RAPID COMMUNICATION

Dupilumab Improves Outcomes in Patients with Chronic Rhinosinusitis with Nasal Polyps and Coexisting Asthma Irrespective of Baseline Asthma Characteristics

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Purpose: Chronic rhinosinusitis with nasal polyps (CRSwNP) is a predominantly type 2 inflammatory disease frequently coexisting with other type 2 conditions including asthma and non-steroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD). Coexisting asthma leads to increased CRSwNP symptom burden. Dupilumab, a monoclonal antibody that blocks the shared receptor component for interleukin-4 and -13, demonstrated efficacy in adults with severe CRSwNP in the Phase 3 SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454) studies, including in patients with coexisting asthma/NSAID-ERD. However, the impact of different asthma characteristics on dupilumab treatment in this population is unknown. We report CRSwNP and asthma outcomes with dupilumab in patients with CRSwNP and coexisting asthma according to baseline asthma characteristics.

Methods: Change from baseline at Week 24 (pooled studies) and Week 52 (SINUS-52) in CRSwNP outcomes (nasal polyp score, nasal congestion, 22-item Sino-Nasal Outcome Test [SNOT-22], loss of smell score, University of Pennsylvania Smell Identification Test) and asthma outcomes (5-item Asthma Control Questionnaire [ACQ-5], pre-bronchodilator forced expiratory volume in 1 second [FEV_1]) were analyzed post hoc for placebo and dupilumab 300 mg every 2 weeks according to baseline blood eosinophils ≥150/≥300 cells/μL, ACQ-5 scores <1.5/≥1.5, and FEV_1 <80%.

Results: In the pooled studies, 428/724 patients (59.1%) had coexisting asthma, of which 181/428 (42.3%) had coexisting NSAID-ERD. Dupilumab significantly improved all CRSwNP and asthma outcomes vs placebo at Week 24 (P < 0.001) regardless of baseline eosinophil or ACQ-5 category, or FEV_1 <80%. Similar magnitude of improvement was seen at Week 52 (SINUS-52) and in patients with NSAID-ERD (pooled studies, Week 24). By Week 24, improvements with dupilumab exceeded the minimum clinically important differences for ACQ-5 and SNOT-22 in 35.2% to 74.2% and 72.0% to 78.7% of patients, respectively.

Conclusion: Dupilumab improved CRSwNP outcomes in patients with CRSwNP and coexisting asthma, and improved asthma outcomes, regardless of differences in baseline asthma characteristics.

Keywords: chronic rhinosinusitis with nasal polyps, dupilumab, asthma

Introduction

Type 2 inflammation plays a central role in the pathophysiology of multiple inflammatory diseases, including chronic rhinosinusitis with nasal polyps (CRSwNP) and asthma.[1] Approximately 85% of patients with CRSwNP[2] and 71% to 84% of adults with asthma[3] have type 2 inflammation. CRSwNP and asthma often coexist, with studies indicating that between 40% and 67% of patients with CRSwNP have coexisting asthma.[4–7]

CRSwNP is associated with a significant clinical, health-related quality of life (HRQoL) and economic burden.[8–10] Those with coexisting asthma have a more severe CRSwNP disease burden and tend to have poorer outcomes for both CRSwNP and asthma than patients without the coexisting condition, adding to the treatment challenge.[7,8,10] Asthma characteristics such as elevated type 2 inflammatory markers, poor asthma control, and reduced lung function have been shown to impact burden of asthma, risk of exacerbation, and treatment outcomes.[6,11–14] The presence of coexisting non-steroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD) has also been shown to increase disease burden in both CRSwNP and asthma.[15]

Dupilumab is a fully human monoclonal antibody that blocks the shared receptor component for interleukin-4 and -13, which are key and central drivers of type 2 inflammation.[16,17] In the Phase 3 SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454) studies in patients with severe CRSwNP, dupilumab significantly improved objective and patient-reported CRSwNP outcomes.[18] Additional post hoc analyses of the SINUS trials also demonstrated that dupilumab was equally effective in improving CRSwNP, asthma, and quality-of-life outcomes in patients with CRSwNP with or without self-reported asthma.[19,20] However, the efficacy of different treatments can be influenced by the type of asthma, or by variation in other physiologic or immunologic characteristics.[21] The efficacy of dupilumab in patients with CRSwNP and varying asthma characteristics is currently unknown. Therefore, the aim of this post hoc analysis of the SINUS studies was to assess the effect of dupilumab on CRSwNP and asthma outcomes in patients with severe CRSwNP and coexisting asthma stratified by baseline asthma characteristics.

