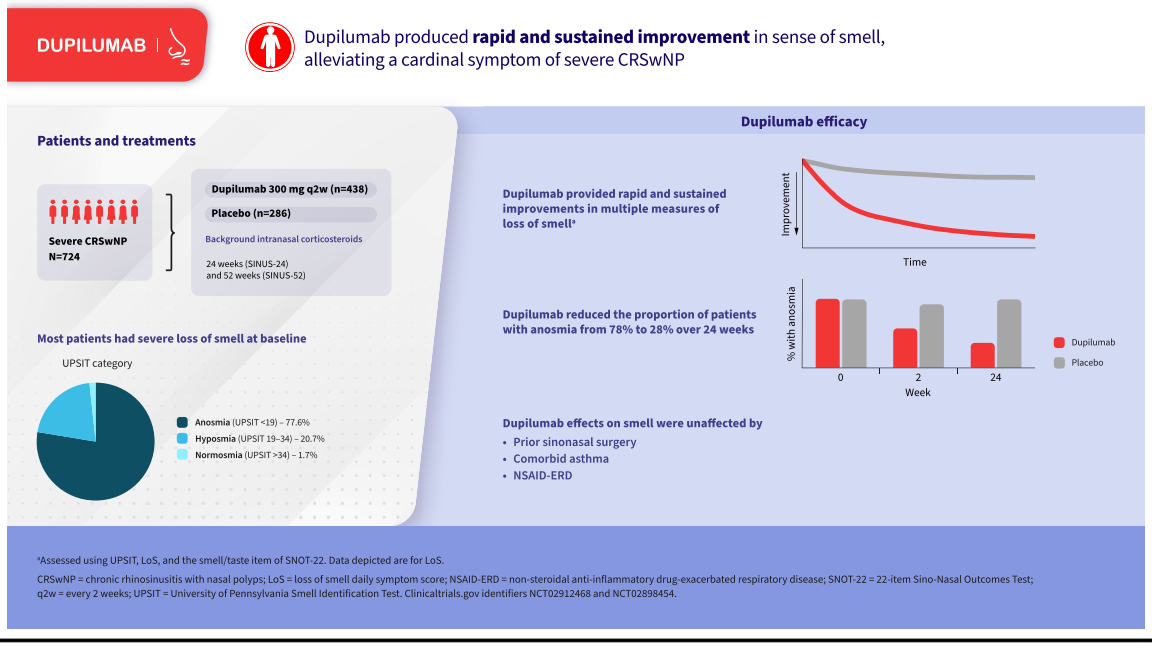
Joaquim Mullol, MD, PhD[a], Claus Bachert, MD, PhD[b,c], Nikhil Amin, MD[d], Martin Desrosiers, MD[e], Peter W. Hellings, MD, PhD[f], Joseph K. Han, MD[g], Roger Jankowski, MD, PhD[h], Jan Vodicka, MD, PhD[i], Philippe Gevaert, MD, PhD[b], Nadia Daizadeh, PhD[j], Asif H. Khan, MBBS, MPH[k], Siddhesh Kamat, MS, MBA[d], Naimish Patel, MD[l], Neil M.H. Graham, MD, MPH[d], Marcella Ruddy, MD[d], Heribert Staudinger, MND, PhD[l], and Leda P. Mannent, MD[k] *Barcelona, Catalonia, Spain; Ghent and Leuven, Belgium; Stockholm, Sweden; Tarrytown, NY; Montreal, Quebec, Canada; Norfolk, Va; Nancy and Chilly-Mazarin, France; Pardubice, Czech Republic; Cambridge, Mass; Bridgewater, NJ*

What is already known about this topic? Loss of smell is one of the most important and difficult-to-treat symptoms for patients with chronic rhinosinusitis with nasal polyps (CRSwNP).

What does this article add to our knowledge? Dupilumab produced rapid, significant, and sustained improvements in sense of smell in patients with severe CRSwNP, including those with prior sinonasal surgery and those with comorbid asthma and nonsteroidal anti-inflammatory drug–exacerbated respiratory disease.

How does this study impact current management guidelines? The ability to alleviate loss of smell, one of the most troublesome and difficult-to-treat symptoms of severe CRSwNP, supports dupilumab as an effective treatment for patients with CRSwNP who otherwise have limited therapeutic options.

VISUAL SUMMARY



[a]Hospital Clínic—IDIBAPS, Universitat de Barcelona, CIBERES, Barcelona, Catalonia, Spain
[b]Ghent University, Ghent, Belgium
[c]Karolinska Institutet, Stockholm, Sweden
[d]Regeneron Pharmaceuticals, Inc., Tarrytown, NY
[e]Centre de recherche du Centre hospitalier de l'Université de Montreal (CRCHUM), Montreal, Quebec, Canada
[f]University Hospitals Leuven, Leuven, Belgium
[g]Eastern Virginia Medical School, Norfolk, Va
[h]Université de Lorraine, ORL CHRU de Nancy, Nancy, France
[i]Faculty of Health Studies, University of Pardubice, Pardubice, Czech Republic
[j]Sanofi, Cambridge, Mass
[k]Sanofi, Chilly-Mazarin, France
[l]Sanofi, Bridgewater, NJ

Abbreviations used
BL- Baseline
CRSwNP- Chronic rhinosinusitis with nasal polyps
CT- Computed tomography
ESS- Endoscopic sinus surgery
HRQoL- Health-related quality of life
IgE- Immunoglobulin E
IL- Interleukin
LMK- Lund-Mackay
LoS- Loss of smell
LS- Least squares
NC- Nasal congestion
NPS- Nasal polyp score
NSAID-ERD- Nonsteroidal anti-inflammatory drug–exacerbated respiratory disease
q2w- Every 2 weeks
SCS- Systemic corticosteroids
SNOT-22- 22-Item Sinonasal Outcome Test
UPSIT- University of Pennsylvania Smell Identification Test

BACKGROUND: Loss of smell (LoS) is one of the most troublesome and difficult-to-treat symptoms of severe chronic rhinosinusitis with nasal polyps (CRSwNP).
OBJECTIVE: To assess the impact of dupilumab on sense of smell in severe CRSwNP.
METHODS: In the randomized SINUS-24 and SINUS-52 studies, adults with severe CRSwNP received dupilumab 300 mg subcutaneously or matching placebo every 2 weeks for 24 or 52 weeks, respectively. Smell was assessed using daily patient-reported LoS score (0–3) and University of Pennsylvania Smell Identification Test (UPSIT; 0–40). Data from the 2 studies were pooled through week 24. Relationships between patient phenotypes and smell outcomes were also assessed.
RESULTS: We randomized 724 patients (286 placebo, 438 dupilumab); mean CRSwNP duration was 11 years; 63% had prior sinonasal surgery. Mean baseline LoS was 2.74. Dupilumab produced rapid improvement in LoS, evident by day 3, which improved progressively throughout the study periods (least squares mean difference vs placebo −0.07 [95% CI −0.12 to −0.02]; nominal $P < .05$ at day 3, and −1.04 [−1.17 to −0.91]; $P < .0001$ at week 24). Dupilumab improved mean UPSIT by 10.54 (least squares mean difference vs placebo 10.57 [9.40–11.74]; $P < .0001$) at week 24 from baseline (score 13.90). Improvements were unaffected by CRSwNP duration, prior sinonasal surgery, or comorbid asthma and/or nonsteroidal anti-inflammatory drug–exacerbated respiratory disease. Baseline olfaction scores correlated with all measured local and systemic type 2 inflammatory markers except serum total immunoglobulin E.
CONCLUSIONS: Dupilumab produced rapid and sustained improvement in sense of smell, alleviating a cardinal symptom of severe CRSwNP. **(J Allergy Clin Immunol Pract 2022;10:1086-95)**

Key words: *Chronic rhinosinusitis with nasal polyps; Sense of smell; Anosmia; Type 2 inflammation; Dupilumab*

INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic inflammatory disease of the nasal and paranasal sinuses characterized by long-term symptoms of rhinosinusitis (nasal congestion, rhinorrhea/postnasal drip, loss of smell [LoS], facial pain/pressure) and presence of nasal polyps on nasal endoscopy.[1] CRSwNP exhibits a type 2 inflammatory signature in the majority of patients in Western countries, characterized by interleukin (IL)-4, IL-5, and IL-13, and infiltration of nasal polyps by eosinophils, basophils, and mast cells.[1-4] Impairment of sense of smell is one of the most troublesome and recalcitrant symptoms in patients with CRSwNP.[2,5] LoS correlates with disease severity, has a substantial impact on quality of life, and may be the first sign of disease recurrence.[6-9]

Existing standard of care does not provide long-lasting restoration of sense of smell in patients with CRSwNP.[5] A 2014 Cochrane review found little evidence of a difference in olfactory outcomes between medical and surgical management of CRSwNP.[10] Long-term topical corticosteroids and repeated bursts/short courses of systemic corticosteroids

This study was funded by Sanofi and Regeneron Pharmaceuticals, Inc. Sanofi and Regeneron Pharmaceuticals, Inc., in collaboration with the academic clinical investigators, provided input on the design and conduct of the study; oversaw the collection, management, and statistical analysis of data; and contributed to the interpretation of the data and the preparation, review, and submission of the manuscript. The final decision on manuscript submission was made by the authors; the sponsors did not have the right to veto or require submission or publication.

