Dupilumab in CRSwNP: Responder Analysis Using Clinically Meaningful Efficacy Outcome Thresholds

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Objectives/Hypothesis: Dupilumab, a fully human monoclonal antibody that blocks the shared interleukin (IL)-4/IL-13 receptor component, significantly improved outcomes for patients with chronic rhinosinusitis with nasal polyps (CRSwNP) in the SINUS-24 and SINUS-52 studies. This post hoc analysis evaluated dupilumab's effect on patient-reported symptoms and objective outcome measures using thresholds of clinically meaningful within-patient change from baseline.

Methods: Patients with CRSwNP receiving subcutaneous dupilumab or placebo every 2 weeks in SINUS-24/SINUS-52 were analyzed. Patients recorded severity of nasal congestion (NC), loss of smell (LoS), and anterior/posterior rhinorrhea (each within range 0–3) daily. Total Symptom Score (TSS) was calculated as a composite severity score (0–9) for these symptoms. Objective measures included University of Pennsylvania Smell Identification Test (UPSIT; 0–40), nasal polyps score (NPS; 0–8), and Lund–Mackay computed tomography score (LMK-CT; 0–24). Thresholds of within-patient change in scores from baseline at weeks 24 and 52 considered clinically meaningful were ≥1.0 (NC, LoS), ≥3.0 (TSS), ≥8.0 (UPSIT), ≥1.0 (NPS), and ≥5.0 (LMK-CT).

Results: A total of 724 and 303 patients were included in the week 24 and 52 analyses, respectively. Responder rates were significantly higher with dupilumab versus placebo at week 24 for NC (64% vs. 24%), LoS (63% vs. 14%), TSS (62% vs. 15%), UPSIT (54% vs. 6%), NPS (63% vs. 14%), and LMK-CT (59% vs. 3%); all $P < .0001$. Results were consistent at week 52.

Conclusion: Significantly greater proportions of dupilumab-treated patients with CRSwNP compared with placebo demonstrated clinically meaningful improvements in patient-reported sinonasal symptoms and objective outcomes.

Key Words: Adult rhinology, quality of life, nose and paranasal sinuses.

Level of Evidence: 2

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INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterized by chronic inflammation of the nasal passages and paranasal sinuses, and the presence of bilateral nasal polyps. CRSwNP is associated with a high symptom burden, high-cost burden, and poor health-

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related quality of life (HRQoL).[1–4] Nasal congestion (NC)/obstruction, reduction or loss of smell (LoS), and anterior/posterior rhinorrhea are reported as the symptoms most important to patients with CRSwNP.[5] These symptoms are among the most troublesome, are often refractory to standard treatment with corticosteroids or surgery,[6,7] and patients with CRSwNP are frequently frustrated with the inadequacy of their current treatment.[8] Postoperative recurrence of polyps requiring further revision surgery is frequently reported in patients with severe CRSwNP.[9–11] Polyp recurrence was reported in approximately 40% of patients at 18 months postsurgery, and in approximately 80% of patients at 12 years postsurgery.[12–14] A systematic review reported that 14%–24% of patients required revision surgery in response to polyp recurrence.[15]

The pathophysiology of CRSwNP is predominantly characterized by type 2 inflammation with interleukin (IL)-4, IL-5, and IL-13 as key cytokines.[16,17] IL-4 and IL-13 are key and central drivers of type 2 inflammation, promoting isotype switching of B cells to immunoglobulin E-producing cells, goblet cell hyperplasia, infiltration of eosinophils, lymphocytes, and mast cells into the nasal mucosa and polyp, and tissue remodeling.[18,19]

Dupilumab is a fully human VelocImmune®-derived monoclonal antibody that blocks IL-4Rα, the shared receptor component for IL-4 and IL-13,[17,19] and is approved as an add-on treatment in adult patients with inadequately controlled CRSwNP.[20] In the phase 3, randomized, double-blind, 24-week SINUS-24 (NCT02912468) and 52-week SINUS-52 (NCT02898454) trials in patients with CRSwNP, dupilumab added to intranasal corticosteroids (INCS) significantly improved patient-reported symptoms (including NC, LoS, and Total Symptom Score [TSS]), as well as objective outcomes, including endoscopic nasal polyps score (NPS), Lund–Mackay computed tomography (LMK-CT) opacification score, and sense of smell using the University of Pennsylvania Smell Identification Test (UPSIT) versus placebo, and was generally well tolerated.[21–23] In patients with CRSwNP and comorbid asthma, dupilumab treatment improved patient-reported and clinical outcomes, in addition to asthma-specific outcomes (5-item Asthma Control Questionnaire scores), versus placebo.[24]

