Dupilumab for Chronic Rhinosinusitis with Nasal Polyps: A Critical Evidence-Based Review

Critical Narrative Review: Otolaryngology, Immunology, and Clinical Pharmacology

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Abstract

Objectives: Nasal polyps are present in a substantial proportion of patients with chronic rhinosinusitis (CRSwNP) and are driven, in most Western populations, by type 2 inflammation. Conventional treatment with corticosteroids and endoscopic sinus surgery frequently fails to provide durable disease control, particularly in patients with marked eosinophilia or comorbid asthma. This review examines dupilumab, a fully human monoclonal antibody directed against the interleukin-4 receptor alpha (IL-4Rα) subunit and the first biologic approved for this indication.

Methods: We integrate disease immunobiology with dupilumab's pharmacology, the pivotal LIBERTY NP SINUS-24 and SINUS-52 trials, the head-to-head EVEREST trial, real-world data from the DUPIREAL and CHRINOSOR cohorts, safety records, comparative performance against the other approved biologic therapies, guideline positions, biomarker research, and cost-effectiveness analyses, drawing throughout on peer-reviewed sources identified by a database search covering January 2020 to June 2026, together with seminal earlier publications, including the pivotal trials, retrieved by hand-searching.

Results: The evidence is consistent in direction. Olfaction recovers, polyp burden decreases, and patients require fewer systemic corticosteroid courses and revision procedures, with benefits that appear to persist over two to five years. Important uncertainties nevertheless remain: no single biomarker reliably predicts response, the optimal duration of therapy is undefined, and published analyses disagree on whether dupilumab is cost-effective relative to surgery.

Conclusions: Biologic therapy is effective when guided by selective, criterion-based patient selection rather than applied as a routine first-line intervention.

Keywords: *dupilumab; chronic rhinosinusitis; nasal polyps; type 2 inflammation; IL-4 receptor alpha; biologics; EPOS; EUFOREA*

How to cite this article: Al-Itbi AOA, Hasan M, Abd Ali ZA, Al Chaabawi H. Dupilumab for chronic rhinosinusitis with nasal polyps: a critical evidence-based review. Int J Drug Deliv Technol. 2026;16(73s):1696-1705. DOI: 10.25258/ijddt.16.73s.181

1. Introduction and Disease Background

Chronic rhinosinusitis, or CRS, is inflammation of the nose and sinuses lasting 12 weeks or more. EPOS2020 defines it by at least two of: nasal blockage, discharge, facial pain or pressure, and loss of smell, with diagnosis confirmed by endoscopy or imaging. Nasal polyps occur in approximately 20 to 30% of CRS cases, and, depending on the country and the definition applied, CRSwNP affects between 1.1% and 4.3% of the population.[1,2,3]

The disease burden is substantial: sinus-specific quality of life is impaired, asthma coexists in 25 to 65% of cases, NSAID-exacerbated respiratory disease is present in up to 40% of the most refractory cases, and healthcare utilisation is high.[3,4]

Surgery provides relief, but only transiently, and it removes the polyps themselves rather than the inflammation that produces them. Recurrence is therefore common, particularly in patients with asthma, eosinophilic disease, or N-ERD. Patients who remain symptomatic despite corticosteroids and surgery correspond to what EPOS2020 defines as "severe uncontrolled CRSwNP," the population targeted by biologic therapy.[1]

Allergic fungal rhinosinusitis (AFRS) constitutes a distinct immunological entity. Driven by type I (IgE-mediated) and, in part, type III (immune-complex-mediated) hypersensitivity to fungal antigens, it is characterised by eosinophilic mucin containing fungal hyphae and, typically, a greater polyp burden and more extensive bony remodelling than conventional CRSwNP.[5] None of the pivotal CRSwNP trials enrolled patients with AFRS, so the on-label evidence base does not extend to this subgroup. A 2025 systematic review pooled six small studies (60 patients) and identified a consistent pattern irrespective of the biologic used, whether dupilumab, mepolizumab, or omalizumab: improvement in quality-of-life scores, endoscopic grading, and blood markers, with no safety concerns over 3 to 14 months, although the constituent studies were small, uncontrolled, and of short duration; with fewer than a hundred patients in total and follow-up not exceeding fourteen months, the evidence in this subtype should be treated as preliminary. A larger multinational trial of dupilumab dedicated to AFRS has been reported as under way.[6]

