Biologics for chronic rhinosinusitis with nasal polyps: a real-world prospective cohort study

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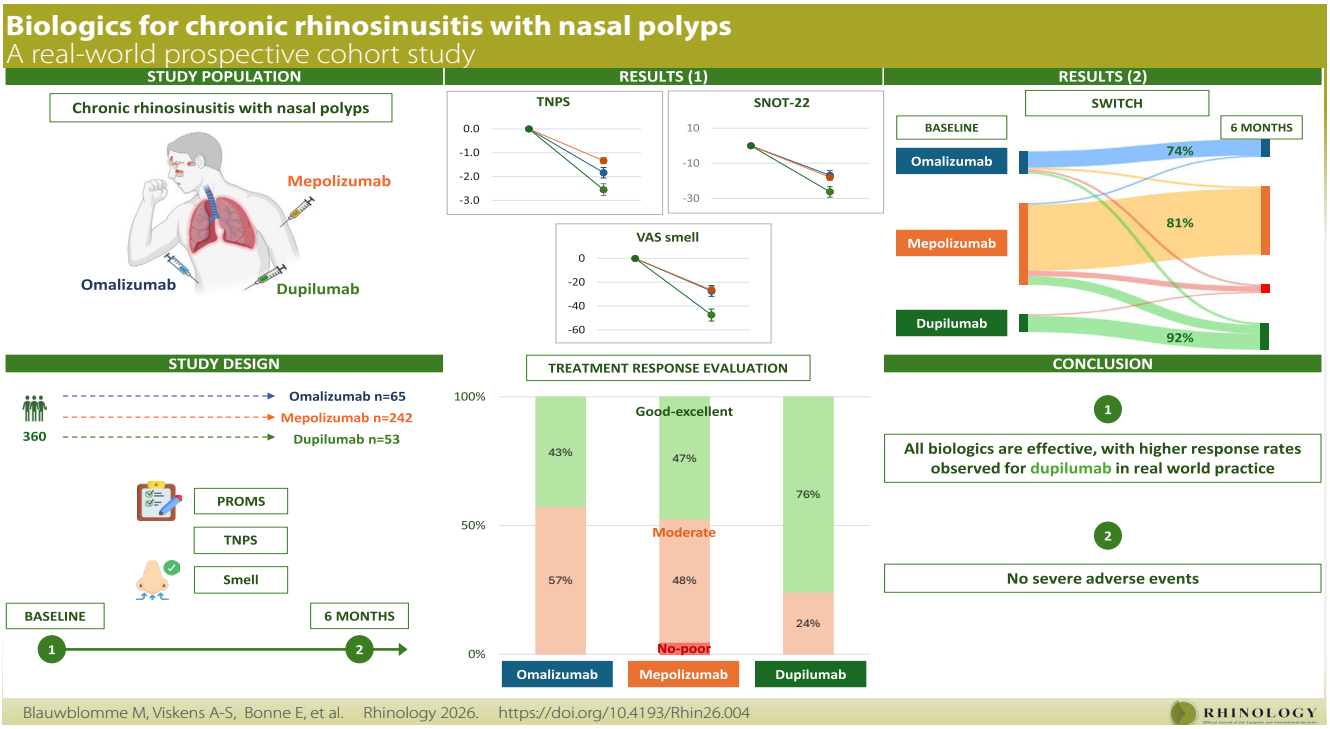

Abstract

Background: Monoclonal antibody therapies targeting type 2 inflammation for chronic rhinosinusitis with nasal polyps (CRSwNP) have shown efficacy in randomized controlled trials (RCTs), however prospective real-world comparative data across all approved biologics remain limited. We aimed to evaluate the real-world effectiveness of omalizumab, mepolizumab, and dupilumab in patients with severe CRSwNP. **Methodology**: A prospective, multicentre, real-world phase IV study in Belgium, enrolling 360 patients with severe CRSwNP initiating treatment with omalizumab (n=65), mepolizumab (n=242), or dupilumab (n=53) between March 2022 and April 2025. Clinical data were collected at baseline and after 6 months. The therapeutic response was evaluated based on EUFOREA criteria. **Results**: After 6 months, nasal polyp score (NPS), olfactory function, and patient-reported outcomes improved across all biologics, with concurrent improvements in asthma control within each treatment group. A good-to-excellent multidomain therapeutic response was achieved in 51% of patients, and treatment continuation beyond 6 months was observed in 74% of omalizumab-, 81% of mepolizumab-, and 92% of dupilumab-treated patients. No severe adverse events were reported. **Conclusion**: In this real-world cohort, the three registered biologics provided significant clinical benefit in severe CRSwNP, with numerically larger improvements observed in patients treated with dupilumab.

Key words: chronic rhinosinusitis, biologics, omalizumab, mepolizumab, dupilumab, real world data

Introduction

Chronic rhinosinusitis (CRS) is a prevalent condition that imposes a significant burden on patients and healthcare systems. Within primary diffuse CRS, endotyping into type 2 or non–type 2 inflammation has become particularly relevant, as this distinction reflects underlying immunologic mechanisms and therapeutic implications [1]. Despite standard therapies such as intranasal corticosteroids and endoscopic sinus surgery, a considerable proportion of patients with CRSwNP remain uncontrolled. In recent years, biologic therapies targeting type 2 inflammatory pathways, anti-IgE (omalizumab), anti–IL-5 (mepolizumab), and anti–IL-4Rα (dupilumab), have been approved for the treatment of severe, uncontrolled CRSwNP. Randomized controlled trials (RCTs) have consistently demonstrated their efficacy in reducing polyp size, improving quality of life, and restoring olfactory function [2-5]. However, RCTs are conducted in highly selected populations under tightly controlled conditions, and their findings may not fully capture treatment effectiveness in daily clinical practice. Following regulatory approvals, an increasing number of real-world studies have been conducted, providing important insights into the effectiveness and safety of biologics outside the highly selected setting of RCTs. However, most real-world studies are retrospective, single-centre, or focus on a single biologic at a time [6-12]. Comparative prospective data across biologics remain scarce, and evidence on switching patterns and response heterogeneity in daily practice is still limited [13]. This study uniquely addresses these evidence gaps because all three biologics are reimbursed for severe CRSwNP in Belgium, allowing their evaluation within the same healthcare setting using consistent assessment methods and real-world clinical decision-making. Consequently, this cohort offers a rare and clinically meaningful opportunity to generate comparative effectiveness data that can inform biologic treatment selection and support shared decision-making in routine practice. The primary aim was to evaluate the clinical effectiveness, treatment response, and switching patterns of omalizumab, mepolizumab, and dupilumab in patients with severe CRSwNP treated in routine clinical practice.