Methods

Study Design and Patients

Data were included for patients with severe CRSwNP and coexisting asthma who received dupilumab 300 mg or placebo once every 2 weeks in SINUS-24 and SINUS-52; full details of these studies are published elsewhere.[18] Both study protocols were approved by 200 Copernicus Group IRB (Protocol # EFC14146, Tracking # SAN4-16-406; Protocol # EFC14280, Tracking # SAN4-16-417). Severe CRSwNP was defined in line with criteria from the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA), and in the eligibility criteria for the SINUS-24 and SINUS-52 studies.[18,22] For this post hoc analysis, patients were divided into groups based on evidence of type 2 inflammation (blood eosinophil levels), asthma control, and reduced lung function, which are known to impact disease burden, exacerbation, or risk of poor treatment outcomes.[6,11–14] Using baseline measures, patients were stratified into the following 5 groups, which were selected to represent relevant categories associated with the above asthma characteristics: 1) blood eosinophil levels ≥150 cells/μL or 2) ≥300 cells/μL (representing evidence of type 2 inflammation); 3) 5-item Asthma Control Questionnaire (ACQ-5) score <1.5 (controlled asthma) or 4) ≥1.5 (uncontrolled asthma); and 5) forced expiratory volume in 1 second (FEV_1) <80% predicted (reduced lung function).

CRSwNP outcomes assessed were nasal polyp score (NPS; range 0 to 8; the sum of the right and left nostril scores, assessed by at least two physicians based on centrally read video recordings of nasal endoscopy), nasal congestion (NC; 0 to 3), loss of smell (LoS) score (0 to 3), 22-item Sino-Nasal Outcome Test (SNOT-22) total (0 to 110) and domain (ear/facial, emotion, function, nasal, and sleep, each computed as the average score of the corresponding items [0 to 5]) scores,[23] and the University of Pennsylvania Smell Identification Test (UPSIT) score (0 to 40). ACQ-5 score (range 0 to 6) and pre-bronchodilator predicted FEV_1 were the asthma outcomes assessed.

CRSwNP and asthma outcomes were also assessed within each asthma characteristic group for patients with or without coexisting NSAID-ERD.

Statistical Analyses

Pooled data from SINUS-24 and SINUS-52 were used for the Week 24 analysis, and data from SINUS-52 were used for the Week 52 analysis. Least squares (LS) mean changes from baseline at 24 and 52 weeks for each outcome were analyzed in each asthma characteristic group using an analysis of covariance model with change from baseline in the outcome as the response, and the corresponding baseline value, treatment group, prior surgery history, regions, and study indicator as covariates. As this was a post hoc analysis, all P values are nominal.

Results

Baseline Characteristics

In the pooled intention-to-treat population, 59.1% (428/724) of patients had self-reported coexisting asthma. Of these patients, 50.9% (218/428) had uncontrolled asthma (ACQ-5 score ≥1.5) and 40.7% (174/428) had predicted FEV_1 <80%. Baseline CRSwNP and asthma disease characteristics were generally balanced across the asthma characteristics groups (Table 1), except for SNOT-22, which was higher in the uncontrolled vs the controlled asthma subgroup; the difference exceeded the minimum clinically important difference (MCID) of 8.9 points.[24]

CRSwNP Outcomes

Dupilumab significantly improved NPS, NC, LoS, and HRQoL vs placebo at Week 24 across all asthma characteristics groups, with improvements maintained at Week 52 (all P < 0.0001) (Figure 1). At Week 24 in the pooled studies, improvements in SNOT-22 total score with dupilumab exceeded the MCID of 8.9 points in 76.1% of patients with baseline eosinophils ≥150/μL, 77.3% of patients with baseline eosinophils ≥300/μL, 78.7% of patients with controlled asthma, 77.4% of patients with uncontrolled asthma, and 72.0% of patients with reduced lung function (all P < 0.0001 vs placebo). The corresponding proportions in SINUS-52 at Week 52 were 73.0%, 74.6%, 78.6%, 67.5%, and 67.5%, respectively (all P < 0.001 vs placebo).

In addition, there were significant improvements in each SNOT-22 domain score vs placebo (Table S1).