Conflicts of interest: J. Mullol has participated in advisory boards for, received research grants from, or participated in speakers' bureaus for ALK-Abelló, AstraZeneca, Genentech, GlaxoSmithKline, Glenmark, Menarini, Mitsubishi Tanabe Pharma, MSD, Mylan-Meda Pharmaceuticals (Viatris), Novartis, Proctor & Gamble, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, UCB Pharma, and Uriach Group. C. Bachert has participated in advisory boards for and/or received speakers' fees from ALK, AstraZeneca, GlaxoSmithKline, Mylan, Novartis, Sanofi, and Stallergenes Greer. N. Amin and S. Kamat are employees of and may hold stock or stock options in Regeneron Pharmaceuticals, Inc. N. M. H. Graham and M. Ruddy are former employees of and may hold stock or stock options in Regeneron Pharmaceuticals, Inc. M. Desrosiers has received clinical trial funding from AstraZeneca, GlaxoSmithKline, Probionase Therapies, and Sanofi; has been an advisory board member of Regeneron Pharmaceuticals, Inc. and Sanofi; and is an equity holder of Probionase Therapies. P. W. Hellings has been an advisory board member of Regeneron Pharmaceuticals, Inc. and Sanofi. J. K. Han has participated in advisory boards for Sanofi. R. Jankowski has participated in advisory boards for ALK, Laboratoire de la Mer, Regeneron Pharmaceuticals, Inc., and Sanofi. J. Vodicka has received clinical trial funding from Novartis. P. Gevaert has received clinical trial funding from and been an advisory board member for 3NT, ALK, Argenx, Genentech, Novartis, Regeneron Pharmaceuticals, Inc., Roche, Sanofi, and Stallergenes Greer. A. H. Khan, N. Patel, H. Staudinger, and L. P. Mannent are employees of and may hold stock or stock options in Sanofi. N. Daizadeh is a former employee of and may hold stock or stock options in Sanofi.

Received for publication May 12, 2021; revised September 15, 2021; accepted for publication September 21, 2021.

Available online October 7, 2021.

Corresponding author: Joaquim Mullol, MD, PhD, Hospital Clínic—IDIBAPS, Universitat de Barcelona, Barcelona, Catalonia, Spain. E-mail: JMULLOL@clinic.cat.

2213-2198

https://doi.org/10.1016/j.jaip.2021.09.037

TABLE I. Demographics and baseline characteristics by anosmia status (pooled studies)*

Characteristic	UPSIT < 19 (anosmic) (n = 551)	UPSIT ≥ 19 (nonanosmic) (n = 159)	Nominal *P*
Age, y, mean (SD)	51.9 (12.9)	49.4 (12.5)	.0259
Male, n (%)	321 (58.3)	107 (67.3)	.0402
NP duration, y, mean (SD)	11.9 (9.7)	8.0 (7.9)	<.0001
Prior sinonasal surgery, n (%)	379 (68.8)	71 (44.7)	<.0001
Number of surgeries, n (% of surgery population)			
1	211 (55.7)	39 (54.9)	
2	74 (19.5)	17 (23.9)	
≥3	94 (24.8)	15 (21.1)	
SCS in the last 2 y, n (%)	408 (74.0)	125 (78.6)	.2407
Any comorbid type 2 medical history† including asthma/NSAID-ERD, n (%)	465 (84.4)	100 (62.9)	<.0001
Asthma, n (%)	358 (65.0)	62 (39.0)	<.0001
NSAID-ERD, n (%)	178 (32.3)	23 (14.5)	<.0001
NPS (0–8), mean (SD)	6.08 (1.22)	5.16 (1.28)	<.0001
NC (morning) score (0–3), mean (SD)	2.44 (0.58)	2.26 (0.56)	.0005
LMK total CT score (0–24), mean (SD)	19.33 (3.58)	15.01 (3.96)	<.0001
Rhinosinusitis severity (VAS 0–10), mean (SD)	8.05 (1.98)	7.19 (2.25)	<.0001
TSS score (0–9), mean (SD)	7.34 (1.34)	6.50 (1.52)	<.0001
SNOT-22 (0–110), mean (SD)	52.34 (20.73)	45.12 (19.35)	.0001
PNIF, L/min, mean (SD)	82.35 (54.80)	103.93 (57.18)	<.0001
FEV_1, L, mean (SD)	2.77 (0.92)	3.16 (0.88)	<.0001
ACQ-6 (patients with asthma), mean (SD)	1.59 (1.10)	1.54 (1.16)	.7362
Blood eosinophils, $\times 10^9$/L, median (95% CI)	0.37 (0.35–0.40)	0.26 (0.23–0.30)	<.0001
Serum total IgE, IU/mL, median (95% CI)	121.0 (105.0–134.0)	118.5 (95.0–150.0)	.3159
Periostin, ng/mL, median (95% CI)	109.0 (104.0–114.0)	86.8 (83.6–93.8)	<.0001
TARC, pg/mL, median (95% CI)	297 (280–310)	270 (243–306)	.0260
Eotaxin-3, pg/mL, median (95% CI)	63.5 (60.5–68.7)	47.3 (42.4–54.7)	<.0001
Nasal‡ total IgE, IU/mL, median (95% CI)	7.0 (5.0–17.0)	4.0 (3.0–5.0)	.0036
Nasal‡ ECP, ng/mL, median (95% CI)	34.0 (24.0–43.0)	8.0 (6.0–41.0)	.0085

ACQ-6, 6-Item Asthma Control Questionnaire; *ECP,* eosinophil cationic protein; *FEV_1,* forced expiratory volume in 1 s; *NP,* nasal polyp; *PNIF,* peak nasal inspiratory flow; *TARC,* thymus and activation–regulated chemokine; *TSS,* total symptom score; *VAS,* visual analog scale.

*Higher scores indicate greater disease severity, except for UPSIT, where higher scores indicate lower disease severity. *P* values are based on *t* test for means, Wilcoxon rank sum test for medians, and chi-square test for categorical variables.

†A patient was considered to have comorbidity history or ongoing comorbid disease if the patient had or has any of the following diseases: atopic dermatitis, allergic conjunctivitis, allergic rhinitis (any, seasonal, perennial), eosinophilic esophagitis, food allergy, and/or hives.

‡Assessed in SINUS-52 only.

(SCS) when symptoms worsen are the standard medical approaches for treatment of olfactory dysfunction in patients with CRSwNP.[5] A recent prospective study of olfactory outcomes after endoscopic sinus surgery (ESS) in patients with CRSwNP found that patients whose olfaction did not respond to oral corticosteroids did not benefit from surgery.[11] Moreover, in those patients who benefited from surgery, improvement in olfaction was often not long-lasting, peaking approximately by 1 month and decreasing by 3 months after surgery.[11] A separate prospective analysis found olfactory disturbance to be the most frequently mentioned postoperative disabling problem at 6 weeks and 7 months postsurgery.[12] In a recent cross-sectional analysis of patient-reported outcomes, patients with a history of ESS did not report improvement in sense of smell compared with patients without a history of ESS, and olfactory impairment worsened with increasing number of ESS procedures.[13]

The mechanism of reversing sensorineural loss in patients with chronic rhinosinusitis with or without polyposis is not well understood. Olfactory dysfunction in CRSwNP appears to be multifactorial, involving effects of chronic inflammation on the olfactory mucosa, edema of the neuroepithelium that impedes the transmission of synaptic impulses (neurosensory processes), in addition to changes in airflow within the olfactory cleft (conductive processes).[14,15] Direct neurotoxic actions of inflammatory mediators have been proposed.[16-19] Superior turbinate eosinophilia and sinus opacification have also been implicated in LoS in CRSwNP.[2,20-22] However, although Lund-Mackay (LMK) computed tomography (CT) scores of sinus opacification correlate with presurgery olfactory dysfunction, there is no correlation between LMK CT scores and postoperative improvements in olfaction.[23] These observations suggest that inflammation within the mucosa of the olfactory cleft may cause irreversible changes that limit postoperative improvement in olfaction following sinonasal surgery. A mouse model of allergic chronic rhinosinusitis demonstrated a decrease of immature olfactory neurons associated with a type 2/Th2 response (including IL-4, IL-13, and IL-5 messenger RNA levels confirmed at protein level) within the olfactory area.[24]

Dupilumab is a fully human VelocImmune-derived monoclonal antibody that inhibits signaling of both IL-4