Treatment effects of standard of care therapies and biologics in CRSwNP that are approved, or are in development, have typically been reported in terms of the absolute change from baseline in these outcome measures. However, responder analyses based on clinically meaningful within-patient change thresholds (i.e., responder definitions) may facilitate interpretation of the treatment effects that are clinically more relevant. Therefore, in clinical studies, the treatment benefits of any intervention using within-patient thresholds of changes in scores derived from patient-reported outcome instruments should be evaluated not solely based on statistical significance, but with a clear understanding of the amount and type of change that is clinically meaningful to patients.[25] The objective of this post hoc analysis was to assess the effect of dupilumab versus placebo on patient-reported sinonasal symptoms and objective measures in patients with CRSwNP who participated in the SINUS-24 and SINUS-52 studies using responder thresholds for clinically meaningful within-patient improvement for NC, LoS, TSS, NPS, UPSIT, and LMK-CT scores that were proposed by Han et al. in the accompanying article.[26]

MATERIALS AND METHODS

Study Design and Population

SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454) were multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies of dupilumab in patients with severe, uncontrolled CRSwNP. The design and methodology of these studies have been reported elsewhere.[21] In brief, patients were randomized 1:1 to double-blind treatment with subcutaneous (SC) dupilumab 300 mg or placebo every 2 weeks (q2w) for 24 weeks in SINUS-24, and 1:1:1 to SC dupilumab 300 mg q2w for 52 weeks, SC dupilumab 300 mg q2w for 24 weeks followed by every 4 weeks to 52 weeks, or placebo q2w for 52 weeks in SINUS-52. All patients in both studies received mometasone furoate nasal spray (100 mg per nostril twice daily) from 4 weeks prior to randomization to the end of the study.

Patients aged ≥18 years with severe CRSwNP despite INCS treatment were eligible if they had received systemic corticosteroids (SCS) in the preceding 2 years and/or had undergone sinus surgery. Patients were required to have NPS of ≥5 out of 8 (≥2 for each nostril), NC (patient-reported symptom severity score of ≥2 out of 3, and weekly average of ≥1), and at least 1 other rhinosinusitis symptom (partial/total LoS, or anterior/posterior rhinorrhea).

The studies were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all patients prior to enrollment, and the protocol and its amendments were approved by the appropriate institutional review boards and ethics committees.

Outcomes

Patients recorded severity of symptoms (NC, LoS, and anterior/posterior rhinorrhea) in a daily symptom e-diary using a 4-point scale (0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; and 3 = severe symptoms). TSS was calculated as a composite severity score consisting of the sum of the NC, LoS, and rhinorrhea (average of anterior/posterior scores for nasal discharge) symptom scores (range 0–9). NPS (range 0–8) was assessed using nasal endoscopy at weeks 0, 8, 16, and 24 (both studies), and 40 and 52 (SINUS-52 only). UPSIT score, assessing olfactory function (range 0–40 points), was administered at weeks 0, 8, 16, and 24 (both studies), and 40 and 52 (SINUS-52 only). Sinus computed tomography scans, for assessment of sinus opacification by LMK-CT scores (range 0–24), were obtained at weeks 0, 24, and 52 (SINUS-52 only). Higher scores indicate worse disease severity for NC, LoS, TSS, NPS, and LMK-CT; for UPSIT, higher scores indicate better smell outcome.

Responder analyses evaluated the proportion of patients achieving clinically meaningful within-patient change thresholds (i.e., responder definitions) for NC and LoS scores (change from baseline ≥1.0 point), TSS (change from baseline ≥3.0 points), UPSIT score (change from baseline ≥8.0 points), NPS (change from baseline ≥1.0 point), and LMK-CT (change from baseline ≥5.0 points) at weeks 24 and 52. Estimation of these

responder definition thresholds has been published elsewhere.[26]

Statistical Analyses

For the week 24 assessment, this post hoc analysis included pooled data for all patients from the SINUS-24 and SINUS-52 studies who had received treatment with SC dupilumab 300 mg q2w or placebo until week 24. For the week 52 analysis, only data for the patients from SINUS-52 who received dupilumab 300 mg q2w or placebo q2w through week 52 were included. All analyses were conducted in the intent-to-treat (ITT) populations.

Baseline values for daily assessed measures are presented as the average of the 7 days leading up to baseline, and the week 24 and week 52 values are the average of the 28 days prior to day 169 and day 365, respectively.