Materials and methods

Study design and population

This phase IV, real-world, prospective, multicentre study was conducted across 11 centres in Belgium between March 2022 and April 2025. The protocol was approved by the ethics committee of University Hospitals Leuven and Ghent (S66646; ONZ-2022-0033) and participating centres. Written informed consent was obtained from all participants. Adult patients (≥18 years) with severe CRSwNP fulfilling national reimbursement criteria for biologics (Table S1), largely overlapping with EPOS criteria and including prior sinus surgery, were consecutively enrolled after initiation of omalizumab, mepolizumab, or dupilumab. Treatment choice was determined by the treating physician according to individual clinical and biological characteristics and fulfilment of the reimbursement criteria; no randomization was performed. Patients were excluded if they had received another biologic therapy for CRSwNP within the 3 months, participated in a biologic trial within 3 months, were unable to consent, or were pregnant.

Baseline characteristics

Demographic and clinical data, including age, sex, diagnosis year, smoking status, comorbidities, and general health status, were recorded and verified against medical records.

Evaluation of outcomes

Clinical assessments were performed at baseline and 6 months in this predefined interim analysis. The primary endpoint was effectiveness, measured by change in total nasal polyp score (TNPS, range 0–4 on each side) on endoscopy, scored according to a predefined and previously published method [14], and sinonasal outcome test-22 (SNOT-22). Secondary endpoints included nasal congestion score (NCS, range 0–3), the University of Pennsylvania smell identification test (UPSIT, range 0–40) and visual analogue scale (VAS) for olfactory function. Lower airways were scored by the asthma control test (ACT) and asthma control questionnaire (ACQ-5).

At each visit, patients were assessed for adverse events, use of antibiotics or systemic corticosteroids, and any (salvage) sinus surgery.

Treatment Response Evaluation (TRE)

Composite treatment response was assessed using EUFOREA/EPOS criteria across five domains [15] at 6 months: TNPS reduction ≥1, no need for systemic corticosteroids or rescue surgery, SNOT-22 reduction ≥9 points and a total score <40, improvement in VAS smell ≥10 points (scale 0–100) and total VAS <50, and control of type 2 comorbidities (e.g. asthma, N-ERD). Response was categorized as no-poor (0-1), moderate (2-3) or good-excellent (4-5).

Statistical analysis

Baseline characteristics were summarized descriptively. No formal sample size calculation was performed due to the prospective real-world design; all eligible patients were consecutively included. Continuous variables are presented as mean ± SD or median (IQR), and categorical variables as counts and percentages. Changes over time were analysed using linear mixed-effects models with patient-level random intercepts and fixed effects for treatment, time, and their interaction. Systematic departures from model assumptions were evaluated using Q–Q plots for residual normality and scatterplots of residuals versus predicted values for homoscedasticity. Missing data were handled within

Table 1. Baseline characteristics.

	Total n=360 (100%)	Omalizumab n=65 (18.1%)	Mepolizumab n=242 (67.2%)	Dupilumab n=53 (14.7%)
Age (mean ± SD)	52.2y (13.20)	50.1y (13.22)	53.2y (13.24)	50.5y (12.78)
BMI (mean ± SD)	26.2 (4.15)	25.4 (3.23)	26.5 (4.55)	26.6 (4.17)
Gender n (%)				
Male	217 (60.6%)	39 (60.0%)	149 (62.1%)	29 (54.7%)
Female	141 (39.4%)	26 (40.0%)	91 (37.9%)	24 (45.3%)
Smoker n (%)				
No	236 (67.6%)	38 (60.3%)	160 (68.7%)	38 (71.7%)
Yes	30 (8.6%)	6 (9.5%)	16 (6.9%)	8 (15.1%)
Ex-smoker	83 (23.8%)	19 (30.2%)	57 (24.7%)	7 (13.2%)
CRSwNP duration (median [min, max])	12.0y [0, 53.0]	11.0y [1.0, 47.0]	12.0y [0, 53.0]	12.0y [1.0, 35.0]
SCS use past year n (%)	236 (69.4%)	46 (73.0%)	151 (67.4%)	39 (73.6%)
Number of prior ESS n (%)				
0	10 (2,9%)	1 (1.6%)	6 (2.6%)	3 (5.7%)
1	149 (43.2%)	25 (39.7%)	101 (44.1%)	23 (43.4%)
2	94 (27.2%)	20 (31.7%)	63 (27.5%)	11 (20.8%)
>2	92 (26.7%)	17 (27.0%)	59 (25.8%)	16 (30.2%)
Asthma * n (%)	274 (77.8%)	60 (92.3%)	178 (76.1%)	36 (67.9%)
N-ERD n (%)	78 (24.5%)	13 (22.0%)	54 (26.1%)	11 (21.2%)
Allergy n (%)	203 (58.2%)	35 (53.8%)	136 (58.6%)	32 (61.5%)
Total nasal polyp score (mean ± SD)	4.23 (1.82)	4.48 (1.72)	4.20 (1.85)	4.08 (1.82)
SNOT-22 (mean ± SD)	48.32 (20.34)	50.37 (21.96)	47.58 (19.54)	49.04 (21.92)
NCS (mean ± SD)	2.08 (0.85)	2.03 (0.82)	2.09 (0.85)	2.1(0.86)
VAS smell (median [min, max])	95.0 [0.0, 100.0]	95.5 [7.0, 100.0]	95.0 [0.0, 100.0]	91.50 [12.0, 100.0]
UPSIT (median [min, max])	14.00 [5.0, 38.0]	13.00 [7.0, 38.0]	14.00 [5.0, 38.0]	14.00 [9.0, 36.0]
ACT (mean ± SD)	18.54 (4.41)	19.09 (4.11)	18.34 (4.42)	18.30 (4.79)
Total IgE (kU/L) (median [min, max])	134 [0.3, 4116.0]	177 [0.3, 1475.0]	124 [4.2, 3041.0]	124.5 [6.7, 4116.0]
Eosinophil count (10^9/L) * (median [min, max])	400.0 [0.0, 2580.0]	272.50 [24.0, 820.0]	440.0 [0.0, 2580.0]	240.0 [0.0, 1390.0]