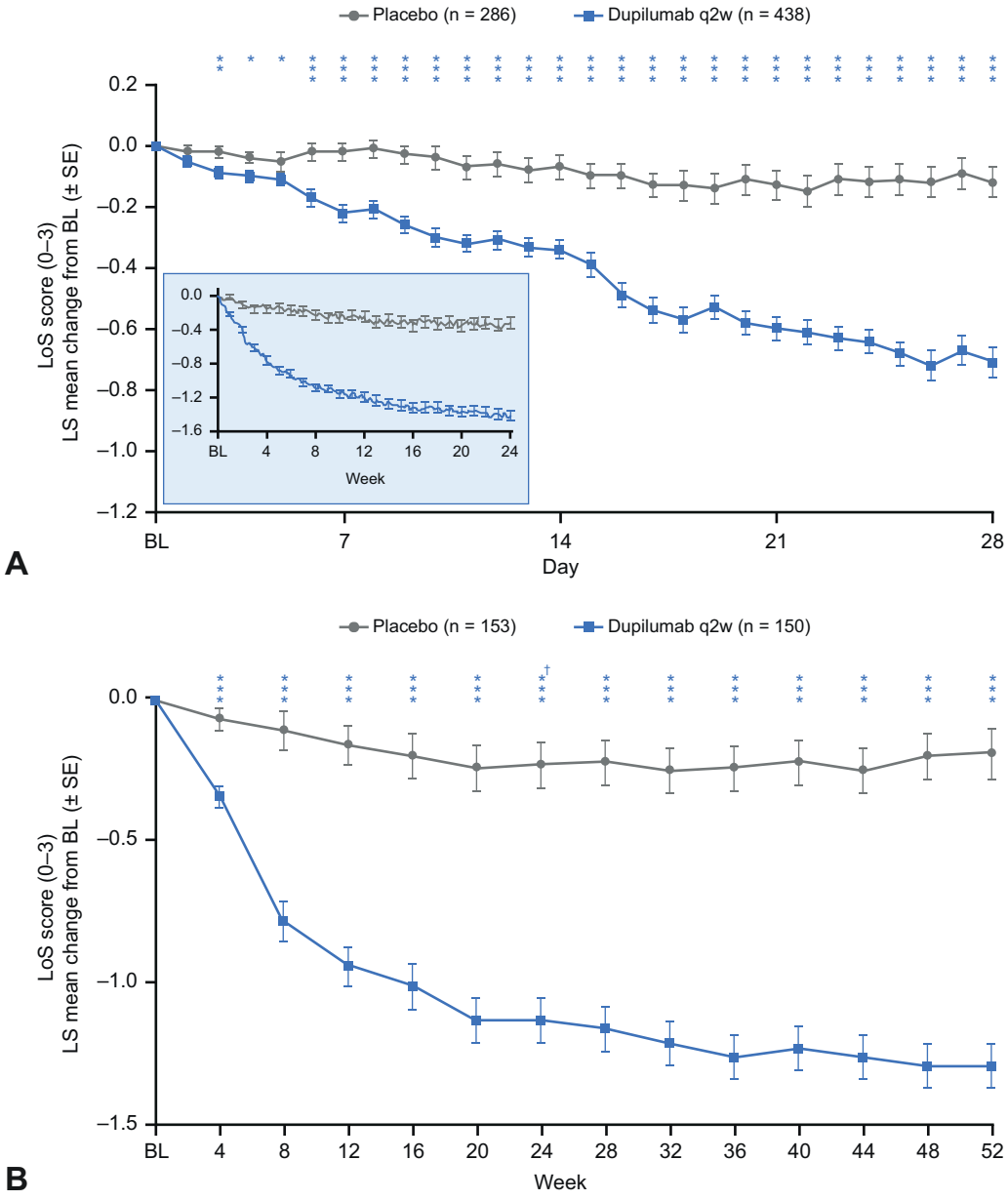


FIGURE 1. Change in daily assessed LoS symptom score. (**A**) Daily scores to day 28 (main panel) and week 24 (inset) in pooled SINUS-24 and SINUS-52. (**B**) Monthly average scores to week 52 in SINUS-52.‡ Nominal *P* versus placebo * < .05; ** < .01; *** < .001. Derived from ANCOVA model with change from BL at the corresponding visit as the response variable and the corresponding BL value, treatment group, asthma/NSAID-ERD status, prior surgery history, region, and study indicator as covariates. The number of imputed values by visit is given in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org). *ANCOVA,* Analysis of covariance; *SE,* standard error. †Prespecified *P* versus placebo < .0001. ‡Average of previous 28 days.

and IL-13, key cytokines involved in type 2–mediated inflammation.[25-27] Dupilumab subcutaneous injection is approved for the treatment of adults with inadequately controlled CRSwNP.[28,29] In the phase 3 SINUS 24-week and 52-week trials in adults with severe CRSwNP (NCT02912468 and NCT02898454), dupilumab added to standard of care significantly reduced polyp size, sinus opacification, and severity of symptoms versus placebo and was generally well tolerated.[30]

The objective of the analyses presented here is to comprehensively assess the impact of dupilumab on olfactory outcomes in patients with severe CRSwNP in the SINUS trials.

METHODS

Study design, patients, and interventions

SINUS-24 and -52 were multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies

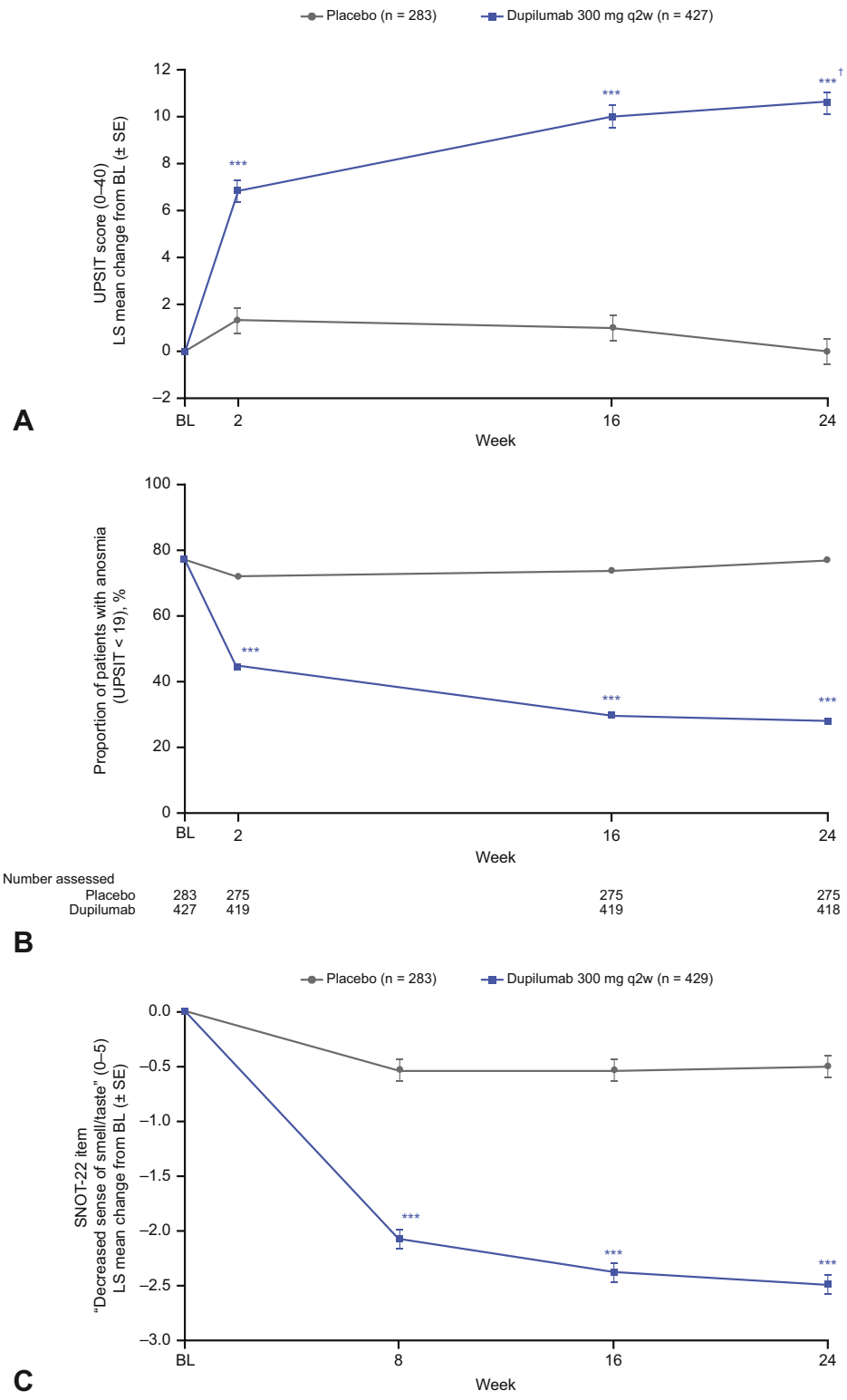


FIGURE 2. Change in UPSIT score, proportion of patients with anosmia, and SNOT-22 item "Decreased sense of smell/taste." (**A**) UPSIT score in pooled SINUS-24 and SINUS-52. (**B**) Proportion of patients with anosmia in pooled SINUS-24 and SINUS-52. (**C**) SNOT-22 item "Decreased sense of smell/taste" in pooled SINUS-24 and SINUS-52. ***Nominal $P < .001$ versus placebo. The *P* values for **A** and **C** were derived using ANCOVA with change from BL at the corresponding visit as the response variable and the corresponding BL value, treatment group, asthma/NSAID-ERD status, prior surgery history, region, and study as covariates (the number of imputed values by visit is given in Table E2). The *P* values for **B** were obtained based on chi-square test. *ANCOVA,* Analysis of covariance; *SE,* standard error. †Prespecified *P* versus placebo $< .0001$.