Odds ratios (ORs) with 95% confidence intervals (CIs) and *P*-values were calculated for dupilumab versus placebo using the responder definition for each outcome measure. *P*-values were calculated using the Cochran–Mantel–Haenszel test 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, regions, and study indicator.

Patients who received SCS for any reason or underwent rescue surgery for nasal polyps were considered nonresponders from time points post-SCS use or surgery. For patients who discontinued treatment without using SCS or rescue surgery, data collected during the off-treatment period were used to determine the responder/nonresponder status. Patients with missing data at the visit of interest were considered nonresponders.

In order to evaluate the treatment effect of dupilumab versus placebo across the entire range of responder definitions, cumulative distribution function (CDF) curves were generated to depict between-group differences in change from baseline in patient-reported symptom scores and objective measures. These curves facilitate the comparison of cumulative probabilities of attaining certain threshold changes from baseline between dupilumab and placebo across the spectrum of responder definitions. *P*-values for the comparison of dupilumab versus placebo in the distribution of change from baseline in NC, LoS, TSS, UPSIT, NPS, and LMK-CT scores were calculated using the Kolmogorov–Smirnov test. Data collected after treatment discontinuation were included and data post-SCS or nasal polyp surgery were set to missing and imputed by worst observation carried forward for this analysis.

RESULTS

Demographics and Baseline Disease Characteristics

A total of 724 patients in the pooled ITT population were included in the week 24 analysis (dupilumab n = 438; placebo n = 286) and 303 patients from the SINUS-52 ITT dupilumab 300 mg q2w and placebo groups were included in the week 52 analysis (dupilumab n = 150; placebo n = 153). Recruitment data for SINUS-24 and SINUS-52 were previously published.[21]

Baseline demographics and disease characteristics in the pooled week 24 population were similar between the dupilumab and placebo treatment groups (Table I). Most patients had undergone prior surgery (62% and 65%, respectively) or received SCS (75% and 73%, respectively).

TABLE I.
Demographics and Baseline Characteristics in the Pooled SINUS-24 and SINUS-52 Population (for Analysis at week 24).

	Placebo (n = 286)	Dupilumab 300 mg q2w (n = 438)
Age, years	51.28 (12.90)	51.47 (12.79)
Female gender, n (%)	121 (42.3)	166 (37.9)
Time since first NP diagnosis, years	10.83 (9.01)	11.12 (9.73)
≥1 prior surgery, n (%)	187 (65.4)	272 (62.1)
SCS use in the previous 2 years, n (%)	209 (73.1)	329 (75.1)
Bilateral endoscopic NPS*, range 0–8	5.91 (1.26)	6.00 (1.24)
Daily NC score*, range 0–3	2.41 (0.54)	2.39 (0.60)
Score ≥2, n (%)	255 (89.2)	373 (85.2)
Score 0, n (%)	0	1 (0.2)
Score >0 and ≤1, n (%)	2 (0.7)	7 (1.6)
Score >1 and ≤2, n (%)	118 (41.3)	174 (39.7)
Score >2 and ≤3, n (%)	166 (58.0)	256 (58.4)
Daily LoS score*, range 0–3	2.72 (0.52)	2.74 (0.54)
Score ≥2, n (%)	271 (94.8)	410 (93.6)
Score 0, n (%)	2 (0.7)	4 (0.9)
Score >0 and ≤1, n (%)	4 (1.4)	7 (1.6)
Score >1 and ≤2, n (%)	48 (16.8)	58 (13.2)
Score >2 and ≤3, n (%)	232 (81.1)	369 (84.2)
Daily rhinorrhea*,†, range 0–3	2.04 (0.70)	2.00 (0.71)
Score ≥2, n (%)	186 (65.0)	278 (63.5)
Score 0, n (%)	3 (1.0)	6 (1.4)
Score >0 and ≤1, n (%)	27 (9.4)	36 (8.2)
Score >1 and ≤2, n (%)	127 (44.4)	205 (46.8)
Score >2 and ≤3, n (%)	129 (45.1)	191 (43.6)
Daily TSS*, range 0–9	7.18 (1.39)	7.14 (1.45)
SNOT-22 total score*, range 0–110	52.27 (21.11)	50.05 (20.33)
LMK-CT score*, range 0–24	18.53 (4.10)	18.26 (4.03)
UPSIT score‡, range 0–40	14.09 (8.30)	13.90 (8.16)
Rhinosinusitis severity (VAS)*, range 0–10	7.97 (2.14)	7.82 (2.02)
Blood eosinophils, Giga/L	0.44 (0.34)	0.43 (0.35)