1.1 What This Review Adds

Several narrative and systematic reviews of dupilumab in CRSwNP have already been published, most centred on the SINUS-24/SINUS-52 pivotal data. The present review differs in several respects. It incorporates the head-to-head EVEREST trial and the largest currently available real-world cohorts (DUPIREAL, CHRINOSOR), extending the evidence base beyond placebo-controlled efficacy toward comparative, real-world effectiveness, while explicitly accounting for the inflation characteristic of uncontrolled before-and-after designs. It also addresses areas that most prior reviews omit or treat only briefly: allergic fungal rhinosinusitis as a mechanistically distinct subtype excluded from the pivotal trials, benralizumab's mixed trial results as a cautionary comparator, and dupilumab's still-unsettled effects on the sinonasal microbiome.

2. Search Strategy and Selection Criteria

This is a critical narrative review rather than a systematic review, and it was not registered with PROSPERO. Searches were conducted in PubMed/MEDLINE, Embase, and the Cochrane Library from January 2020 to June 2026 using the terms dupilumab, chronic rhinosinusitis, nasal polyps, CRSwNP, IL-4 receptor, biologics, network meta-analysis, and real-world evidence, supplemented by hand-searching the reference lists of major trials and guidelines (EPOS2020, EPOS/EUFOREA 2023, AAAAI/JTF 2023). Seminal publications predating 2020, including the pivotal SINUS trials, were identified through this hand-search.

Randomised controlled trials, real-world cohorts, systematic reviews, network meta-analyses, and formal guidelines were prioritised; conference abstracts and preprints were excluded, with a single exception: one conference presentation reporting EVEREST lung-function and asthma-control outcomes was retained because those data are not yet available in a peer-reviewed publication, and is identified as such where cited. Studies were selected on relevance to the questions addressed here and on methodological standing, with randomised trials and formal guidelines carrying the greatest weight, followed by systematic reviews and network meta-analyses, then prospective registries and cohorts, and finally single-centre retrospective series. Where sources disagreed, precedence was given to randomised over observational data and to direct over indirect comparison, and the disagreement is reported rather than resolved in the text. No formal instrument such as GRADE or ROBIS was applied. Dual independent screening and a PRISMA flow diagram were not used either, as neither is appropriate to a narrative format; these limitations are addressed in Section 14.

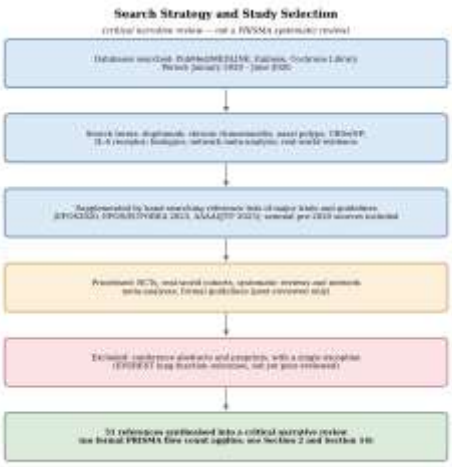

Figure 1. Search and selection strategy underlying this critical narrative review. As this is not a systematic review, no formal PRISMA record-count flow diagram applies; the steps shown reflect the search and prioritisation process described in Section 2.