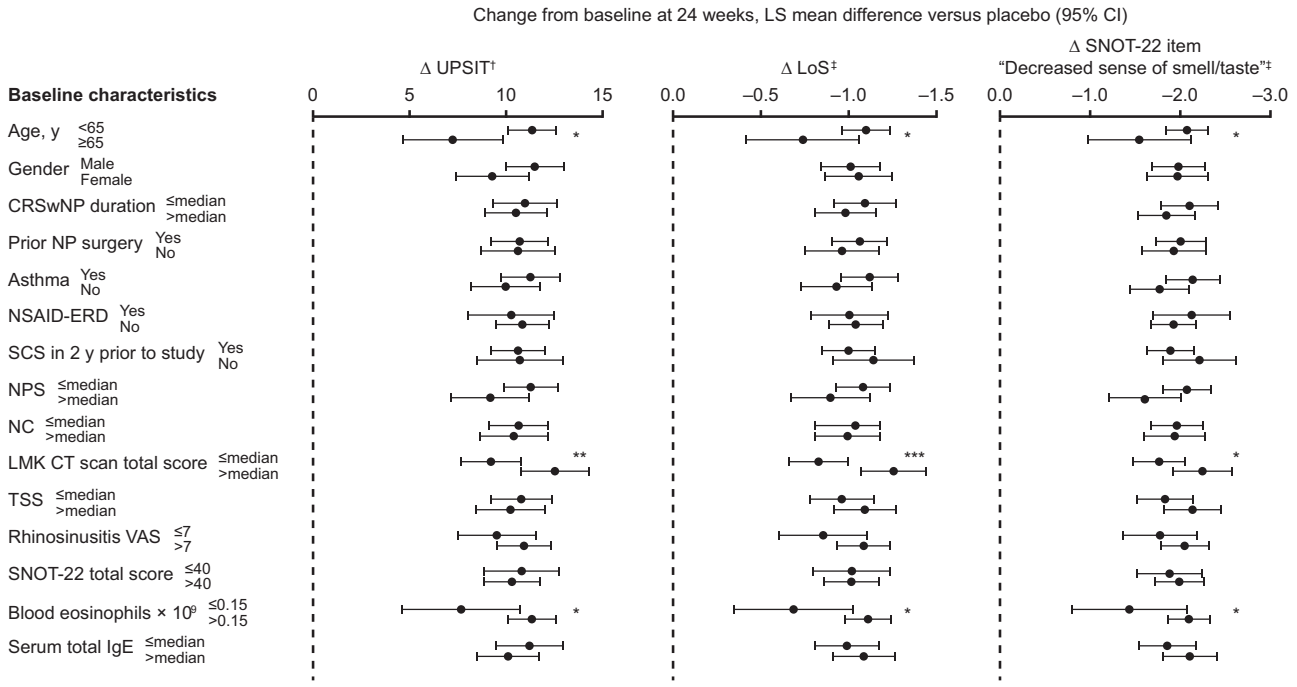


FIGURE 3. Treatment effect at 24 weeks in 3 measures of olfaction by specified BL characteristics (pooled studies). Overall *P* for interaction * < .05, ** < .01, *** < .001. Each of the imputed complete data was analyzed by fitting an ANCOVA model with the corresponding BL value, treatment group, asthma/NSAID-ERD status, prior surgery history, region, and study indicator as covariates, plus the subgroup variable and the subgroup-by-treatment interaction. Analysis was based on the same imputed dataset using WOCF/MI from primary analysis of the end point in each of the 2 studies. *ANCOVA,* Analysis of covariance; *MI,* multiple imputation; *NP,* nasal polyp; *TSS,* total symptom score; *VAS,* visual analog scale; *WOCF,* worst observation carried forward. †Lower scores indicate more severe disease. ‡Higher scores indicate more severe disease.

conducted in hospitals or referral centers in 25 countries.[30] The studies were conducted in accordance with Good Clinical Practice and with the principles ordained in the Declaration of Helsinki, protocols were approved by appropriate ethical review boards, and all patients provided written informed consent. Patients 18 years of age or older with bilateral nasal polyps (nasal polyp score [NPS] ≥ 5 out of maximum 8) and symptoms of chronic rhinosinusitis despite intranasal corticosteroid therapy were eligible if they had received SCS in the preceding 2 years (or had a medical contraindication or intolerance to SCS) or previous sinonasal surgery. Patients received 100 μg of mometasone furoate nasal spray in each nostril twice daily from 4 weeks prior to randomization to the end of the study. Patients were randomized 1:1 to double-blind treatment with subcutaneous dupilumab 300 mg or matching placebo every 2 weeks (q2w) for 24 weeks in SINUS-24, and 1:1:1 to either subcutaneous dupilumab 300 mg q2w for 52 weeks, subcutaneous dupilumab 300 mg q2w for 24 weeks followed by every 4 weeks to 52 weeks, or placebo throughout in SINUS-52. Both studies achieved their primary objective of reduction in their coprimary end points: (1) nasal congestion/obstruction (NC) score and (2) bilateral NPS at week 24. Further details of the studies have been described previously.[30]

Assessments

Sense of smell was assessed using a patient-reported LoS symptom score recorded daily using an eDiary with a scale of 0 to 3, where 0 = no symptom, 1 = mild LoS, 2 = moderate LoS, and 3 = severe LoS. In addition, the University of Pennsylvania Smell Identification Test (UPSIT; scale 0–40) was administered in the clinic at baseline (BL) and at weeks 2, 8, 16, and 24 in SINUS-24, and weeks 2, 4, 16, 24, and 52 in SINUS-52. Higher scores indicate better sense of smell in UPSIT, and scores less than 19 indicate anosmia. Sense of smell was also assessed in the health-related quality of life (HRQoL) 22-item Sinonasal Outcome Test (SNOT-22) with the item "Decreased sense of smell/taste," which has a scale of 0 to 5, with 0 being "No problem" and 5 being "Problem as bad as it can be." The SNOT-22 was completed in the clinic at BL and at weeks 8, 16, and 24 in SINUS-24 and weeks 4, 8, 16, 24, 40, and 52 in SINUS-52.

Statistical methods

Power calculations for the primary end points and procedures for randomization and blinding were detailed previously.[30] Data are presented for placebo and dupilumab 300 mg q2w, pooled from SINUS-24 and SINUS-52 up to week 24, and from SINUS-52 up to week 52. The BL differences between patients with and without anosmia (UPSIT < 19) were tested using Student *t* test or Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables. Among patients who were anosmic at BL, the proportion who became nonanosmic at week 24 was compared using Cochran–Mantel–Haenszel test with treatment, asthma/nonsteroidal anti-inflammatory drug–exacerbated respiratory disease (NSAID-ERD) status, surgery history, region, and study as covariates. Associations between BL smell scores and other BL measures were analyzed by Spearman correlation.

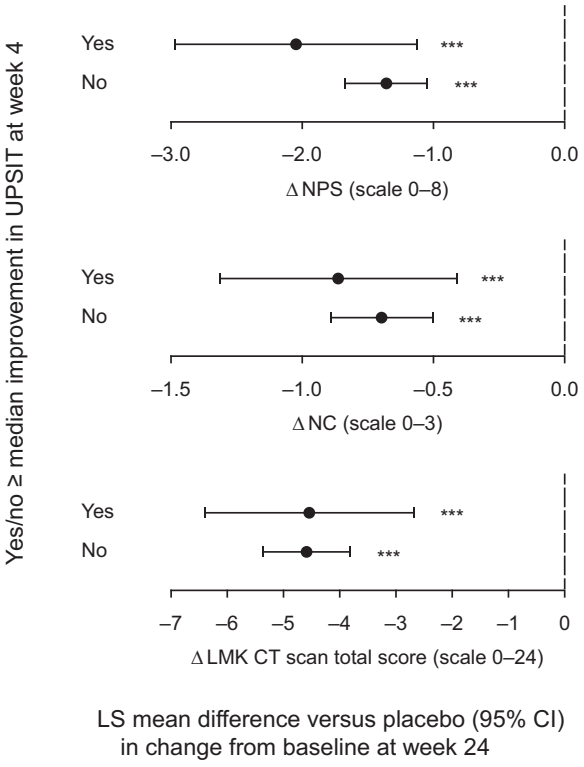


FIGURE 4. Week 24 treatment effect on NPS, NC, and LMK score by week 4 UPSIT response† in SINUS-52‡. ***Nominal $P < .001$ versus placebo. †Responses classified as ≥ or < median change at week 4. ‡Among patients with impaired sense of smell (UPSIT ≤ 33) at BL (n = 429).

Change from BL at week 24 in UPSIT and LoS symptom score were prespecified secondary end points.[30] Other analyses reported here are *post hoc* and associated *P* values are not multiplicity-adjusted and are reported as nominal accordingly. BL LoS was taken as the average of daily scores over the 7 days prior to day 1. LoS analyses at weeks 24 and 52 used the average of daily LoS scores for days 142 to 169 and days 338 to 365, respectively. Change from BL in smell outcomes was analyzed for the intention-to-treat population using a hybrid of the worst observation carried forward and multiple imputation methods, followed by an analysis of covariance model, with the BL value of the corresponding end point, treatment, asthma or NSAID-ERD status, surgery history, study indicator, and region as covariates. For patients who received SCS or who underwent sinonasal surgery for any reason, data collected postsurgery or post-SCS treatment were set to missing in the worst observation carried forward multiple imputation approach, and the worst post-BL value on or before the time of surgery or SCS treatment was used to impute missing week 24 values. For patients who discontinued treatment without rescue by surgery or SCS, a multiple imputation approach was used to impute missing values, using values of all patients who had not been rescued by surgery or were not receiving SCS. Statistical inference obtained from all imputed data was combined using Rubin's rule.[31] To compare effects between subgroups, a similar analysis of covariance model was carried out, with the addition of the subgroup covariate and the subgroup-by-treatment interaction. The interaction *P* value was calculated from this model.

RESULTS

Patient characteristics

The pooled intention-to-treat population comprised 724 patients: 286 in placebo groups and 438 in dupilumab-treatment groups. Demographic and BL characteristics were well balanced across treatment groups, as reported previously (Table E1; available in this article's Online Repository at www.jaci-inpractice.org).[30] Mean duration of CRSwNP was 11.0 years (SD 9.5), 459 patients (63.4%) had prior sinonasal surgery, of whom 205 (44.7%) had 2 or more prior sinonasal surgeries, and 538 patients (74.3%) had received SCS in the previous 2 years. The great majority of patients had severely impaired sense of smell; mean self-reported LoS symptom score was 2.74 (SD 0.53) out of maximum 3. Among the 710 patients who completed an UPSIT assessment at BL, mean UPSIT score was 14.0, 551 patients (77.6%) were anosmic (UPSIT score < 19), 147 (20.7%) were hyposmic (UPSIT 19−34), and only 12 patients (1.7%) were normosmic (UPSIT > 34; Table E1). The SNOT-22 questionnaire item ranked most important by patients was "Decreased sense of smell/taste" (87.4% of patients), and this item had the greatest mean BL score (4.28 out of maximum 5; Figure E1; available in this article's Online Repository at www.jaci-inpractice.org).

Baseline associations of smell dysfunction

Patients who were anosmic at BL (UPSIT < 19) had lower HRQoL assessed by SNOT-22, greater prevalence of asthma and/or NSAID-ERD, and more of them had undergone prior sinonasal surgery than patients without anosmia (UPSIT ≥ 19; Table I). Moreover, compared with patients without anosmia, patients with anosmia had longer duration of CRSwNP, more severe CRSwNP disease measured by rhinosinusitis severity visual analog scale, NC, NPS, total symptom score, and LMK CT scores, lower peak nasal inspiratory flow, worse lung function assessed by forced expiratory volume in 1 s, and higher levels of all assessed type 2 inflammatory markers in blood (eosinophils, periostin, thymus and activation−regulated chemokine, eotaxin-3) and nasal secretions (eosinophil cationic protein, total immunoglobulin E [IgE]), except serum total IgE (Table I). Similar associations of BL disease activity scores and biomarker levels with BL olfactory function were observed across the 3 measures of olfaction (Figure E2; available in this article's Online Repository at www.jaci-inpractice.org).