Data are mean (SD) values unless otherwise stated.
*Higher mean scores indicate more severe disease.
†Average of scores for anterior and posterior rhinorrhea.
‡Higher mean scores indicate better smell outcome.
LMK-CT = Lund–Mackay computed tomography; LoS = loss of smell; NC = nasal congestion; NP = nasal polyp; NPS = nasal polyps score; q2w = every 2 weeks; SCS = systemic corticosteroids; SD = standard deviation; SNOT-22 = 22-item Sinonasal Outcome Test; TSS = Total Symptom Score; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.

Similar proportions of patients had moderate-to-severe NC/LoS/rhinorrhea (score ≥2 points) in the dupilumab and placebo treatment groups at baseline, ranging from 64% for rhinorrhea to 94% for LoS. Moderate-to-severe rhinorrhea was observed in a smaller proportion of patients (in both treatment groups) compared with moderate-to-severe NC and LoS. In the dupilumab and placebo treatment groups, mean rhinosinusitis severity visual analog scale scores (range 0–10, where 8–10 = severe) were 7.82 and 7.97, respectively. Similar mean scores were reported between the dupilumab and placebo treatment groups for NPS (6.00 and 5.91, respectively), UPSIT score (13.90 and 14.09,

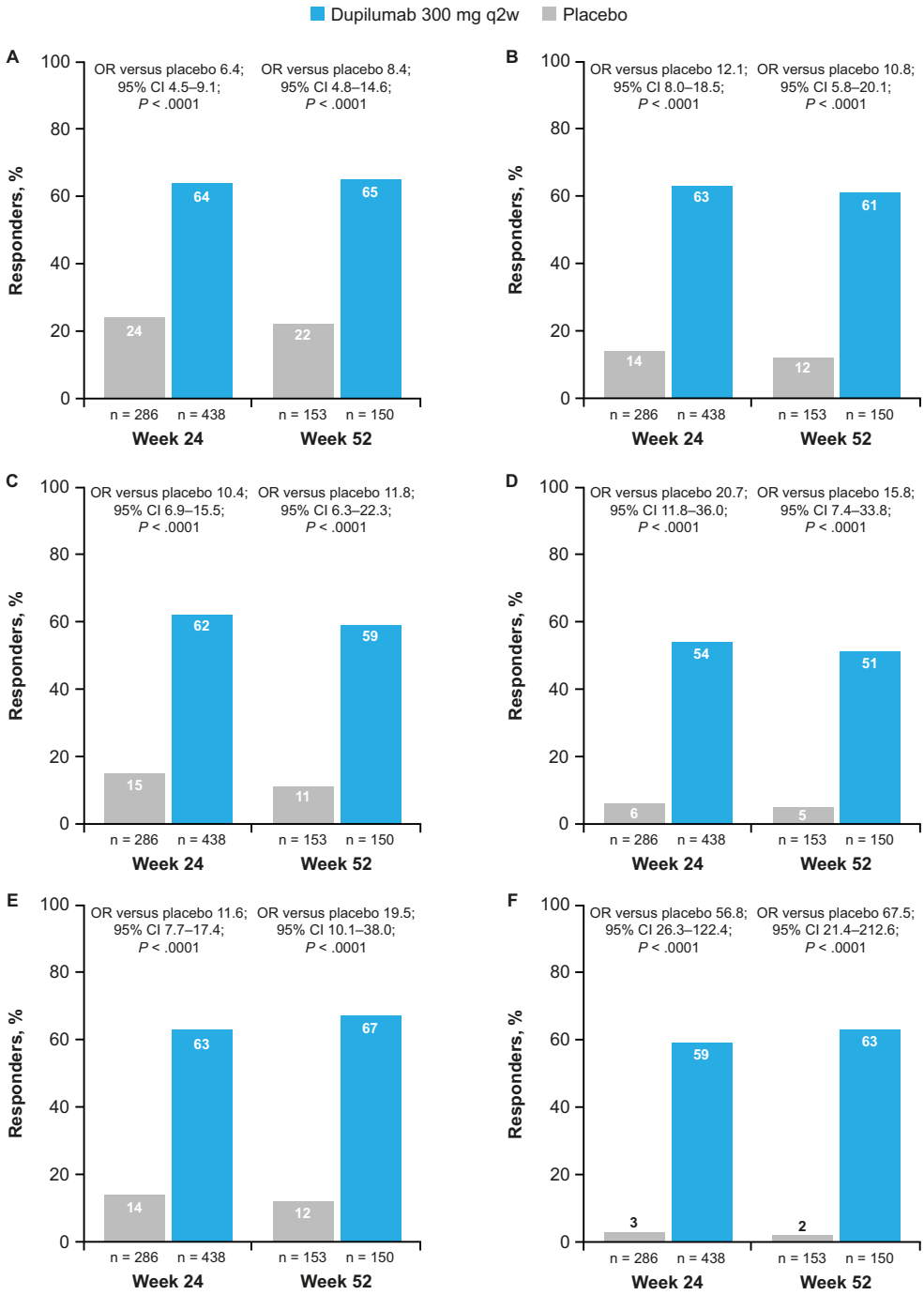

Fig. 1. Percentage of responders (responder definitions represent clinically meaningful within-patient change from baseline thresholds proposed in post hoc analyses of SINUS-24 and SINUS-52 [Han et al. accompanying article]) at week 24 in SINUS-24 and SINUS-52 (pooled) and week 52 in SINUS-52 for: (A) NC score (range 0–3, responder threshold ≥1 point improvement), (B) LoS score (range 0–3, responder threshold ≥1 point improvement), (C) TSS (range 0–9, responder threshold ≥3 points improvement), (D) UPSIT score (range 0–40, responder threshold ≥8 points improvement), (E) NPS (range 0–8, responder threshold ≥1 point improvement), and (F) LMK-CT score (range 0–24, responder threshold ≥5 points improvement) (ITT population). CI = confidence interval; ITT = intent-to-treat; LMK-CT = Lund–Mackay computed tomography; LoS = loss of smell; NC = nasal congestion; NPS = nasal polyps score; OR = odds ratio; q2w = every 2 weeks; TSS = Total Symptom Score; UPSIT = University of Pennsylvania Smell Identification Test. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

respectively), and LMK-CT score (18.26 and 18.53, respectively). Baseline data for patients in the week 52 analysis are provided (Supporting Table 1, in the online version of this article).

Responder Analysis