3. Immunopathogenesis

Type 2 inflammation underlies approximately 80 to 85% of Western CRSwNP cases, although this proportion cannot be considered universal. East Asian cohorts have historically shown a more neutrophilic, Th1/Th17-skewed profile, and only in recent decades has the endotype distribution in these populations begun to shift toward the eosinophilic end of the spectrum.[7,8]

Impairment of the epithelial barrier is frequently the initiating event, whether attributable to *Staphylococcus aureus* toxins, pollutants, or an intrinsically weak barrier. Three principal alarmins, the epithelium-derived signals released when the barrier is injured, are implicated: IL-25, IL-33, and TSLP, which activate group 2 innate lymphoid cells (ILC2s) and mast cells and drive type 2 cytokine production.[9,10]

IL-4 subsequently signals through STAT6 to induce GATA3, which in turn drives further production of IL-4, IL-5, and IL-13, so that the response amplifies itself once initiated.[8]

IL-4Rα is the receptor subunit shared by both cytokines, and it is expressed on B cells, epithelial cells, fibroblasts, and smooth muscle. Signalling through it drives IgE class-switching, eosinophil recruitment, mucus hypersecretion, and tissue remodelling. The result is the oedematous, eosinophil-rich polyp tissue that characterises type 2 disease, and it is this convergence on a single shared subunit that provides the mechanistic rationale for dupilumab.[10,11]

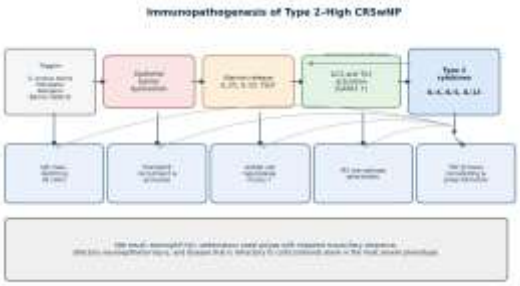

Figure 2. The type 2 inflammatory cascade in CRSwNP, from epithelial barrier dysfunction through alarmin release, ILC2/Th2 activation, and type 2 cytokine amplification, to the downstream effector mechanisms that produce eosinophil-rich nasal polyps.

4. Mechanism of Action and Clinical Pharmacology

Dupilumab is a fully human IgG4 antibody, about 147 kDa, expressed in Chinese hamster ovary cells. It binds IL-4Rα with high affinity, blocking both receptor complexes that incorporate this subunit (type I and type II) and thereby inhibiting IL-4 and IL-13 signalling through a single molecular target.[11,12] Its pharmacokinetics are non-linear, as is characteristic of this antibody class: subcutaneous bioavailability is approximately 60 to 64%, and the volume of distribution is small, approximately 4.8 ± 1.3 L.[13,14] The approved CRSwNP dose is 300 mg every two weeks, selected on the basis of population pharmacokinetic modelling to saturate the target-mediated clearance pathway; after stopping, serum levels take about 9 to 13 weeks to become undetectable.[13,14]

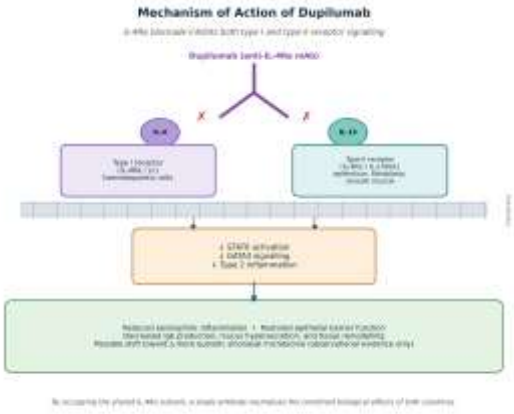

Figure 3. Dupilumab's mechanism of action. Binding to the shared IL-4Rα subunit blocks both type I and type II receptor signalling, inhibiting STAT6/GATA3-driven type 2 inflammation through a single therapeutic target.