Baseline demographic and clinical characteristics of patients initiating treatment with omalizumab, mepolizumab, or dupilumab. Between-group differences were assessed using chi-square tests for categorical variables, one-way ANOVA for normally distributed continuous variables, and Kruskal–Wallis tests for non-normally distributed continuous variables. Statistical significance was defined as $p < 0.05$. Significant differences are indicated with *. CRSwNP; Chronic rhinosinusitis with nasal polyps; SCS; Systemic corticosteroids; ESS; Endoscopic sinus surgery; N-ERD; Nonsteroidal anti-inflammatory drug exacerbated respiratory disease; SNOT-22; Sinonasal outcome test; NCS; Nasal congestion score; VAS; Visual analogue Scale; UPSIT; University of Pennsylvania smell identification test; ACT, Asthma control test; IgE; Immunoglobulin E

the mixed-model framework, which includes all available data under the missing-at-random (MAR) assumption; no imputation was performed. Estimates of treatment effects are presented with 95% confidence intervals (CI). All tests were two-sided with a significance level of $p < 0.05$; suggestive p-values (0.05–0.10) are also reported. Treatment response was dichotomized (0 = poor-to-moderate, 1 = good-to-excellent). Logistic regression was used for dichotomized treatment response and selected secondary outcomes, with exploratory adjustment for clinically relevant baseline variables. Group differences in response rates across biologics were additionally evaluated using Chi-square tests where appropriate. Analyses were performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

A total of 360 patients with severe, uncontrolled CRSwNP were enrolled at baseline, of whom 65 (18.1%) initiated omalizumab, 242 (67.2%) mepolizumab, and 53 (14.7%) dupilumab. The mean age was 52 years (SD 13.2) and mean body mass index 26.2 kg/m^2 (SD 4.2). The average disease duration exceeded 10 years, and patients had undergone a mean of 2 prior sinus surgeries (SD 1.4). Omalizumab and mepolizumab became reimbursed for CRSwNP in Belgium in 2022, whereas dupilumab reimbursement was introduced later, in 2024. Nearly all patients receiving omalizumab had comorbid asthma (92%), compared with 76% in the mepolizumab and 68% in the dupilumab group, reflecting

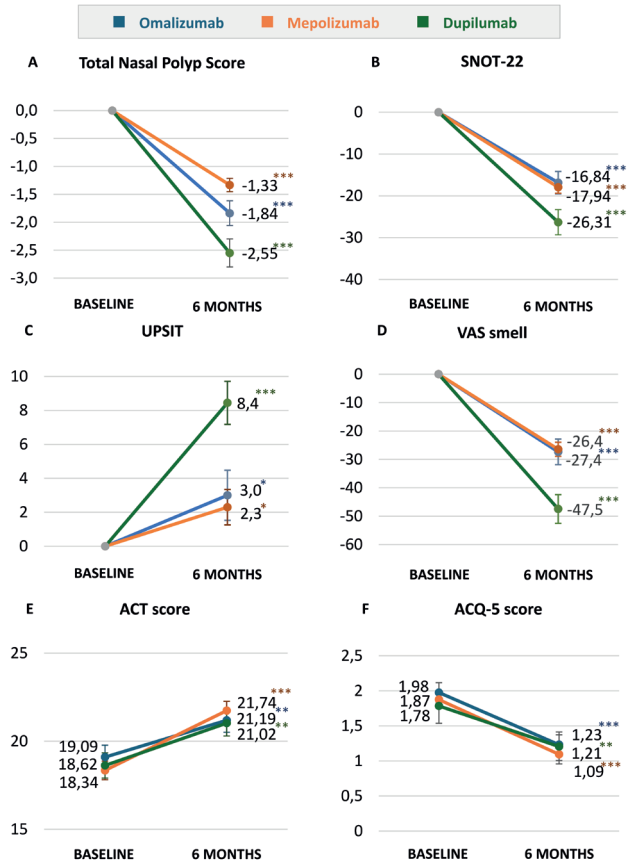

Figure 1. Model-estimated outcomes for key CRSwNP and asthma-related measures from baseline to 6 months. Panels A–D show estimated mean changes (± SE) from baseline to 6 months in TNPS (A), SNOT-22 (B), UPSIT (C), and VAS smell (D). Panels E–F display model-estimated marginal means (± SE) at baseline and 6 months for ACT score (E) and ACQ-5 score (F). Estimates were derived from linear mixed-effects models with random intercepts for patients. Error bars indicate standard errors. Asterisks denote statistically significant within-group changes from baseline (p<0.05, *p<0.01, **p<0.001). TNPS; Total nasal polyp score; SNOT-22; Sinonasal outcome test questionnaire; UPSIT; University of Pennsylvania smell identification test; VAS; Visual analogue scale; ACT; Asthma control test; ACQ-5; Asthma control questionnaire; SE; Standard error.

Belgian reimbursement criteria for omalizumab requiring concomitant asthma until November 2023. Patients receiving mepolizumab had significantly higher baseline blood eosinophil counts compared to those on omalizumab ($p < 0.05$). Other demographic and clinical characteristics, including total Immunoglobulin E (IgE), SNOT-22, total nasal polyp score (TNPS), and VAS measure for smell, were comparable between treatment groups. A detailed overview of baseline characteristics is provided in Table 1.