Asthma Outcomes

Improvements in FEV_1 were observed with dupilumab across all asthma characteristics groups at Week 24 and Week 52, with all changes reaching significance (Week 24, all P < 0.001; Week 52, all P < 0.05), except at Week 52 in patients with uncontrolled asthma at baseline (P = 0.0511) (Figure 2).

Dupilumab significantly improved ACQ-5 at Week 24 across all asthma characteristics groups, with improvements maintained at Week 52 (all P < 0.0001) (Figure 2). At Week 24 in the pooled studies, improvements exceeded the MCID of 0.5 points for ACQ-5[25] in 53.0% of patients with baseline eosinophils ≥150/μL, 53.4% of patients with baseline eosinophils ≥300/μL, 35.2% of patients with controlled asthma, 74.2% of patients with uncontrolled asthma, and 61.7%

Table 1 Baseline CRSwNP and Asthma Characteristics for Dupilumab and Placebo Treatment Groups in Patients with CRSwNP and Coexisting Asthma from the SINUS-24 and SINUS-52 Studies (Pooled), Stratified by Asthma Subgroups

	Type 2 Asthma[a]		Asthma Control		Lung Function
	Eosinophils ≥150 cells/μL (n=387)	Eosinophils ≥300 cells/μL (n=300)	ACQ-5 <1.5 (n=194)	ACQ-5 ≥1.5 (n=218)	FEV₁ <80% (n=174)
CRSwNP Characteristics					
NPS (range 0 to 8)	6.00 (1.26)	6.06 (1.28)	6.10 (1.24)	5.86 (1.29)	5.99 (1.26)
NC (range 0 to 3)	2.43 (0.57)	2.49 (0.55)	2.37 (0.57)	2.49 (0.56)	2.40 (0.61)
LoS score (range 0 to 3)	2.82 (0.44)	2.85 (0.39)	2.80 (0.49)	2.83 (0.42)	2.83 (0.43)
UPSIT (range 0 to 40)	12.26 (6.92)	11.70 (6.39)	12.36 (6.65)	12.34 (7.27)	11.53 (6.31)
SNOT-22 total score (range 0 to 110)	54.07 (20.36)	56.15 (20.38)	45.77 (18.15)	61.47 (19.09)	53.15 (19.81)
Asthma Characteristics					
ACQ-5 (range 0 to 6)	1.72 (1.21)	1.80 (1.26)	0.68 (0.47)	2.67 (0.84)	1.99 (1.13)
FEV₁ (L)	2.62 (0.89)	2.60 (0.91)	2.79 (0.93)	2.43 (0.79)	2.11 (0.70)