Anti-drug antibodies develop in a minority of patients. These are predominantly low-titre and do not compromise clinical efficacy. Rare serum sickness-like reactions have been reported at high antibody titres.[14]

A secondary aspect has recently attracted attention: dupilumab may also alter the sinonasal microbiome. Type 2 inflammation tends to co-occur with dysbiosis and heavier Staphylococcus aureus colonisation, whose superantigens amplify eosinophilic inflammation and raise local IgE production. In atopic dermatitis, dupilumab consistently reduces S. aureus abundance and increases bacterial diversity.[15] The sinonasal picture is less consistent. Observational CRSwNP cohorts report a broad shift toward more eubiotic compositions (increased Corynebacterium, Dolosigranulum, and Lawsonella), but S. aureus has shown no consistent reduction, and in at least one cohort its abundance remained stable or increased.[16,17] Whether this barrier–microbiome interaction is clinically meaningful in CRSwNP remains an open question.

5. Pivotal Trials: LIBERTY NP SINUS-24 and SINUS-52

SINUS-24 and SINUS-52 were twin phase 3 trials: randomised, double-blind, placebo-controlled, run across multiple countries, enrolling adults with a nasal polyp score of 5 or higher, symptoms despite nasal steroids, and a history of oral steroids and/or sinus surgery, all on background mometasone nasal spray. Table 1 summarises the key results.[18]

Parameter	SINUS-24 (NCT02912468)	SINUS-52 (NCT02898454)
Design	RCT, DB, PC, 1:1	RCT, DB, PC, 1:1:1
N randomised	276	448
Regimen(s)	300 mg Q2W vs placebo, 24 wk	300 mg Q2W (52 wk) or Q2W→Q4W step-down vs placebo
Background therapy	Mometasone furoate nasal spray, both arms	Mometasone furoate nasal spray, both arms
NPS, LS-mean diff vs placebo (wk 24)	−2.06 (95% CI −2.43 to −1.69); p<0.0001	−1.80 (95% CI −2.10 to −1.51); p<0.0001
Nasal congestion, LS-mean diff	−0.89 (95% CI −1.07 to −0.71)	−0.87 (95% CI −1.03 to −0.71)
Lund-Mackay CT, LS-mean diff	−7.44 (95% CI −8.35 to −6.53)	−5.13 (95% CI −5.80 to −4.46)
SNOT-22, LS-mean diff vs placebo (wk 24)	−21.12 (95% CI −25.17 to −17.06); p<0.0001	−17.36 (95% CI −20.87 to −13.85); p<0.0001
SCS use or NP surgery, treatment period	Assessed in the pooled analysis (see adjacent column)	12.5% vs 41.8% over 52 wk; HR 0.243; p<0.0001
Comorbid asthma outcomes	Comorbid-asthma subgroup (pooled analysis)	FEV_1 and ACQ-6 significantly improved vs placebo

Table 1. Design and key efficacy outcomes of the LIBERTY NP SINUS-24 and SINUS-52 trials.18 The co-primary endpoints of both trials were nasal polyp score and nasal congestion score at week 24; the remaining rows report key secondary outcomes. In SINUS-52 both dupilumab arms received 300 mg Q2W up to week 24, so week-24 estimates are pooled across those arms. NPS, nasal polyp score; SNOT-22, 22-item Sino-Nasal Outcome Test; LS, least-squares; SCS, systemic corticosteroid; ACQ-6, Asthma Control Questionnaire-6.

Olfactory recovery was rapid: patients reported subjective improvement by day 3, and objective olfactory testing demonstrated a significant difference by week 2, well before substantial tissue remodelling could plausibly have occurred.[19] The programme was methodologically robust but carried important limitations. Both arms used nasal spray rather than the nasal drops preferred in some countries, so it is unclear how far the findings transfer to those settings. Enrolled patients had severe, treatment-refractory disease, and the same effect size should not be assumed for milder or biologic-naïve cases. Whether blood eosinophils predict response was, moreover, never fully resolved in the original reports. Both trials were funded and run by the manufacturer.[18,20]