Smell outcomes

Dupilumab produced rapid improvements in sense of smell. Differences versus placebo were evident by day 3 for daily patient-reported LoS (least squares [LS] mean difference −0.07; 95% CI −0.12 to −0.02; nominal $P < .01$; Figure 1, *A*), and at the first assessments for UPSIT (week 2; LS mean difference 5.53; 95% CI 4.38−6.69) and SNOT-22 item "Decreased sense of smell/taste" (week 8; LS mean difference −1.54; 95% CI −1.77 to −1.32; both nominal $P < .0001$; Figure 2).

Daily patient-reported mean LoS improved progressively throughout the study (Figure 1). In the pooled population, LS mean change in LoS with dupilumab was −1.30 by week 24 (average of previous 28 days' daily assessments), representing a 47.5% improvement from BL, and the difference versus placebo was −1.04 (95% CI −1.17 to −0.91); *P* less than .0001. In SINUS-52, LS mean change in LoS with dupilumab was −1.21 at week 24 and −1.29 at week 52, with differences versus

placebo of −0.98 (95% CI −1.15 to −0.81) and −1.10 (95% CI −1.31 to −0.89), respectively; both P less than .0001 (Figure 1, *B*). Mean UPSIT increased with dupilumab at each assessment to week 24 in the pooled population (LS mean change 10.54 at week 24; difference vs placebo 10.57 [95% CI 9.40−11.74]; $P < .0001$; Figure 2, *A*). The proportion of patients with anosmia in the dupilumab group declined from 78% at BL to 45% at week 2 and 28% at week 24 (both nominal $P < .0001$; Figure 2, *B*). In the placebo group, the proportion of patients who were anosmic was unchanged at week 24 relative to BL (77%). Among patients who were anosmic at BL, 62.3% of dupilumab-treated patients became nonanosmic at week 24 compared with 5.5% of placebo patients (using nonresponder imputation; odds ratio 45.1 [95% CI 21.0−97.2]; nominal $P < .0001$). In SINUS-52, LS mean change in UPSIT with dupilumab was 9.71 at week 24 and 9.53 at week 52, with differences versus placebo of 10.52 (95% CI 8.98−12.07) and 10.30 (95% CI 8.5−12.10), respectively; both $P < .0001$ (Figure E3, *A*; available in this article's Online Repository at www.jaci-inpractice.org). In the pooled population, improvement in SNOT-22 item "Decreased sense of smell/taste" with dupilumab increased at each assessment to LS mean change −2.49 at week 24 (difference vs placebo −1.97 [95% CI −2.19 to −1.75]; nominal $P < .0001$; Figure 2, *C*). In SINUS-52, LS mean change in SNOT-22 item "Decreased sense of smell/taste" with dupilumab was −2.46 at week 24 and −2.59 at week 52, with differences versus placebo of −1.92 (95% CI −2.21 to −1.63) and −2.23 (95% CI −2.57 to −1.88), respectively; both P less than .0001 (Figure E3, *B*). Smell outcomes worsened after discontinuation of dupilumab at week 24 in patients in SINUS-24.[30]

Association of BL characteristics with smell outcomes

Dupilumab effects on smell were unaffected by gender, CRSwNP duration, prior surgery, SCS use in the previous 2 years, history of comorbid asthma or NSAID-ERD, BL NPS, NC score, total symptom score, rhinosinusitis severity visual analog scale, HRQoL (SNOT-22), or serum total IgE levels (Figure 3). Rapid improvement in smell was achieved with dupilumab regardless of prior sinonasal surgery (Figure E4; available in this article's Online Repository at www.jaci-inpractice.org). Even patients with multiple prior sinonasal surgeries achieved improvements in smell with dupilumab (Figure E5; available in this article's Online Repository at www.jaci-inpractice.org). Dupilumab improved smell outcomes versus placebo in patients with BL blood eosinophil count 0.15×10^9/L or less, and also in patients with BL blood eosinophil count greater than 0.15×10^9/L, with greater improvements in the latter group (Figure 3). Similarly, dupilumab improved smell outcomes versus placebo in patients older and younger than 65 years, and in patients with BL LMK CT scan total score 19 or less and greater than 19 (the study population median), with greater improvements observed in the younger than 65 years old group and the LMK CT scan score greater than 19 group, respectively.

Effect of week 4 smell response on week 24 outcomes

To investigate any association of early smell response with subsequent effects on CRSwNP disease outcomes, we analyzed patients with impaired sense of smell at BL in SINUS-52 (UPSIT $\leq$ 33; n = 429; 96% of the study population) according to above- and below-median UPSIT response at week 4. Nasal congestion, NPS, and LMK CT scan total score at week 24 were significantly better with dupilumab than placebo at week 24 in both the group with above-median UPSIT and the group with below-median UPSIT response at week 4 (Figure 4).

DISCUSSION

Loss or reduction in sense of smell is one of the most troublesome and difficult-to-treat symptoms in CRSwNP.[2,5] Patients in our cohort reported "Decreased sense of smell/taste" as the most important HRQoL item in SNOT-22, consistent with previous reports about the major burden associated with LoS in CRSwNP.[32,33] Dupilumab improved sense of smell significantly and rapidly according to 3 measures of olfaction (patient-reported LoS severity, UPSIT, and SNOT-22 item "Decreased sense of smell/taste"), with effects observed within the first week for daily assessed LoS severity, and at the first assessment for UPSIT and SNOT-22 item "Decreased sense of smell/taste." Improvements increased thereafter, with more than 60% of patients with anosmia (UPSIT < 19) achieving improvement in sense of smell (UPSIT $\geq$ 19) by 24 weeks. The rapidity and magnitude of smell recovery observed in this trial support a key role of type 2 inflammatory processes in smell loss in CRSwNP, and indicate that these processes may be reversible with dupilumab treatment.

Notably, dupilumab's effects on olfaction were unaffected by duration of CRSwNP, prior sinonasal surgery, previous SCS use, presence of comorbid asthma and/or NSAID-ERD, or BL polyp score. The observed absence of treatment-by-subgroup interaction for smell outcomes in prior surgery, asthma, and NSAID-ERD subgroups is consistent with the findings of similar efficacy in NPS, NC, LMK CT scan, and SNOT-22 scores regardless of prior surgery, asthma, and NSAID-ERD in the SINUS studies.[34-36]

Durable restoration of sense of smell following surgery is uncommon,[11-13] and our findings confirm that sense of smell can be restored and maintained with dupilumab even in patients with multiple prior surgeries. Improvements in sense of smell with dupilumab were greater in patients with higher LMK total CT score at BL than in patients with lower LMK total CT score. Assessment of volumetric olfactory cleft opacification could have provided better understanding of this finding because there is a negative correlation between quantitative olfactory test scores and volumetric olfactory cleft opacification.[37,38]

Patients with anosmia had higher BL levels of systemic (blood) and local (nasal secretion) type 2 inflammatory biomarkers than patients without anosmia, suggesting that the degree of ongoing type 2 inflammatory processes affects the severity of olfactory dysfunction in CRSwNP. Of the biomarkers assessed at BL, only serum total IgE was not associated with anosmia. Our findings are consistent with those of an observational cross-sectional study of patients with CRSwNP, in whom smell function (assessed using Sniffin' Sticks odor tests) was found to correlate with blood eosinophil count but not with serum total IgE.[39]

The findings of this analysis, demonstrating severe loss of sense of smell in patients with CRSwNP, as well as the significant improvement in smell outcomes after treatment with dupilumab, support the use of sense of smell and its improvement after

treatment as criteria for patient selection and response to biologics, respectively. Sense of smell has been included in criteria for both patient selection and response to biologics in recent international expert consensus statements from the European Forum for Allergy and Airway Diseases (EUFOREA) and the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS).[1,40] In our cohort, BL smell scores were significantly correlated with other BL measures of disease, despite all patients having severe disease, thereby limiting the range of values available for correlation. Moreover, the cardinal importance of LoS to patients, confirmed in this study, supports its value as a patient-centered indicator of disease response. Nevertheless, NPS, NC, and LMK CT scan score outcomes at 24 weeks were significantly improved with dupilumab in patients with both better than and worse than median week 4 UPSIT response among those who had impaired sense of smell at BL in SINUS-52, suggesting that improvement in sense of smell has limited value as a proxy for improvement in other outcomes. A contributory factor in this finding could be that some patients might have irreversible anosmia; among patients with anosmia at BL, 38% in the dupilumab group were still anosmic after 24 weeks of dupilumab treatment.

In conclusion, dupilumab, by inhibiting the key and central type 2 cytokines IL-4/IL-13 involved in type 2 inflammation, provided rapid (within 1 week) and lasting (up to 52 weeks) improvements in sense of smell in patients with severe CRSwNP, regardless of prior sinonasal surgery, SCS use, or presence of asthma and/or NSAID-ERD. The ability to reverse LoS, one of the most troublesome and difficult-to-treat symptoms of severe CRSwNP, supports the effectiveness of dupilumab in patients who otherwise have limited therapeutic options.

NOTE

For a video summary of this article, please see Video 1 (available in this article's Online Repository at www.jaci-inpractice.org).

Acknowledgments

We thank Mei Zhang, PhD, Xuezhou Mao, PhD, and Jérôme Msihid, MSc, of Sanofi for statistical analyses, and Matt Lewis, PhD, of Adelphi Communications Ltd (Macclesfield, UK) for medical writing support, which was funded by Sanofi (Bridgewater, NJ) and Regeneron Pharmaceuticals, Inc. (Tarrytown, NY) in accordance with Good Publication Practice (GPP3) guidelines.