Evaluation of main clinical parameters

Significant improvements were observed across all main clinical parameters after 6 months of biologic treatment, including TNPS, SNOT-22, UPSIT, and VAS for smell (Figure 1A, 1B, 1C, 1D). All three biologics significantly reduced TNPS at 6 months, with mixed-effects models confirming overall improvement and a significant visit-by-treatment interaction. Model-estimated mean reductions were largest in the dupilumab group (–2.55 points, 95% CI –3.04 to –2.06), followed by omalizumab (–1.84, 95% CI –2.27 to –1.40) and mepolizumab (–1.33, 95% CI –1.57 to –1.10). Pairwise comparisons confirmed significant within-group reductions for all biologics (all $p < 0.001$). Patients initiating dupilumab reached the lowest absolute TNPS at 6 months. Baseline TNPS was slightly higher for omalizumab and mepolizumab than for dupilumab. Overall, model estimates suggest a numerically larger TNPS reduction with dupilumab over 6 months (Figure 1A).

Baseline SNOT-22 did not differ between groups, and all biologics produced significant improvement exceeding the MCID (≥9 points). Estimated mean reductions were greatest with dupilumab (–26), followed by mepolizumab (–18) and omalizumab (–17), with a significant visit-by-treatment interaction indicating greater improvement with dupilumab (Figure 1B).

Nasal congestion improved in all groups. Logistic regression showed higher odds of no/mild congestion with dupilumab compared with omalizumab (OR 0.20, 95% CI 0.06–0.64, $p = 0.007$) and mepolizumab (OR 0.14, 95% CI 0.05–0.40, $p < 0.001$) (Table S3). The longitudinal generalized linear mixed model (GLMM) confirmed overall improvement but no significant difference in improvement patterns (interaction $p = 0.216$) (Figure 2).

Olfactory function, assessed by the UPSIT, improved significantly across all treatment groups. Baseline scores were comparable among the 3 groups. Mixed-effects modelling demonstrated a clear overall improvement over time and a significant visit-by-treatment interaction, indicating differences in the magnitude of olfactory recovery. Mean UPSIT improvement was greatest with dupilumab (+8.44, 95% CI +5.94 to +10.95), compared with omalizumab (+3.00, 95% CI +0.09 to +5.92) and mepolizumab (+2.30, 95% CI +0.23 to +4.36) (Figure 1C). At 6 months, patients treated with dupilumab reached the highest absolute UPSIT values. Most patients had severe olfactory dysfunction at baseline (severe hyposmia or anosmia), with a shift toward milder categories across all biologics after 6 months (Figure 3).

VAS smell scores demonstrated a pattern consistent with UPSIT: all biologics produced significant improvement, but dupilumab showed the largest reduction (–47 points), compared with omalizumab (–27) and mepolizumab (–26). Baseline VAS smell was similar among the three groups (Figure 1D).

Evaluation of the lower airways

Asthma control improved significantly within each treatment group over 6 months. Mean ACT scores increased by +2.1 points for omalizumab, +3.4 points for mepolizumab, and +2.4 points

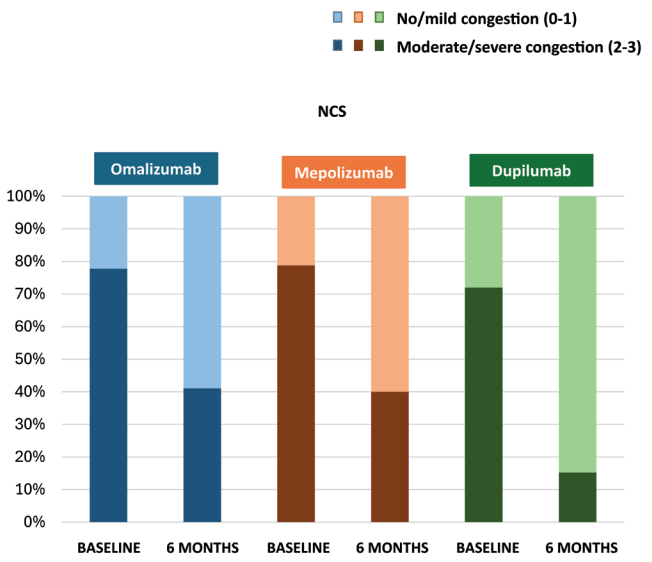

Figure 2. Proportion of patients with moderate–severe congestion (NCS 2–3) at baseline and 6 months. Stacked bar chart illustrating the proportions of patients with moderate–severe nasal congestion (score 2–3) versus no/mild congestion (score 0–1) at baseline and after 6 months of treatment for omalizumab, mepolizumab, and dupilumab. All treatment groups showed a reduction in the proportion of patients with moderate–severe congestion over time. NCS; Nasal congestion score.

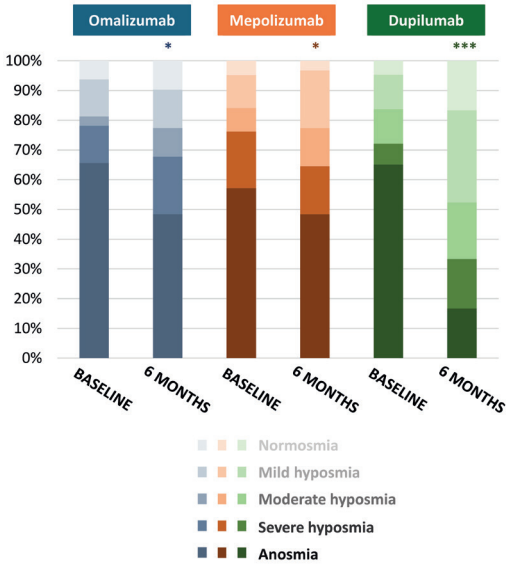

Figure 3. Distribution of olfactory function categories at baseline and 6 months across biologics (derived from UPSIT). Stacked bar charts show the proportion of patients within each UPSIT-defined olfactory category (normosmia, mild hyposmia, moderate hyposmia, severe hyposmia, and anosmia) at baseline and after 6 months of treatment with omalizumab, mepolizumab, or dupilumab. Categories are shown as proportions of the total number of patients with available UPSIT data at each time point. Asterisks indicate statistically significant within-group improvements in UPSIT scores (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

for dupilumab (Figure 1E). Similarly, ACQ-5 scores decreased in all groups, with mean reductions of –0.75, –0.78, and –0.58 points, respectively, indicating better asthma symptom control (Figure 1F). All within-group changes exceeded the established minimal clinically important difference. Because baseline asthma prevalence differed across biologics, these outcomes were interpreted descriptively.