6. Long-Term Durability and Real-World Evidence

The largest real-world dataset comes from DUPIREAL, an Italian observational study. Median nasal polyp score fell from 6 to 1.0 by 12 months, SNOT-22 dropped from 58 to 11, both highly significant, and approximately 97% of patients achieved an excellent-to-moderate response by EPOS2020 criteria. A 2-year follow-up of 926 patients confirmed that the benefit was sustained: 91% were good-to-excellent responders, and the lowest observed remission rate was 64.2% at 24 months.[21,22]

A separate European registry, CHRINOSOR, covering 752 patients across six centres and five countries, corroborates these findings.[23] A related analysis within the same registry identified a noteworthy discrepancy. Only 61.8% of patients met the EUFOREA 2021 criteria for biologic treatment, and only 79.8% met the newer EPOS/EUFOREA 2023 criteria. Real-world prescribing therefore does not consistently follow guideline criteria.[24]

A pooled analysis of real-world studies reported larger mean improvements: a 37-point reduction in SNOT-22 and a 3.6-point reduction in nasal polyp score, exceeding those observed in the placebo-controlled trials.[25] These estimates should be interpreted with caution. Uncontrolled before-and-after designs confound the true treatment effect with natural fluctuation, regression to the mean, and selection bias toward well-resourced centres; patients in these cohorts also had greater baseline severity, which inflates apparent improvement. Real-world data confirm broad effectiveness, but do not establish that the effect size exceeds that demonstrated in the randomised trials.

Whether the dosing interval can be extended once disease control is established has been examined in several independent cohorts, which report that 40 to 77% of patients were successfully transitioned to every-4-week dosing or longer without loss of benefit, and in the DUPIREAL 2-year extension, 18.7% underwent interval extension while maintaining response.[22,26,27] This evidence remains observational rather than randomised, and interval extension should therefore not yet be regarded as standard

practice. It should also be noted that DUPIREAL and several of the cohorts cited in this section received manufacturer support or included investigators with disclosed ties to the manufacturer.

7. Safety Profile

Safety has not proved to be the limiting factor. Injection-site reactions, mild conjunctivitis, arthralgia, and a transient rise in blood eosinophils account for most of what has been reported, and across the one-year controlled trials there was no excess of serious infection, thromboembolism, or cardiovascular events.[18,28] The eosinophil rise is best explained by blockade of eotaxin-3. With tissue recruitment interrupted, cells that would ordinarily have left the bloodstream stay in it, so the change reflects redistribution rather than worsening disease. Counts climb over roughly six months and then fall away in step with total IgE.[29,30]

One situation deserves particular caution. Eosinophilic granulomatosis with polyangiitis has occasionally emerged, or become apparent for the first time, after dupilumab was started. Such reports remain rare, and they have tended to involve patients in whom an eosinophilic or ANCA-related background was arguably already present. The practical implication is vigilance and early specialist referral rather than avoidance of the drug. Where the diagnosis is established rather than emergent, the picture differs: a small prospective series of nine such patients, treated for refractory chronic rhinosinusitis, reported complete response in 55.6% at three months and 83.3% at twelve, so a prior diagnosis of EGPA does not in itself preclude treatment.[31] A GRADE-based AAAAI/JTF review found no clear difference in overall adverse event rates between dupilumab, omalizumab, and mepolizumab versus placebo, though certainty was rated low.[32]

8. Comparative Evidence Against Other Biologics

The 2023 AAAAI/JTF guideline panel judged dupilumab superior to omalizumab and mepolizumab across several outcomes, including SNOT-22, nasal symptom scores, polyp size, endoscopic and CT scores, and the need for rescue corticosteroids or surgery, although certainty of evidence ranged from low to moderate depending on the outcome.[32] Several 2026 network meta-analyses are concordant, placing dupilumab in the highest efficacy tier alongside tezepelumab and, more recently, stapokibart. None of these analyses compared the agents directly: all rankings are generated by indirect comparison across separate placebo-controlled trials, and they carry the assumptions of that method rather than the evidential weight of a head-to-head study. these rankings derive from indirect comparison rather than head-to-head trials and should be regarded as hypothesis-generating. Omalizumab tends to rank higher on composite efficacy-and-safety measures, largely because of a lower adverse-event burden, with mepolizumab intermediate. Table 2 summarises these comparisons.[33,34,35,36]