J. Mullol had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. J. Mullol, C. Bachert, N. Amin, M. Desrosiers, A. H. Khan, S. Kamat, N. M. H. Graham, H. Staudinger, and L. P. Mannent were responsible for the study concept and design. J. Mullol, C. Bachert, N. Amin, M. Desrosiers, P. W. Hellings, J. K. Han, R. Jankowski, J. Vodicka, P. Gevaert, N. Daizadeh, A. H. Khan, S. Kamat, N. Patel, N. M. H. Graham, M. Ruddy, H. Staudinger, and L. P. Mannent were responsible for acquisition, analysis, or interpretation of data. J. Mullol, C. Bachert, N. Amin, M. Desrosiers, P. W. Hellings, J. K. Han, R. Jankowski, J. Vodicka, P. Gevaert, N. Daizadeh, A. H. Khan, S. Kamat, N. Patel, N. M. H. Graham, M. Ruddy, H. Staudinger, and L. P. Mannent were responsible for drafting or critical revision of the manuscript for important intellectual content.

Qualified researchers may request access to patient-level data and related study documents including clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access can be found at https://www.clinicalstudydatarequest.com.

REFERENCES

1. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European position paper on rhinosinusitis and nasal polyps 2020. Rhinology 2020;58:1-464.
2. Mullol J, Marino-Sanchez F, Valls M, Alobid I, Marin C. The sense of smell in chronic rhinosinusitis. J Allergy Clin Immunol 2020;145:773-6.
3. Schleimer RP. Immunopathogenesis of chronic rhinosinusitis and nasal polyposis. Annu Rev Pathol 2017;12:331-57.
4. Stevens WW, Peters AT, Tan BK, Klingler AI, Poposki JA, Hulse KE, et al. Associations between inflammatory endotypes and clinical presentations in chronic rhinosinusitis. J Allergy Clin Immunol Pract 2019;7:2812-20.e3.
5. Hummel T, Whitcroft KL, Andrews P, Altundag A, Cinghi C, Costanzo RM, et al. Position paper on olfactory dysfunction. Rhinol Suppl 2017;54:1-30.
6. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life—an updated review. Chem Senses 2014;39:185-94.
7. Litvack JR, Mace JC, Smith TL. Olfactory function and disease severity in chronic rhinosinusitis. Am J Rhinol Allergy 2009;23:139-44.
8. Simmen DB, Jones NS. Olfaction and nasal polyposis. In: Önerci TM, Ferguson BJ, editors. Nasal Polyposis: Pathogenesis, Medical and Surgical Treatment. Springer; 2010:163-73.
9. Alobid I, Bernal-Sprekelsen M, Mullol J. Chronic rhinosinusitis and nasal polyps: the role of generic and specific questionnaires on assessing its impact on patient's quality of life. Allergy 2008;63:1267-79.
10. Rimmer J, Fokkens W, Chong LY, Hopkins C. Surgical versus medical interventions for chronic rhinosinusitis with nasal polyps. Cochrane Database Syst Rev 2014;12:CD006991.
11. Bogdanov V, Walliczek-Dworschak U, Whitcroft KL, Landis BN, Hummel T. Response to glucocorticosteroids predicts olfactory outcome after ESS in chronic rhinosinusitis. Laryngoscope 2020;130:1616-21.
12. Nguyen DT, Bonfort G, Arous F, Felix-Ravelo M, Nguyen-Thi PL, Jankowski R. Evaluation of residual symptoms: a method to assess surgical outcomes for nasal polyposis. Am J Rhinol Allergy 2016;30:e36-41.
13. Seys SF, De Bont S, Fokkens WJ, Bachert C, Alobid I, Bernal-Sprekelsen M, et al. Real-life assessment of chronic rhinosinusitis patients using mobile technology: the Mysinusitiscoach Project by EUFOREA. Allergy 2020;75:2867-78.
14. Rombaux P, Huart C, Levie P, Cingi C, Hummel T. Olfaction in chronic rhinosinusitis. Curr Allergy Asthma Rep 2016;16:41.
15. Kern RC. Chronic sinusitis and anosmia: pathologic changes in the olfactory mucosa. Laryngoscope 2000;110:1071-7.
16. Imamura F, Hasegawa-Ishii S. Environmental toxicants—induced immune responses in the olfactory mucosa. Front Immunol 2016;7:475.
17. Epstein VA, Bryce PJ, Conley DB, Kern RC, Robinson AM. Intranasal aspergillus fumigatus exposure induces eosinophilic inflammation and olfactory sensory neuron cell death in mice. Otolaryngol Head Neck Surg 2008;138:334-9.
18. Yee KK, Pribitkin EA, Cowart BJ, Rosen D, Feng P, Rawson NE. Analysis of the olfactory mucosa in chronic rhinosinusitis. Ann N Y Acad Sci 2009;1170:590-5.
19. Holbrook EH, Leopold DA, Schwob JE. Abnormalities of axon growth in human olfactory mucosa. Laryngoscope 2005;115:2144-54.
20. Lavin J, Min JY, Lidder AK, Huang JH, Kato A, Lam K, et al. Superior turbinate eosinophilia correlates with olfactory deficit in chronic rhinosinusitis patients. Laryngoscope 2017;127:2210-8.
21. Loftus C, Schlosser RJ, Smith TL, Alt JA, Ramakrishnan VR, Mattos JL, et al. Olfactory cleft and sinus opacification differentially impact olfaction in chronic rhinosinusitis. Laryngoscope 2020;130:2311-8.
22. Soler ZM, Yoo F, Schlosser RJ, Mulligan J, Ramakrishnan VR, Beswick DM, et al. Correlation of mucus inflammatory proteins and olfaction in chronic rhinosinusitis. Int Forum Allergy Rhinol 2020;10:343-55.
23. Konstantinidis I, Triaridis S, Printza A, Vital V, Ferekidis E, Constantinidis J. Olfactory dysfunction in nasal polyposis: correlation with computed tomography findings. ORL J Otorhinolaryngol Relat Spec 2007;69:226-32.

24. Rouyar A, Classe M, Gorski R, Bock MD, Le-Guern J, Roche S, et al. Type 2/Th2-driven inflammation impairs olfactory sensory neurogenesis in mouse chronic rhinosinusitis model. Allergy 2019;74:549-59.
25. Macdonald LE, Karow M, Stevens S, Auerbach W, Poueymirou WT, Yasenchak J, et al. Precise and *in situ* genetic humanization of 6 Mb of mouse immunoglobulin genes. Proc Natl Acad Sci U S A 2014;111:5147-52.
26. Murphy AJ, Macdonald LE, Stevens S, Karow M, Dore AT, Pobursky K, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. Proc Natl Acad Sci U S A 2014;111:5153-8.
27. Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. Expert Rev Clin Immunol 2017;13:425-37.
28. U.S. Food and Drug Administration (FDA). Dupixent highlights of prescribing information. 2019. Accessed October 15, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761055s014lbl.pdf.
29. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. JAMA 2016;315:469-79.
30. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet 2019;394:1638-50.
31. Rubin DB. Multiple Imputation for Nonresponse in Surveys; 2004. John Wiley & Sons.
32. Chung JH, Lee YJ, Kang TW, Kim KR, Jang DP, Kim IY, et al. Altered quality of life and psychological health (SCL-90-R) in patients with chronic rhinosinusitis with nasal polyps. Ann Otol Rhinol Laryngol 2015;124:663-70.
33. Kohli P, Naik AN, Harruff EE, Nguyen SA, Schlosser RJ, Soler ZM. The prevalence of olfactory dysfunction in chronic rhinosinusitis. Laryngoscope 2017;127:309-20.
34. Desrosiers M, Mannent LP, Amin N, Canonica GW, Hellings PW, Gevaert P, et al. Dupilumab reduces systemic corticosteroid use and sinonasal surgery rate in CRSwNP. Rhinology 2021;59:301-11.
35. Laidlaw TM, Bachert C, Amin N, Desrosiers M, Hellings PW, Mullol J, et al. Dupilumab improves upper and lower airway disease control in chronic rhinosinusitis with nasal polyps and asthma. Ann Allergy Asthma Immunol 2021;126:584-92.e1.
36. Mullol J, Laidlaw T, Bachert C, Mannent LP, Canonica GW, Han JK, et al. Efficacy and safety of dupilumab in patients with uncontrolled severe CRSwNP and a clinical diagnosis of NSAID-ERD: results from two randomized placebo controlled phase 3 trials. Allergy. Published online August 30, 2021. https://doi.org/10.1111/all.15067
37. Kohli P, Schlosser RJ, Storck K, Soler ZM. Olfactory cleft computed tomography analysis and olfaction in chronic rhinosinusitis. Am J Rhinol Allergy 2016;30:402-6.
38. Saito T, Tsuzuki K, Yukitatsu Y, Sakagami M. Correlation between olfactory acuity and sinonasal radiological findings in adult patients with chronic rhinosinusitis. Auris Nasus Larynx 2016;43:422-8.
39. Hox V, Bobic S, Callebaux I, Jorissen M, Hellings PW. Nasal obstruction and smell impairment in nasal polyp disease: correlation between objective and subjective parameters. Rhinology 2010;48:426-32.
40. Bachert C, Han JK, Wagenmann M, Hosemann W, Lee SE, Backer V, et al. EUFOREA expert board meeting on uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) and biologics: Definitions and management. J Allergy Clin Immunol 2021;147:29-36.