Notes: Data are mean (standard deviation). [a]Other type 2 asthma characteristics, such as fractional exhaled nitric oxide or serum immunoglobulin E, were either not assessed or not captured for this analysis.
Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; CRSwNP, chronic rhinosinusitis with nasal polyps; FEV₁, forced expiratory volume in 1 second; L, liters; LoS, loss of smell; NC, nasal congestion; NPS, nasal polyp score; SNOT-22, 22-item Sino-Nasal Outcome Test; UPSIT, University of Pennsylvania Smell Identification Test.
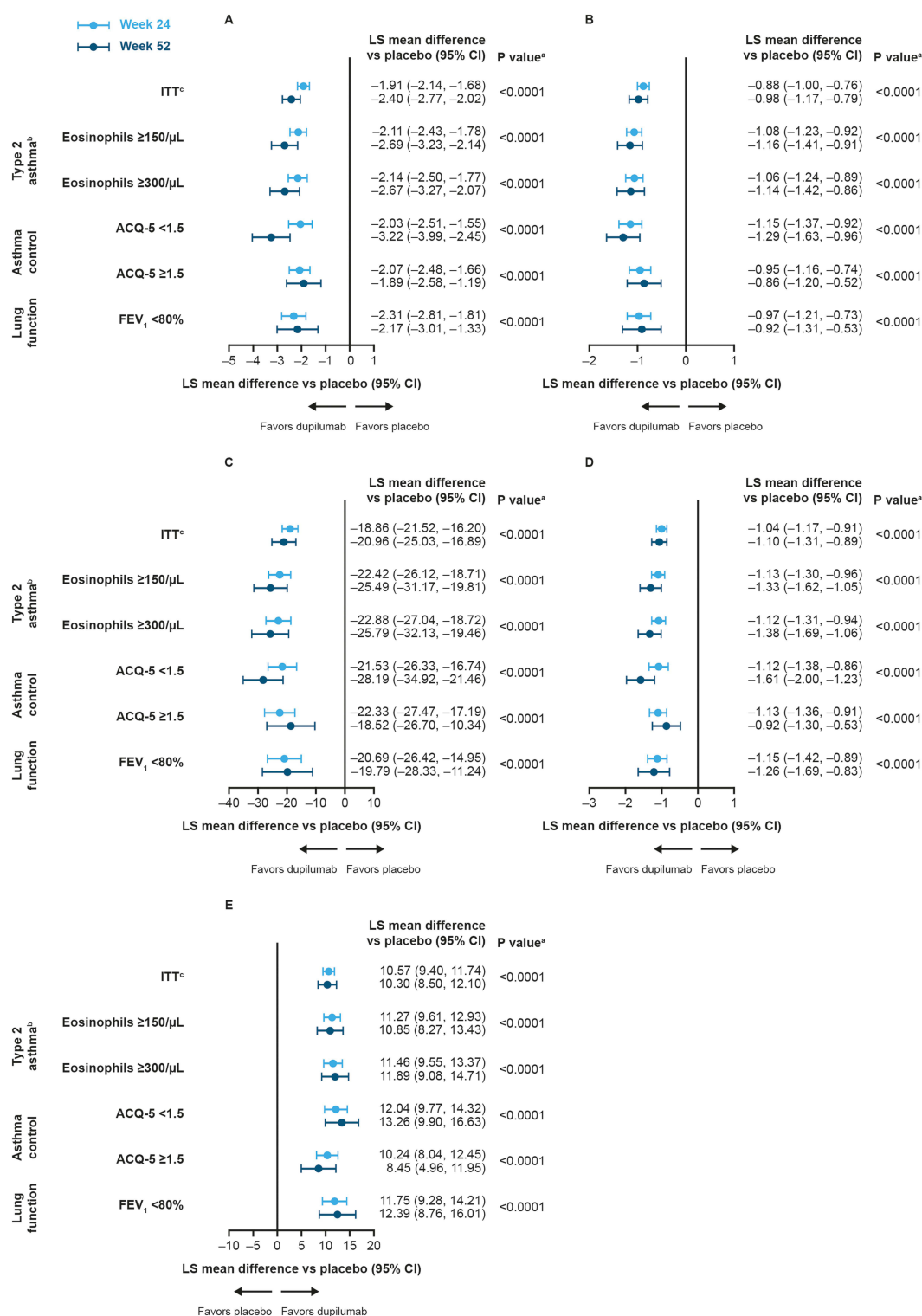
Figure 1 Forest plots of least squares mean difference vs placebo in CRSwNP outcomes at Week 24 (Pooled SINUS-24 and SINUS-52) and Week 52 (SINUS-52) in patients with CRSwNP and coexisting asthma, stratified by baseline asthma characteristics (**A**) NPS, (**B**) NC, (**C**) SNOT-22 total, (**D**) LoS score, (**E**) UPSIT.

Notes: [a]P values apply to LS mean difference vs placebo for Week 24 and Week 52 across each of the 5 outcome measures. Data were analyzed using an ANCOVA model with change from baseline in the outcome at the corresponding visit as the response, and the corresponding baseline value, treatment group, prior surgery history, regions, and study indicator as covariates. [b]Other type 2 asthma characteristics, such as fractional exhaled nitric oxide or serum immunoglobulin E, were either not assessed or not captured for this analysis. [c]The ITT population comprised all patients from the original ITT populations of SINUS-24 and SINUS-52 (pooled for Week 24; SINUS-52 only for Week 52).

Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; ANCOVA, analysis of covariance; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; FEV_1, forced expiratory volume in 1 second; ITT, intention-to-treat; LoS, loss of smell; LS, least squares; NC, nasal congestion; NPS, nasal polyp score; SNOT-22, 22-item Sino-Nasal Outcome Test; UPSIT, University of Pennsylvania Smell Identification Test.
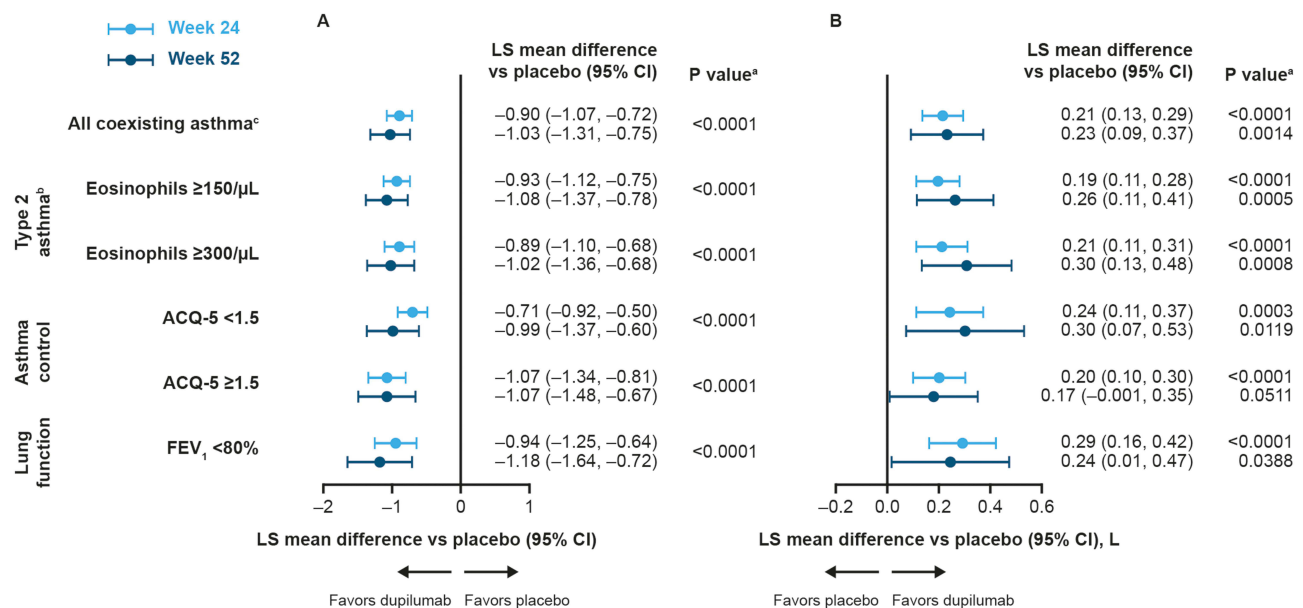
Figure 2 Forest plots of least squares mean difference vs placebo in asthma outcomes at Week 24 (Pooled SINUS-24 and SINUS-52) and Week 52 (SINUS-52) in patients with CRSwNP and coexisting asthma, stratified by baseline asthma characteristics (**A**) ACQ-5, (**B**) FEV₁.
Notes: [a]P values apply to LS mean difference vs placebo for Week 24 and Week 52. Data were analyzed using an ANCOVA model with change from baseline in the outcome at the corresponding visit as the response, and the corresponding baseline value, treatment group, prior surgery history, regions, and study indicator as covariates. [b]Other type 2 asthma characteristics, such as fractional exhaled nitric oxide or serum immunoglobulin E, were either not assessed or not captured for this analysis. [c]The "all coexisting asthma" population comprised all patients from the original ITT populations of SINUS-24 and SINUS-52 who also had coexisting asthma (pooled for Week 24; SINUS-52 only for Week 52).
Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; ANCOVA, analysis of covariance; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; FEV₁, forced expiratory volume in 1 second; ITT, intention-to-treat; L, liters; LS, least squares.

of patients with reduced lung function (all P < 0.0001). The corresponding proportions in SINUS-52 at Week 52 were 45.9%, 45.8%, 28.6%, 62.5%, and 47.5%, respectively (all P < 0.01).

CRSwNP and Asthma Outcomes in Patients with Coexisting NSAID-ERD

In the SINUS studies, 28.2% of patients had CRSwNP with coexisting NSAID-ERD. Among patients with CRSwNP and asthma, the frequency of coexisting NSAID-ERD was similar across the asthma characteristic groups (37.9% to 42.2%) (Table S2). Improvements with dupilumab were seen for all CRSwNP and asthma outcomes across all asthma characteristics groups at Week 24 regardless of the presence of NSAID-ERD at baseline (Table S2). All changes were significant (P < 0.05), except for change in FEV₁ in patients with an ACQ-5 score <1.5 and without NSAID-ERD at baseline (P = 0.0743).