Therapeutic Response Evaluation (TRE)

Of 360 patients, 268 (74%) had complete data for all five EUFOREA criteria of TRE. After 6 months, 51% were classified as good–excellent responders, 46% moderate, and 3% poor responders. Response differed significantly between biologics, with good–excellent response rates of 41.8% for omalizumab, 47.3% for mepolizumab, and 77.3% for dupilumab (Figure 4). Using dupilumab as reference, omalizumab (OR 0.21, 95% CI 0.09–0.51, $p < 0.001$) and mepolizumab (OR 0.26, 95% CI 0.12–0.57, $p < 0.001$) had lower odds of achieving a good–excellent response, with no difference between omalizumab and mepolizumab. After adjustment for baseline asthma and eosinophils, omalizumab remained associated with lower odds compared with dupilumab (adjusted OR 0.16, 95% CI 0.06–0.40, $p < 0.001$), whereas the difference for mepolizumab was no longer significant (adjusted OR 0.23, 95% CI 0.05–1.19, $p = 0.258$). Baseline asthma and eosinophils were not independently associated with response.

Therapy continuation and switching at 6 months

At 6 months, 81.3% of patients continued their initial biologic, 11.7% switched to a different biologic, and 7.0% discontinued without switching. Continuation rates were highest in the dupilumab group (approximately 92%), compared with 81.0% for mepolizumab and 73.8% for omalizumab (Figure 5). Notably, no patients initially treated with dupilumab switched to another biologic after 6 months. Most switches were directed toward dupilumab. While the overall three-category distribution (continue/switch/stop) did not reach statistical significance, a significant linear trend suggested fewer therapy changes in dupilumab-treated patients. Reasons for switching were most frequently insufficient response, though adverse events and pregnancy desire were also reported.

Adverse events

Among 212 patients with available safety data, 78 (36.8%) reported at least one adverse event (AE) within 6 months. The proportion of patients reporting at least one AE was 31.9% (15/47) in the omalizumab group, 40.2% (49/122) in the mepolizumab group, and 32.6% (14/43) in the dupilumab group. A total of 102 AEs were recorded. Most patients reported a single

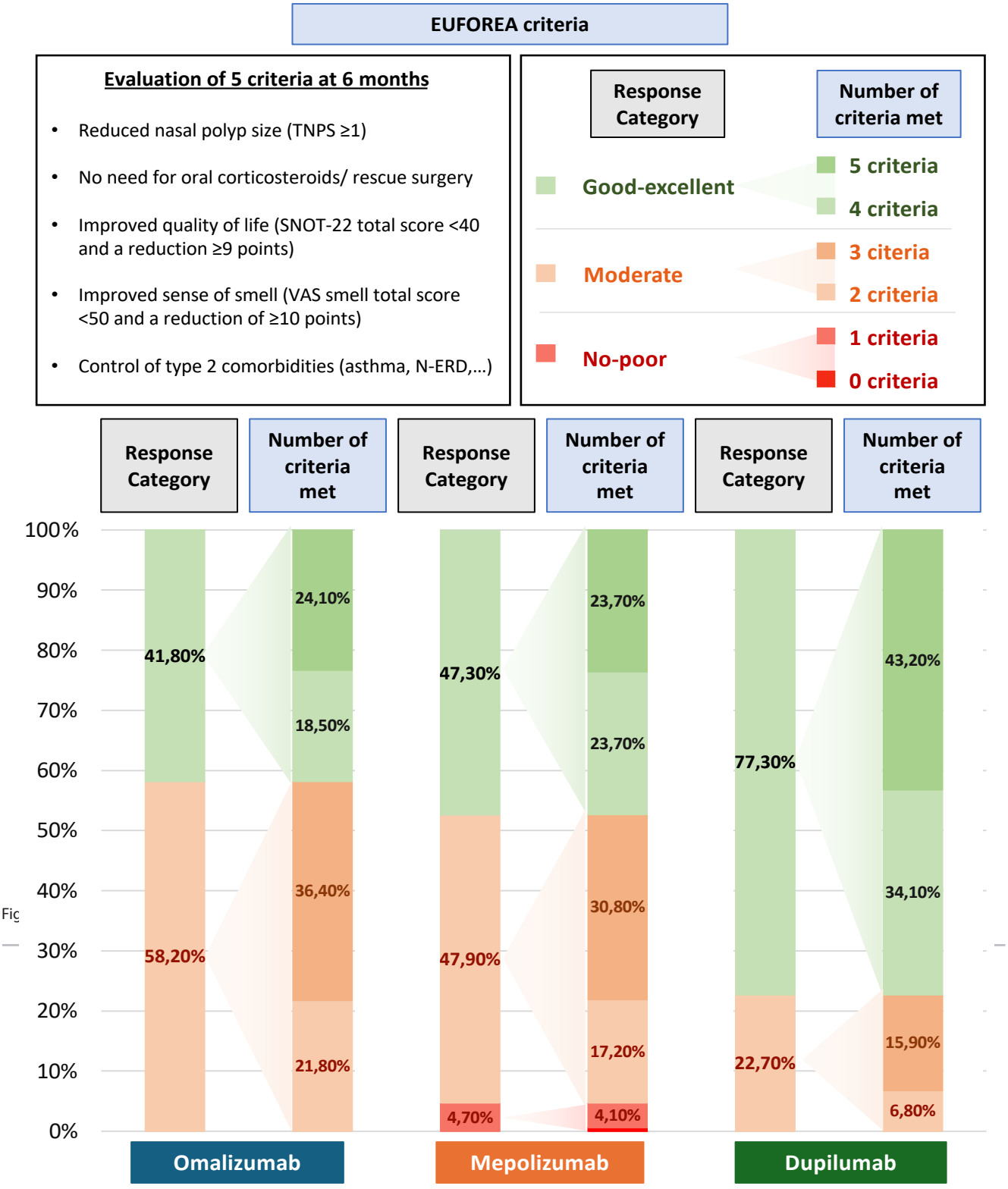

Figure 4. Distribution of EUFOREA Treatment Response Evaluation (TRE) across biologic treatments. For each biologic, the left stacked bar represents the distribution of overall response categories ("no–poor", "moderate", and "good–excellent"), while the right stacked bar shows the distribution according to the exact number of EUFOREA criteria met (0–5) after 6 months of treatment with omalizumab, mepolizumab, or dupilumab. Percentages are calculated among patients with complete EUFOREA data. A "good–excellent" response corresponds to meeting 4 or 5 criteria, "moderate" to 2 or 3 criteria, and "no–poor" to 0 or 1 criterion.