Feature	Dupilumab	Omalizumab	Mepolizumab	Tezepelumab
Target	IL-4Rα (blocks IL-4 + IL-13)	IgE	IL-5	TSLP (upstream alarmin)
Approved dosing	300 mg SC Q2W	Weight/IgE-tiered SC Q2–4W	100 mg SC Q4W	210 mg SC Q4W (approved Oct 2025)
NMA efficacy tier (NPS)	Top tier	Lower-intermediate; best safety profile	Intermediate	Top tier alongside dupilumab
Head-to-head evidence	EVEREST: superior to omalizumab	Compared directly in EVEREST	Real-world comparison emerging	No head-to-head RCT to date
Notable safety signal	Transient hypereosinophilia; rare EGPA unmasking	Lowest reported AE rate	Class-typical monitoring	Consistent with asthma profile; limited long-term CRSwNP data
Cost-effectiveness (Canada)	ICER $235,305/QALY vs omalizumab	Most cost-effective option	Dominated by both others	Not yet modelled

Table 2. Comparative summary of the biologics currently approved for CRSwNP.32-36,38,49-51 Benralizumab is discussed separately in Section 12, as its OSTRO trial used different co-primary endpoints, limiting tabular comparability. NMA, network meta-analysis; Efficacy tiers are derived from indirect comparison across separate trials, not from head-to-head evidence. NMA, network meta-analysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

One caveat should be stated first. Enrolment criteria, background therapy, and follow-up duration differed across the contributing trials, and several independent groups have pointed out that this heterogeneity weakens any ranking derived by this method.[37] EVEREST provides the only direct comparative evidence: a head-to-head phase 4 trial comparing dupilumab with omalizumab in 360 patients with CRSwNP and coexisting asthma across 17 countries. Dupilumab was superior on both co-primary endpoints (nasal polyp score and olfactory testing), with separation apparent by week 4, and also outperformed omalizumab on lung function and asthma control, although the latter outcomes are so far reported only in a conference presentation and await peer-reviewed publication.[38,39] This constitutes strong evidence, although the trial enrolled only patients with asthma, compared dupilumab against a single competitor, and was funded by the manufacturer.

9. Guideline Recommendations

EPOS2020 first established a place for biologics in severe, uncontrolled CRSwNP, provided that patients meet at least 3 of 5 defined criteria, without designating a preferred agent.[1] The 2023 EPOS/EUFOREA update refined those criteria, lowering the blood eosinophil threshold to 150 cells/μL and deferring the first response assessment from 16 weeks to 6 months, after evidence indicated that the earlier timepoint underestimated eventual response.[40] The 2023 AAAAI/JTF GRADE guideline issued only a conditional,

rather than strong, recommendation for biologics, since intranasal corticosteroids, surgery, and aspirin desensitisation in N-ERD remain first-line, and patients adequately controlled without a biologic derive limited additional benefit from an expensive injectable therapy.[32,41]

Figure 4. Stepped EPOS/EUFOREA 2023 treatment algorithm for severe CRSwNP, from foundational therapy through biologic therapy, with the multi-criterion threshold for step 4 and the recommended 6-month response assessment.