ONLINE REPOSITORY

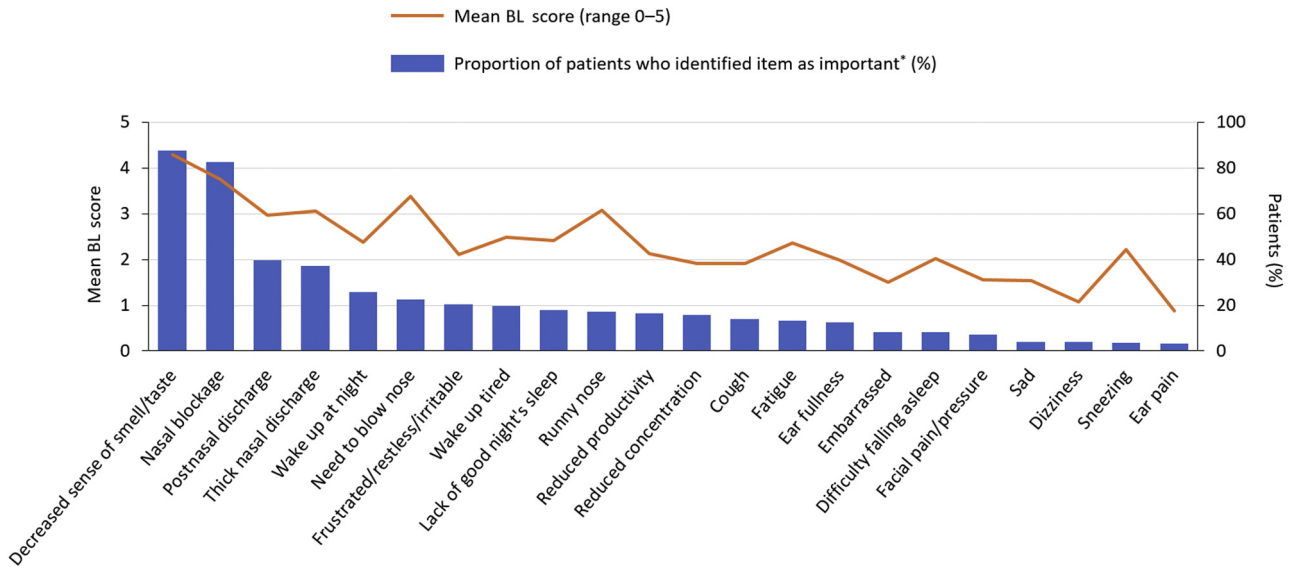


FIGURE E1. The SNOT-22 items BL score and importance to patients* (pooled studies). *Proportion of patients who identified the item in response to the SNOT-22 summary question, "Please mark the most important items affecting your health (maximum of 5 items)." All patients with SNOT-22 data at BL (n = 712). Score range for each item is 0–5, with 0 = No problem and 5 = Problem as bad as it can be.

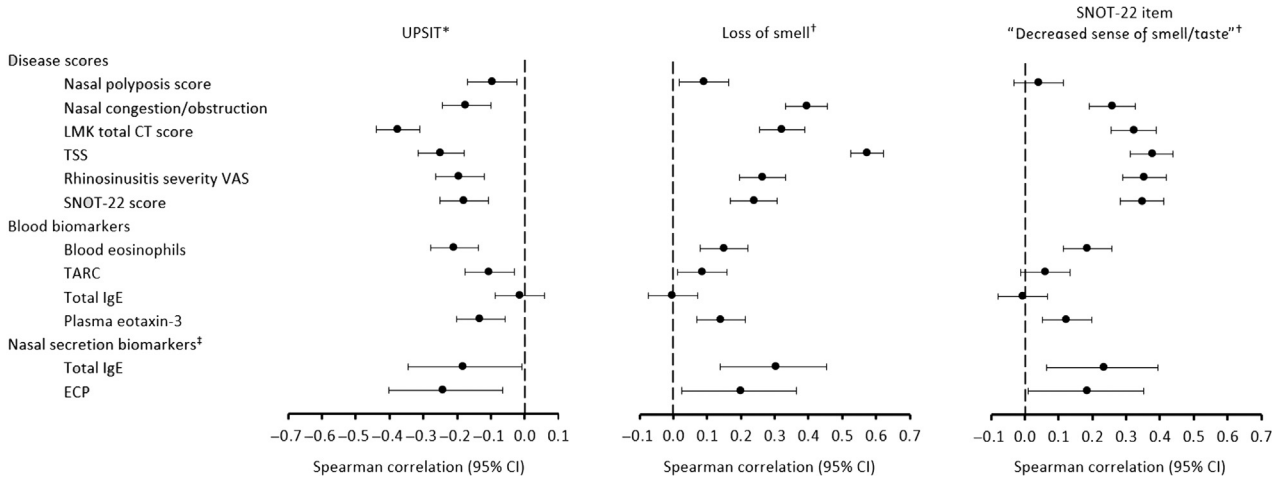


FIGURE E2. Association of BL disease activity scores and biomarker levels with BL olfactory function across 3 measures of olfaction (pooled studies). *ECP,* Eosinophil cationic protein; *TARC,* thymus and activation-regulated chemokine; *TSS,* total symptom score; *VAS,* visual analog scale. *Lower scores indicate more severe disease. †Higher scores indicate more severe disease. ‡Assessed in SINUS-52 only.

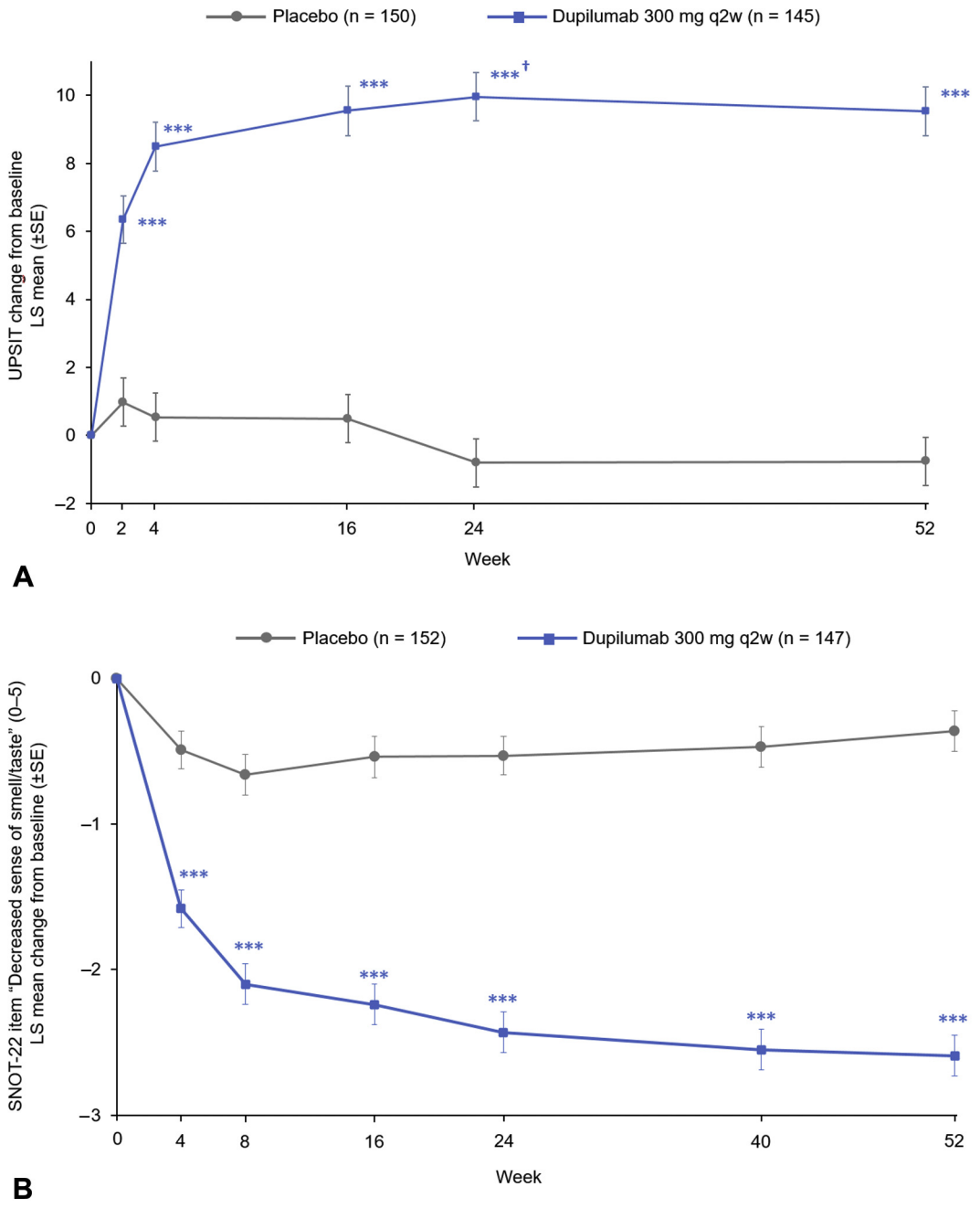


FIGURE E3. The LS mean change from BL to 52 weeks in (**A**) UPSITand (**B**) SNOT-22 item "Decreased sense of smell/taste" in SINUS-52. ***Nominal $P < .001$ versus placebo. *SE,* Standard error. †Prespecified $P < .0001$ versus placebo.