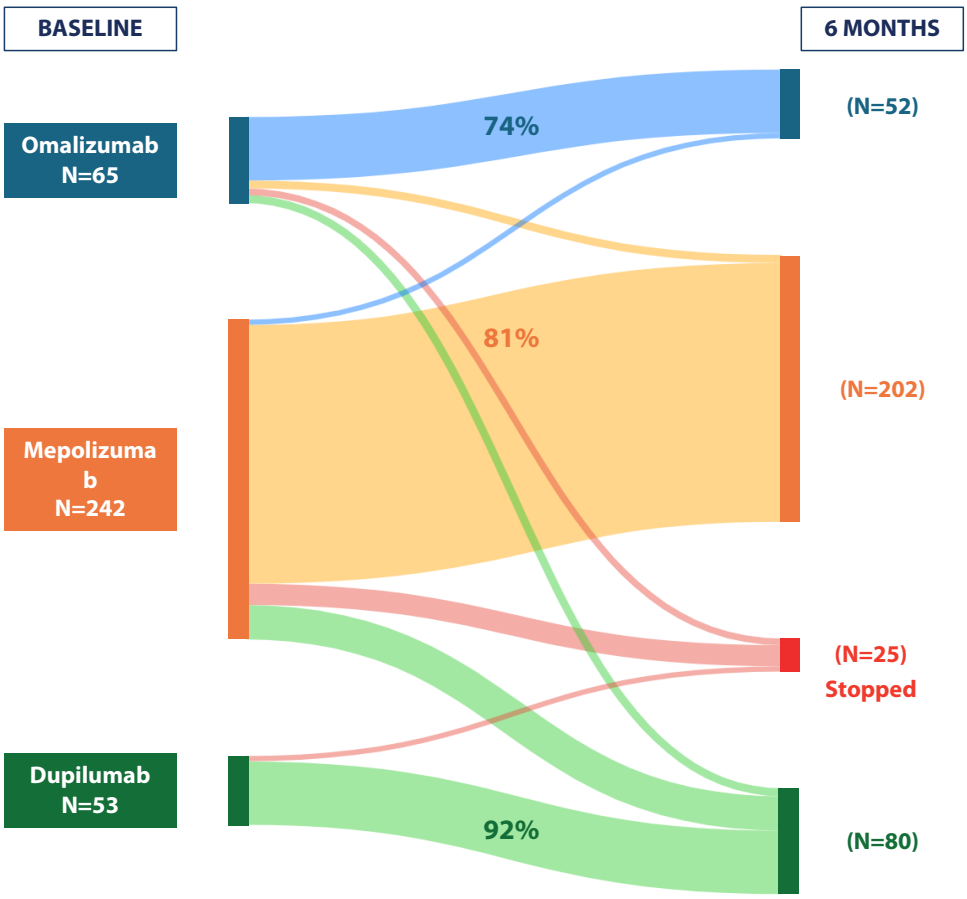

Figure 5. Treatment continuation, switching, and discontinuation over 6 months. Sankey diagram illustrating transitions in biologic therapy from baseline to 6 months for patients initiating omalizumab, mepolizumab, or dupilumab. Flows represent the number of patients who continued their initial biologic, switched to another biologic, or discontinued treatment. Width of the streams corresponds to the relative number of patients in each transition pathway.

AE, while a smaller proportion experienced multiple events. The majority of reported AEs were mild and self-limiting, most commonly post-injection headache, transient myalgia or arthralgia, local injection-site reactions, and upper respiratory tract infections (Table S2). Dermatologic AEs (including psoriasiform rash, erythema multiforme, lichen planus, and alopecia) were reported in 2.1–7.0% of patients, while metabolic symptoms such as weight gain occurred in 1.6–4.7%. Serious AEs were rare, one dupilumab-treated patient discontinued treatment due to a psoriasiform reaction, while one mepolizumab-treated patient developed erythema exsudativum multiforme that was managed with a short course of oral corticosteroids without discontinuing biologic therapy. No biological demonstrated a distinct adverse-event profile suggestive of a safety signal.

Discussion

In this large prospective real-world cohort of 360 adults with severe CRSwNP, treatment with omalizumab, mepolizumab, or dupilumab was associated with substantial clinical improvement across multiple disease domains, including polyp burden, olfactory function, sinonasal symptoms, and patient-reported outcomes. These findings align with results from randomized controlled trials (RCTs) while providing comparative effectiveness data in a more heterogeneous, unselected population than typically included in phase III studies.

Baseline TNPS in our cohort (mean 4.1–4.5) was lower than in the RCTs, which required a minimum TNPS of ≥5 for inclusion, whereas Belgian reimbursement criteria for this cohort required only the presence of bilateral nasal polyps, as symptom severity does not always correlate with endoscopic polyp size. Nevertheless, the magnitude of TNPS improvement in this real-world study was larger for omalizumab (–1.84, 95% CI –2.27 to –1.40), mepolizumab (–1.33, 95% CI –1.57 to –1.10), and dupilumab (–2.55, 95% CI –3.04 to –2.06) compared with the reductions reported in POLYP 1/2 (–1.00), SYNAPSE (–0.90), and SINUS-24/52 (–1.90), respectively (2-4). Similar observations have been described in several real-world studies, which frequently report more pronounced clinical improvement than phase III trials, likely

reflecting broader patient heterogeneity and real-life treatment patterns [8, 16]. In addition, differences in outcome assessment may contribute to this observation, as TNPS in RCTs is based on blinded centralized video scoring, whereas in real-world settings it is typically assessed by the treating physician. In our cohort, the largest numerical reduction was observed in dupilumab-treated patients, which is directionally consistent with the greater TNPS effect sizes described in the SINUS trials relative to the other RCTs. However, direct cross-trial comparisons should be interpreted cautiously due to differences in baseline severity, comorbidities, and concomitant treatments. The present study adds comparative real-world evidence, showing that these patterns may extend outside the controlled trial environment, though interpretation remains observational and not causal.