10. Biomarkers and Patient Selection

No biomarker is yet sufficiently validated for routine clinical decision-making, although several candidates appear promising. Blood eosinophil count correlates weakly but significantly with polyp reduction; other blood-count-derived inflammatory indices show no useful predictive value.[29] Tissue eosinophil count follows a similar pattern: patients with 50 or more eosinophils per high-power field showed significantly greater SNOT-22 improvement (p=0.045) than those with lower counts, although no corresponding difference was observed in endoscopic or CT scores. This finding derives from a single retrospective monocentric series and requires prospective confirmation.[42] FeNO and total IgE predict response reliably in asthma and COPD, but in CRSwNP these type 2 markers add only marginal predictive value, which is why EPOS/EUFOREA retains a multi-criterion checklist rather than relying on a single biomarker.[30,40,43]

11. Cost-Effectiveness

The answer on cost-effectiveness depends heavily on two things: which treatment dupilumab is compared against, and the healthcare setting in which the comparison is made. Against best supportive care alone, pooled SINUS-24/52 data modelled in an Italian analysis produced an incremental cost of €21,817 per QALY gained, below the threshold conventionally regarded as acceptable in that setting.[44]

The comparison against surgery is far less consistent: the result varies with modelling conventions, drug pricing, time horizon, and structural assumptions. One 36-year Markov model found dupilumab to cost substantially more while delivering fewer QALYs than endoscopic sinus surgery. A separate 10-year model estimated more QALYs with dupilumab, but at $691,691 per QALY gained, a prohibitively high figure. A Colombian analysis found that surgery generated more QALYs at approximately one-eighth of the cost.[45,46,47] A Korean meta-analysis pooling eight studies (1,251 patients) reached a comparable conclusion: dupilumab improved every outcome relative to its own baseline, but in direct comparison with surgery it performed less well on quality of life and nasal congestion, with only olfactory recovery comparable.[48] A Canadian analysis compared biologics directly on cost per QALY gained. The incremental cost-effectiveness ratio for dupilumab versus omalizumab was $235,305 per QALY, and even after raising the willingness-to-pay threshold to $150,000 per QALY, dupilumab remained cost-effective in only 22.5% of simulations.[49]

Several structural factors account for this dispersion: list price versus the net price actually paid by payers after rebates, disagreement over the conversion of SNOT-22 scores into QALY utilities, and models that almost universally assume lifelong treatment, an assumption that emerging interval-extension data may not support. Clinical benefit and economic value do not align automatically, and surgery frequently prevails in that second comparison.

12. Future Perspectives and Prioritised Research Gaps

Dupilumab is no longer the only approved option. Tezepelumab, which acts further upstream at the level of TSLP and may therefore extend beyond strictly type 2-driven disease, was approved for CRSwNP in October 2025 on the basis of the phase 3 WAYPOINT trial: at 52 weeks it reduced nasal polyp score by −2.07 (95% CI −2.39 to −1.74) and nasal congestion by −1.03 (95% CI −1.20 to −0.86) versus placebo, with a 98% reduction in the need for nasal-polyp surgery (HR 0.02, 95% CI 0.00 to 0.09) and an 88% reduction in systemic corticosteroid use (HR 0.12, 95% CI 0.04 to 0.27).[50,51] Stapokibart, evaluated principally in Chinese cohorts, addresses a genuine gap, given that the existing evidence base derives largely from Western, type 2-high populations. Longer-acting anti-IL-5 agents such as depemokimab reduce dosing to once every 26 weeks, lowering treatment burden, although no head-to-head comparison with dupilumab in CRSwNP is available. Benralizumab, an anti-IL-5 receptor alpha antibody already approved for severe eosinophilic asthma, illustrates that a shared type 2 mechanism does not guarantee equivalent performance in CRSwNP. Its phase 3 OSTRO trial (n=413) met both co-primary endpoints, nasal polyp score and nasal blockage score, at week 40, yet quality of life (SNOT-22), olfactory testing, and time to first rescue surgery or systemic corticosteroid course all remained close to placebo.[52] OSTRO demonstrates that a shared mechanistic class does not translate into a shared outcome profile. Mechanism of action alone is not decisive, and the field is moving toward a more targeted approach: matching the patient's dominant inflammatory profile, whether IL-4/IL-13-driven, IL-5/eosinophil-driven, or alarmin-driven, to the biologic whose mechanism corresponds most closely.[33,36]

Table 3 ranks the principal open questions and indicates how each might realistically be addressed.