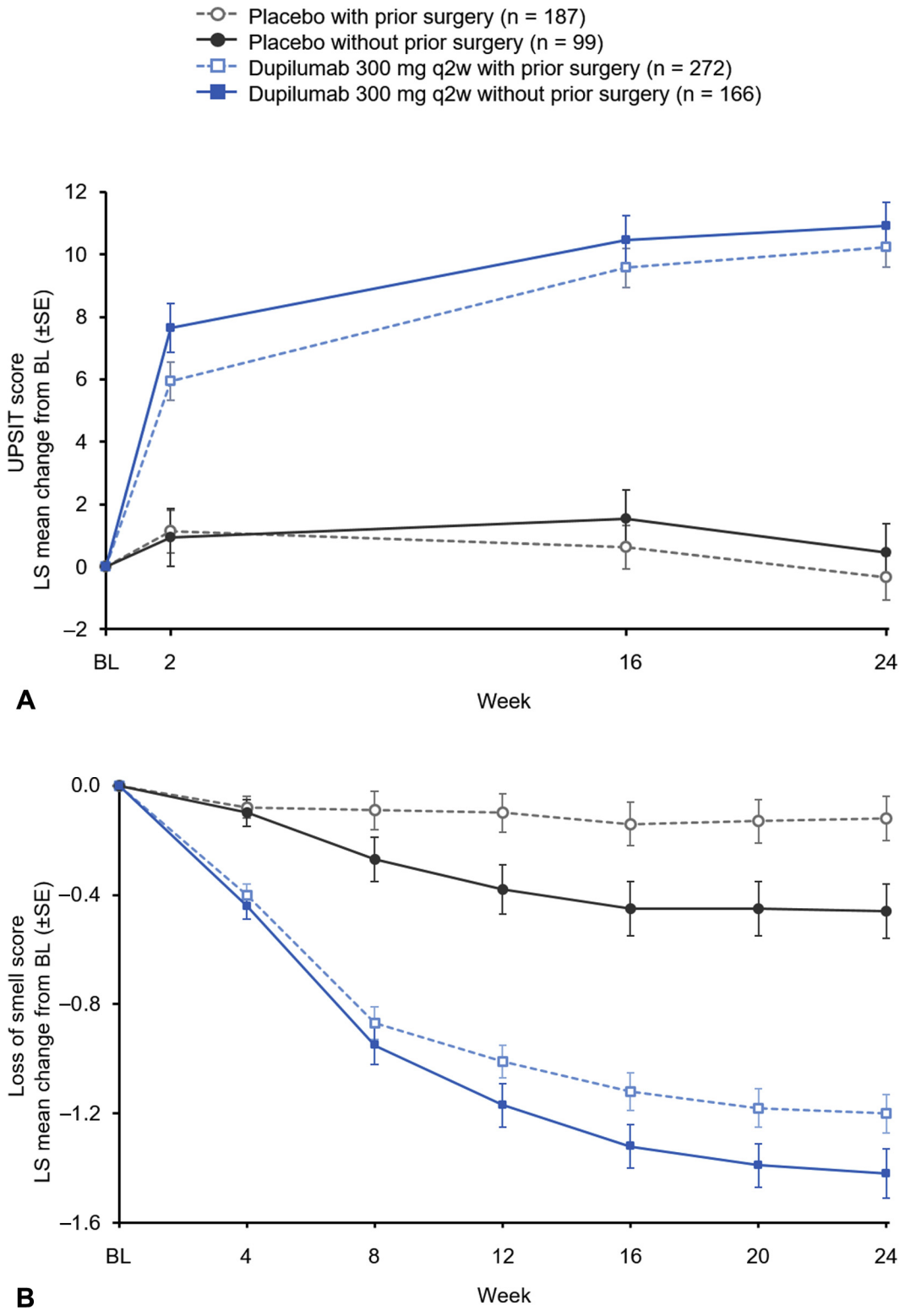


FIGURE E4. The LS mean change to week 24 in (**A**) UPSIT and (**B**) LoS symptom score* in patients with and without prior sinonasal surgery (pooled SINUS-24 and SINUS-52). *SE,* Standard error. *LoS symptom score monthly values are the average of the previous 28 days.

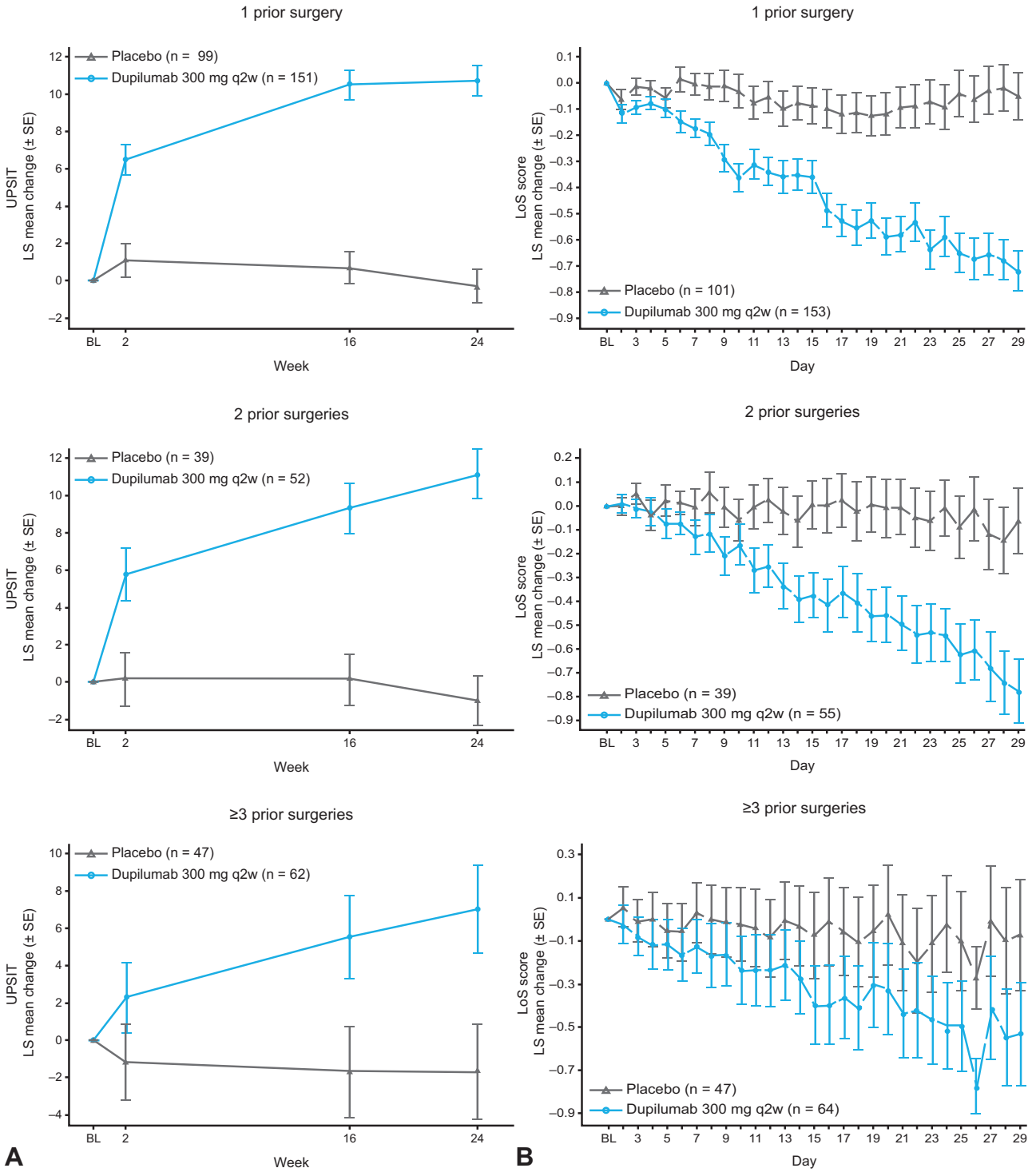


FIGURE E5. The LS mean change to week 24 in (**A**) UPSIT and (**B**) LoS symptom score by number of prior sinonasal surgeries (pooled SINUS-24 and SINUS-52). *SE,* Standard error.

TABLE E1. Demographics and BL characteristics by treatment allocation in the pooled SINUS-24 and SINUS-52 studies

Characteristic	Placebo (n = 286)	Dupilumab 300 mg q2w (n = 438)	All patients (n = 724)
Age, y, mean (SD)	51.3 (12.9)	51.5 (12.8)	51.4 (12.8)
Male, n (%)	165 (57.7)	272 (62.1)	437 (60.4)
NP duration, y, mean (SD)	10.83 (9.01)	11.12 (9.73)	11.01 (9.45)
Prior sinonasal surgery, n (%)	187 (65.4)	272 (62.1)	459 (63.4)
SCS in the last 2 y, n (%)	209 (73.1)	329 (75.1)	538 (74.3)
Any comorbid type 2 medical history* including asthma/NSAID-ERD, n (%)	226 (79.0)	351 (80.1)	577 (79.7)
Asthma, n (%)	170 (59.4)	258 (58.9)	428 (59.1)
NSAID-ERD, n (%)	82 (28.7)	122 (27.9)	204 (28.2)
UPSIT (0–40),†‡ mean (SD)	14.1 (8.3)	13.9 (8.2)	14.0 (8.2)
UPSIT category, n (%)			
<19 (anosmia)	219 (77.4)	332 (77.8)	551 (77.6)
19–34 (hyposmia)	61 (21.6)	86 (20.1)	147 (20.7)
>34 (normal)	3 (1.1)	9 (2.1)	12 (1.7)
LoS (0–3),§ mean (SD)	2.72 (0.52)	2.74 (0.54)	2.74 (0.53)
SNOT-22 item "Decreased sense of smell/taste" (0–5),§ mean (SD)	4.30 (1.20)	4.26 (1.14)	4.28 (1.17)

NP, Nasal polyp.
*A patient was considered to have comorbidity history or ongoing comorbid disease if the patient had or has any of the following diseases: atopic dermatitis, allergic conjunctivitis, allergic rhinitis (any, seasonal, perennial), eosinophilic esophagitis, food allergy, and/or hives.
†Lower scores indicate greater disease severity.
‡BL data were available for 710 patients.
§Higher scores indicate greater disease severity.

TABLE E2. Number of imputed values by visit

	Visit wk*												
LoS score	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Placebo	1	2	4	3	7	9	8	8	8	8	9	9	9
Dupilumab q2w	1	2	4	5	8	8	4	4	5	4	4	5	5

	Visit wk*			
UPSIT	**2**	**16**	**24**	**52**
Placebo	8	8	8	8
Dupilumab q2w	8	8	9	6

	Visit wk*				
SNOT-22 taste/smell item	**8**	**16**	**24**	**40**	**52**
Placebo	6	7	10	12	9
Dupilumab q2w	9	15	12	7	4

*Pooled SINUS-24 and SINUS-52 up to wk 24 (placebo N = 286; dupilumab q2w N = 438); SINUS-52 only for wk 28–52 (placebo N = 153; dupilumab q2w N = 150).