Improvements in SNOT-22 scores are consistent with findings from the RCT's. All three biologics demonstrated significant reductions in total SNOT-22 scores, with baseline values in our cohort (47.6–50.4) comparable to those reported in the omalizumab and dupilumab trials and somewhat lower than in the mepolizumab trial. The magnitude of SNOT-22 improvement observed in this cohort closely paralleled the mean differences reported in the respective RCTs, reinforcing the consistency of patient-reported outcome benefits across both controlled and real-world settings.

Olfactory outcomes followed a similar pattern, improvements in UPSIT and VAS smell were observed for all biologics. The marked improvement among dupilumab-treated patients aligns with prior findings from SINUS-24/52, where robust effects on olfaction were reported [4]. The more modest olfactory gains seen with anti-IgE and anti–IL-5 therapies are likewise consistent with existing evidence suggesting a more direct role of IL-4/IL-13 signalling in olfactory epithelial dysfunction [2, 17].

Asthma-related outcomes (ACT and ACQ) also improved within each treatment group. Because baseline asthma prevalence differed considerably, being highest in the omalizumab cohort, these results were interpreted descriptively rather than comparatively. Mixed-effects models adjust for baseline outcome levels but do not account for differential asthma burden, and caution is warranted in attributing between-group differences or similarities to pharmacologic effect rather than population characteristics.

Composite response frameworks provided additional insight into global treatment benefit. Using EUFOREA criteria of therapeutic response, approximately half of patients were classified as good–excellent responders, with distribution differing by biologic. The higher response proportion observed among dupilumab-treated patients is consistent with real-world studies and registry data suggesting strong multidomain improvement with IL-4Rα blockade [6, 9, 12, 18-20].

Patterns of treatment switching further illustrate real-world complexity. Approximately one in five patients changed therapy by 6 months, most commonly transitioning to dupilumab after insufficient response to another biologic. While switching behaviour reflects clinical decision-making rather than comparative efficacy, the consistent directionality toward dupilumab aligns with the multidomain improvements observed in this study. Still, switching should be interpreted cautiously, as decisions may be influenced by patient preference, comorbidities, reimbursement policies, clinician experience, and the later introduction of dupilumab reimbursement in Belgium, which may have contributed to unidirectional switching from previously initiated biologics to a more recently reimbursed option.

A recent systematic review and meta-analysis by Cai et al. synthesized all available real-world evidence on biologic therapies for CRSwNP, including 35 studies on dupilumab, 9 on omalizumab, 8 on mepolizumab, and 9 on benralizumab [13]. While these studies consistently demonstrated clinical benefits across outcomes such as polyp size reduction and quality-of-life improvement, the majority were retrospective, single-centre, or limited to one biologic at a time. Only a few real-world comparisons between two biologics have been published, and to date, no study has concurrently evaluated omalizumab, mepolizumab, and dupilumab within a single multicentre prospective cohort [16]. Other strengths of this study are the large sample size, prospective design, comprehensive multidomain assessment, and use of mixed-effects models that account for repeated measures.

Nonetheless, limitations inherent to observational research should be acknowledged. Treatment allocation was non-randomized and influenced by reimbursement criteria, including mandatory asthma for omalizumab during part of the study period and elevated blood eosinophils (≥ 300 cells/μL) for mepolizumab initiation, explaining higher baseline eosinophil counts in the mepolizumab group. Although very high baseline eosinophil levels occasionally influenced physician choice, this applied to few patients, and differences mainly reflect reimbursement-driven selection rather than distinct disease phenotypes. Dupilumab was reimbursed approximately two years later, resulting in a shorter inclusion period and fewer treated pateints. This temporal imbalance may partially explain differences in sample size and treatment sequencing patterns and should be considered when interpreting comparative analyses. The follow-up was limited to 6 months, longer-term effectiveness, durability of response, and predictors of switching were not evaluated. Additionally, although AEs were infrequent and no severe events were reported, underreporting is possible in routine practice. Finally, although this dataset offers comparative insights, causal inference between biologics should not be drawn.

Conclusion

This prospective real-world cohort demonstrates that omalizumab, mepolizumab, and dupilumab all confer significant clinical

benefit across key CRSwNP domains over 6 months, with numerically larger improvements observed with dupilumab. These findings complement RCT evidence and provide comparative real-world data to support clinical decision-making. Future studies should evaluate long-term outcomes, head-to-head comparisons, and phenotype-guided treatment selection.

Author contributions

PH, TVZ, PG: conceptualization, methodology, data collection, review and editing, supervision; MB: conceptualization, methodology, data collection, formal analysis, writing, original draft preparation, review and editing; ASV: conceptualization, methodology, data collection, formal analysis, review and editing; EB, EB, CC, GDV, LD, ASE, SH, VH, PJ, WL, FR, KS, OV, BV, AV: data collection, review and editing; PJ, MS, EV: review and editing; All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

MB: has served as an advisor or speaker and received grant/research support from GSK and Sanofi. ASV: has served as an advisor or speaker and received grant/research support from GSK and Sanofi. PG: has served as an advisor or speaker and received grant/research support from ALK, Astra Zeneca, Celltrion, GSK, Lilly, Insmed, Novartis, Regeneron, Roche, Sanofi, and Stallergenes-Greer. PH: recipient of honoraria and/or research grants by Sanofi/Regeneron, GSK, Novartis, Celltrion. VH: received speaker's and consultancy fees from ALK, Sanofi, Astra Zeneca, Novartis, GSK and Celltrion. FR: has served on advisory boards for Sanofi and received grants from GSK and Sanofi. AV: has served as an advisor or speaker for GSK. The other authors have no relevant disclosures.