The proportion of patients who showed within-patient change from baseline that exceeded the responder thresholds for patient-reported symptoms (NC, LoS, and

TSS) were statistically significantly higher for dupilumab versus placebo at weeks 24 and 52 (Fig. 1A–C). At week 24 in the pooled population, 64% of the dupilumab-treated patients compared with 24% of the placebo-treated patients had ≥1 point improvement from baseline in NC (OR 6.4; 95% CI 4.5–9.1; $P < .0001$). For LoS, 63% (dupilumab) and 14% (placebo) of patients had ≥1 point improvement from baseline (OR 12.1; 95% CI 8.0–18.5; $P < .0001$), and for TSS, 62% (dupilumab) and 15% (placebo) of patients had ≥3 points improvement from baseline (OR 10.4; 95% CI 6.9–15.5; $P < .0001$). Results were consistent at week 52.

The proportion of patients who showed within-patient change from baseline that exceeded the responder thresholds for the objective measures (Fig. 1D–F) were also statistically significantly higher for dupilumab versus placebo at weeks 24 and 52. At week 24, 54% (dupilumab), and 6% (placebo) had ≥8 points improvement from baseline for UPSIT (OR 20.7; 95% CI 11.8–36.0; $P < .0001$). For NPS, 63% (dupilumab) and 14% (placebo) had ≥1 point improvement from baseline at week 24 (OR 11.6; 95% CI 7.7–17.4; $P < .0001$), and for LMK-CT score, 59% (dupilumab) and 3% (placebo) had ≥5 points improvement from baseline at week 24 (OR 56.8; 95% CI 26.3–122.4; $P < .0001$).

CDF Across the Range of Responder Definitions

A distinct separation was observed between the CDF curves for dupilumab and placebo across a range of responder definitions at weeks 24 and 52 in all patient-reported symptom scores and objective measures (all $P < .0001$; Supporting Figures 1 and 2, in the online version of this article). The separation in CDF curves for dupilumab treatment versus placebo was statistically significant for all measures, and dupilumab consistently showed higher responder rates than placebo, regardless of the responder definition.

DISCUSSION

This post hoc analysis of data from the phase 3 SINUS-24 and SINUS-52 studies demonstrated a statistically significant benefit of dupilumab treatment versus placebo that was observed consistently across the responder definitions for change from baseline to weeks 24 (pooled SINUS-24/SINUS-52) and 52 (SINUS-52) in patient-reported symptoms as well as objective measures. Statistically significant differences were also observed between the CDF curves for change from baseline for dupilumab and placebo at weeks 24 and 52 across a wide range of responder thresholds. The results observed from the CDF curves favored dupilumab versus placebo in all outcome measures.