Research gap	Priority	Feasible study design
Validated predictive biomarker	Highest	Prospective biomarker-stratified cohort
Randomised discontinuation / interval-extension trial	Highest	RCT of fixed Q2W vs protocolised extension
Head-to-head vs mepolizumab and tezepelumab	High	Phase 4 trials analogous to EVEREST
Efficacy in non-Western / T2-low populations	High	Multiregional RCT stratified by endotype
Long-term safety, incl. EGPA/HES risk	Moderate	Pharmacovigilance registry
Economic models with biomarker-guided selection	Moderate	Updated Markov models, net pricing

Table 3. Prioritised research agenda for dupilumab and biologic therapy in CRSwNP.

13. Conclusion and Clinical Implications

Dupilumab has changed how severe CRSwNP is managed. Randomised trials, long-term follow-up, a head-to-head trial, and independent real-world data converge on the same conclusion: polyp burden decreases, olfaction returns, quality of life improves, and patients require fewer corticosteroid courses and revision procedures. The safety record is favourable, with a small number of signals warranting clinical vigilance.

A measured interpretation nonetheless resists overstatement. The more favourable real-world estimates arise principally from the way uncontrolled observational studies are constructed, not from the drug performing better once it leaves the trial setting. Cost-effectiveness against surgery is frequently unfavourable, the optimal duration of therapy remains undefined, and the identification of durable responders before treatment still rests on clinical judgement rather than on any validated biomarker.

The EPOS/EUFOREA 2023 definition of severe, uncontrolled CRSwNP should be applied before any biologic is considered. Surgery warrants careful deliberation in surgically naive patients, since it is effective and, in most models, costs less for appropriately selected candidates. Comorbid asthma favours dupilumab, which was superior to omalizumab in EVEREST. That trial enrolled patients with CRSwNP and coexisting asthma; N-ERD was not a stratifying criterion, and the result should not be extended to that phenotype without direct evidence. Response should be adjudicated at a full 6 months, in line with the current standard, rather than at an earlier checkpoint. In clearly stable patients, extension of the dosing interval is a reasonable option, although it remains supported by observational rather than randomised evidence. Every major guideline converges on the same principle: biologics for a carefully selected group of patients with severe disease, not a default treatment for all.

14. Limitations of This Review

This is a critical narrative synthesis, not a formal systematic review or new meta-analysis. No dual independent screening, PRISMA reporting, or new pooled statistics were used. Several cited cost-effectiveness and comparative studies apply different definitions and time horizons, which limits direct comparison; this is flagged at the relevant points in the text. Screening and appraisal were not conducted in duplicate, and no formal risk-of-bias instrument was applied to the included studies. Finally, several of the pivotal trials and the largest real-world cohorts were funded by the manufacturer, and the conclusions drawn here should be read with that in mind. A related caveat concerns the composition of the evidence base itself: eight of the fifty-two cited works are first-authored by two investigators (C. Bachert and E. De Corso) whose groups conducted the pivotal trial, the head-to-head trial, the largest real-world cohort, and one of the favourable cost-utility analyses. This concentration reflects the structure of the published literature rather than selective citation, but it does mean that several of the strongest results derive from a small number of closely connected research groups.

Author Contributions

A.O.A.-R.A.-I.: conceptualisation, literature search, evidence appraisal, drafting of the original manuscript, and revision for critical intellectual content. M.H.: appraisal of the immunopathogenesis and pharmacology sections, and critical revision. Z.A.A.A.: literature search, data extraction, and critical revision. H.A.C.: appraisal of the clinical, guideline, safety, and cost-effectiveness sections, and critical revision. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work in accordance with ICMJE criteria.

Conflicts of Interest

The authors declare no conflicts of interest related to this research review.

Funding

This review received no specific grant, funding, or financial support from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability Statement

No new data were generated or analysed for this review. All data discussed are available in the cited publications and their respective supplementary materials.

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