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Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of AI-assisted technologies in the manuscript preparation process

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) to assist with language editing and improvement of English expression. After using this tool/service, the author reviewed and edited the content as needed and takes full responsibility for the content of the published article.

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SUPPLEMENTARY MATERIAL

Omalizumab	Mepolizumab	Dupilumab
01/02/2022	01/06/2022	01/03/2024

• ≥ 18 years
• Bilateral presence of nasal polyps
• Persistent symptoms despite INCS treatment
• History of FESS (or contraindication)
• At least 2 of the following:
  ◦ 1 treatment with OCS in the last 2 years (or contraindication)
  ◦ Asthma
  ◦ Anosmia
• Total serum IgE ≥ 30 and ≤ 1500 IU/mL and a weight of ≥ 30 and ≤ 150 kg
	• ≥ 18 years
	• Bilateral presence of nasal polyps
	• Persistent symptoms despite INCS treatment
	• History of FESS (or contraindication)
	• At least 3 of the following:
	  ◦ 1 treatment with OCS in the last 2 years (or contraindication)
	  ◦ Asthma
	  ◦ Anosmia
	  ◦ Blood value ≥ 300 cells/µL in the last 12 months prior to treatment AND/OR tissue eosinophilia
		• ≥ 18 years
		• Bilateral presence of nasal polyps
		• Persistent symptoms despite INCS treatment
		• History of FESS (or contraindication)
		• At least 3 of the following:
		  ◦ 1 treatment with OCS in the last 2 years (or contraindication)
		  ◦ Asthma
		  ◦ Anosmia
		  ◦ Blood value ≥ 300 cells/µL in the last 12 months prior to treatment AND/OR tissue eosinophilia

Dose: Based on serum IgE and weight	Dose: 100 mg / 4 weeks	Dose: 300 mg/ 2 weeks

Table S1. Reimbursement criteria for omalizumab, mepolizumab, and dupilumab for severe CRSwNP in Belgium. Overview of the national reimbursement criteria applicable to the use of omalizumab, mepolizumab, and dupilumab for severe chronic rhinosinusitis with nasal polyps. Criteria include general eligibility requirements, disease severity parameters, prior treatments, and biologic-specific conditions as defined by Belgian regulatory authorities. Dosing regimens according to the approved product labels are indicated at the bottom of the table. INCS; Intranasal corticosteroids; FESS; Functional endoscopic sinus surgery; OCS; Oral corticosteroids.

Table S2. Adverse event categories reported at 6 months according to biologic received.

AE category	Omalizumab n/N (%)	Mepolizumab n/N (%)	Dupilumab n/N (%)
Neurological (headache, migraine, paresthesia)	4/47 (8.5%)	6/122 (4.9%)	
Local injection-site reactions	1/47 (2.1%)	3/122 (2.5%)	1/43 (2.3%)
Infections (URTI, sinusitis, viral infections, COVID-19)	7/47 (14.9%)	26/122 (21.3%)	8/43 (18.6%)
Musculoskeletal (myalgia, arthralgia, tendinopathy, cramps)		4/122 (3.3%)	3/43 (7.0%)
Dermatologic/allergic (urticaria, rash, EM, psoriasiform reaction, alopecia, blefaritis)	1/47 (2.1%)	7/122 (5.7%)	3/43 (7.0%)
Gastrointestinal (diverticulitis, GI infection)		1/122 (0.8%)	1/43 (2.3%)
Cardiovascular (palpitations, hypertension, Raynaud's)	1/47 (2.1%)	4/122 (3.3%)	2/43 (4.7%)
Endocrine/metabolic (weight gain, menstrual irregularities, erectile dysfunction)	3/47 (6.4%)	3/122 (2.5%)	2/43 (4.7%)
Other (general malaise, fatigue, taste disturbance, concentration issues, dosing error, instability)	2/47 (4.3%)	9/122 (7.4%)	

Percentages of adverse event reported within each predefined category (neurological, local injection-site reactions, infections, musculoskeletal, dermatologic/allergic, gastrointestinal, cardiovascular, endocrine/metabolic, and other), stratified by biologic therapy (omalizumab, mepolizumab, dupilumab). Patients were counted once per category if they reported ≥1 adverse event in that category. Patients could contribute to multiple categories. AE; Adverse event; URTI; Upper respiratory tract infection; EM; Erythema (exsudativum) multiforme; GI; Gastrointestinal.

Table S3. Logistic regression analyses of binary clinical outcomes at 6 months.

A. Nasal congestion score. Univariable logistic regression (n=142)

Comparison (reference: dupilumab)	OR (95% CI)	P value
Omalizumab vs Dupilumab	0.20 (0.06 – 0.64)	0.007
Mepolizumab vs Dupilumab	0.14 (0.05 – 0.40)	< 0.001

B. Treatment Response Evaluation. Univariable logistic regression (n=268)

Comparison (reference: dupilumab)	OR (95% CI)	P value
Omalizumab vs Dupilumab	0.21 (0.09 – 0.51)	< 0.001
Mepolizumab vs Dupilumab	0.26 (0.12 – 0.57)	< 0.001

C. Treatment Response Evaluation. Multivariable logistic regression adjusted for baseline asthma and blood eosinophil count (n=246)

Comparison (reference: dupilumab)	OR (95% CI)	P value
Omalizumab vs Dupilumab	0.16 (0.06 – 0.40)	< 0.001
Mepolizumab vs Dupilumab	0.23 (0.05 – 1.19)	0.258

A. Univariable logistic regression for nasal congestion score (no/mild vs moderate/severe) (n = 142). B. Univariable logistic regression for Treatment Response Evaluation (Good–Excellent vs Poor–Moderate) (n = 268). C. Multivariable logistic regression for Treatment Response Evaluation (n = 246), adjusted for baseline asthma status and blood eosinophil count. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented relative to dupilumab as the reference category. The multivariable model includes biologic type, baseline asthma status, and baseline eosinophil count entered simultaneously. OR; Odds ratio; NCS; Nasal congestion score; TRE, treatment response evaluation; CI; confidence interval