This is the first analysis of the effects of dupilumab versus placebo according to clinically meaningful within-patient responder definitions of patient-reported symptoms and objective measures in CRSwNP. We applied responder definitions, which were proposed in post hoc analyses from the SINUS-24 and SINUS-52 trials.[26] Our findings suggest a significantly greater proportion of dupilumab-treated patients versus placebo achieved the clinically meaningful responder thresholds across key patient-reported symptoms and objective measures. Approximately 60% of dupilumab-treated patients achieved the clinically meaningful responder definition for each of these 6 outcome measures, compared with 2%–24% in the placebo arm. Given that objective measures (i.e., NPS, CT-LMK) are moderately correlated with patient-reported outcomes,[26] patients who may not meet the threshold for clinical meaningful change on NPS/CT-LMK may still have derived benefit from dupilumab on one or more of the subjective measures. Among the patients who did not achieve the thresholds for clinically meaningful change, at weeks 24 and 52, the magnitude of improvement across all objective and patient-reported outcome measures was still significantly greater for dupilumab patients versus placebo (data not shown). Improvements among placebo patients can be attributed to optimized standard of care in the context of a clinical trial setting.

Data reported from the SINUS-24/SINUS-52 phase 3 trials demonstrate a substantial reduction in the proportion of dupilumab-treated patients with anosmia determined by the clinician-observed measure of smell, UPSIT.[21] At week 24 in SINUS-24 and SINUS-52, there were decreases of 50% and 49%, respectively, in the proportion of dupilumab-treated patients with anosmia, compared with negligible changes in placebo-treated patients.[21] Our findings on UPSIT further show that more than half of the dupilumab-treated patients, compared with approximately 6% of placebo-treated patients, reached the clinically meaningful responder threshold of smell improvement.

Several biologic treatments are either approved or being evaluated in clinical trials for the treatment of patients with CRSwNP. The European Position Paper on Rhinosinusitis (EPOS) and European Forum for Research and Education in Allergy and Airway diseases (EUFOREA) consensus guidelines on biologics for CRSwNP have outlined criteria that are important when considering biologic therapy.[27,28] The EPOS concluded that biologics should be indicated in patients with 3 of the following criteria: evidence of type 2 inflammation (tissue eosinophils ≥10/high power field, hpf [×400], or blood eosinophils ≥250/μL, or total IgE ≥100 IU/mL); need for SCS in the previous 2 years; significant impairment in HRQoL; significant LoS; or diagnosis of comorbid asthma.[27] The EUFOREA criteria for the indication of biologics included a confirmed diagnosis of uncontrolled severe CRSwNP, a high likelihood of type 2 inflammation (blood eosinophils ≥300/μL), and a diagnosis of comorbid NSAID-ERD or asthma, for which a collaboration with an asthma specialist is required.[28] To date, no baseline clinical or biomarker parameters have been identified to select individual patients most likely to respond to biologic treatments and there are no validated response criteria.[27,28] In the absence of such parameters, treatment effect size and responder analysis results may guide the choice of treatment. The responder definitions for sinonasal symptoms and objective measures applied in this post hoc analysis may help physicians contextualize the observed improvements in patient-reported symptoms, polyp size, and sinus opacification in terms of clinical relevance to patients, with an aim to improve overall

patient care and disease management. This also provides evidence for policy decision makers and/or payers to be able to meaningfully differentiate between different available treatments. The use of post hoc analyses is appropriate in reporting on the original clinical trials, where there was a lack of validated clinically meaningful change criteria for these outcomes. The responder definitions for sinonasal symptoms and objective measures applied in this analysis, pooled across trials, may help to inform real-world clinical practice.

Limitations of this analysis include its post hoc nature, and the clinically meaningful responder thresholds used in this analysis would benefit from additional validation in a broader patient population outside of a clinical trial setting.

CONCLUSION

Dupilumab treatment added to daily standard of care was associated with statistically significant, clinically meaningful improvements in patient-reported symptom (NC, LoS, and TSS) outcomes and objective measures versus placebo using the proposed responder definitions.[26] These clinically relevant data may enhance meaningful interpretation and understanding of dupilumab treatment effects by physicians, patients, and policy decision makers. Real-world studies are needed to further validate study findings in the routine clinical practice setting.

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