Discussion

The results of this analysis demonstrate that dupilumab significantly improved both CRSwNP and asthma outcomes vs placebo, with improvements seen irrespective of relevant baseline asthma characteristics. Patients with type 2 asthma— an inflammatory characteristic that typically presents with more severe and difficult-to-treat disease, and is associated with coexisting conditions and increased risk of poor asthma outcomes[11]—demonstrated improvement in CRSwNP and asthma outcomes. As dupilumab targets the shared receptor component for interleukin-4 and -13, which are key and central drivers of type 2 inflammation, this provides a likely mechanism to explain the clinical effects of dupilumab in patients with type 2 asthma and CRSwNP.

Patients with uncontrolled asthma also demonstrated improvement, which is significant as this characteristic is associated with increased risk of asthma exacerbation and increased burden on healthcare resources.[12,13] Interestingly, approximately one-third of patients with controlled asthma achieved the ACQ-5 MCID, which indicates that further

improvement may be gained with dupilumab in those with already well-controlled asthma. Dupilumab also demonstrated improvement in CRSwNP and asthma outcomes irrespective of the presence of coexisting NSAID-ERD.

Most (90%) of the patients with self-reported asthma in our cohort showed characteristics of type 2 asthma based on elevated blood eosinophils ≥150/μL, with approximately 70% with blood eosinophils ≥300/μL. The type 2 asthma group definition was based solely on eosinophil count, which is a narrow definition and highlights a potential limitation of the study, as other type 2 biomarkers need to be considered to fully determine the effectiveness of dupilumab treatment in patients with coexisting type 2 asthma, as well as determining that the outcomes of the current analysis are independent of other type 2 biomarkers. Other type 2 biomarkers that are common in asthma are missing from our definition, including high total immunoglobulin E and high fractional exhaled nitric oxide (FeNO).[26] The latter omission is particularly important as high FeNO has been shown to provide prognostic value of exacerbation risk and predict patient response to dupilumab independently of blood eosinophil count.[27–30] Furthermore, this study only assesses the impact of asthma severity based on airway obstruction, and patients with severe airway obstruction (FEV_1 <50%) were excluded from the SINUS-24 and SINUS-52 trials, meaning that dupilumab efficacy in patients with severe airway obstruction is uncertain. Additional analyses could consider other markers for asthma disease severity, including asthma medication use, exacerbation history, and asthma severity per Global Initiative for Asthma guidelines.

More generally, in the context of other biologics and their efficacy in patients with coexisting disease, post hoc analyses of the PROXIMA (omalizumab) and ANANKE studies (benralizumab) demonstrated improvements in asthma outcomes in patients with severe eosinophilic/allergic asthma regardless of coexisting CRSwNP, though neither of these studies was focused on CRSwNP and did not report CRSwNP outcomes in these populations.[31,32] Biologics have also demonstrated efficacy in a real-world setting, with improvements in asthma outcomes and some CRSwNP outcomes observed with dupilumab, benralizumab, mepolizumab, and omalizumab in patients with asthma, with or without coexisting CRSwNP.[33–40] However, the impact of baseline disease characteristics on treatment outcomes evaluated in this analysis was not assessed in these studies.

In conclusion, dupilumab significantly improved upper and lower airway outcomes in patients with severe CRSwNP and coexisting asthma, in line with other studies of biologics in the treatment of coexisting disease. Improvements were seen in patients with type 2 asthma, irrespective of relevant baseline measures of asthma control or lung function, and irrespective of coexisting NSAID-ERD. These data add to our understanding of the effects of dupilumab in patients with coexisting upper and lower airway disease.

Abbreviations

ACQ-5, 5-item Asthma Control Questionnaire; ANCOVA, analysis of covariance; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; HRQoL, health-related quality of life; ITT, intention-to-treat; LoS, loss of smell; LS, least squares; MCID, minimum clinically important difference; NC, nasal congestion; NPS, nasal polyp score; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated respiratory disease; SNOT-22, 22-item Sino-Nasal Outcome Test; UPSIT, University of Pennsylvania Smell Identification Test.

Data Sharing Statement

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.vivli.org/.

Ethics Approval and Informed Consent

The studies were conducted in accordance with the Declaration of Helsinki, approved by the local institutional review board or ethics committee at each study site (Table S3), and all patients provided written informed consent.

Acknowledgments

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all of these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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