Replacing Long-Term Response Extrapolation With Real-World Registry Data: AROMA-Informed Cost-Effectiveness Analysis of Dupilumab for Severe Chronic Rhinosinusitis With Nasal Polyps in the United Kingdom

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Conclusions

- **In the NICE and SMC appraisals, weighted AROMA registry data replaced constant trial extrapolation of long-term response to dupilumab.**
- **Among patients still responding at month 12, fitted loss of response fell from about 4% to under 1% by month 24.**
- **Over years 2–10, the re-analysis projects 23% losing control (28% in NICE's base case) vs 52% with constant trial extrapolation; most is all-cause discontinuation, counted in full as loss of control.**

Objective

To describe how weighted AROMA registry data replaced constant trial extrapolation of long-term response to dupilumab in the National Institute for Health and Care Excellence (NICE) appraisal, and to re-analyse them with NICE's preferred population, fitting window and response criterion.

Background

- SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454) ran 24 and 52 weeks,[1] but most incremental quality-adjusted life years (QALYs) accrued after the trial period, in the Scottish Medicines Consortium (SMC) analysis[2] and in NICE's committee-preferred model.[3] NICE's real-world evidence framework supports registry data for long-term outcomes.[4]
- **First appraisal committee meeting (ACM1; July 2025):** the company used unmatched AROMA data in the prior-surgery population; SINUS-based constant extrapolation was its sensitivity analysis and the external assessment group (EAG) base case. The committee asked for AROMA matched to SINUS, without months 0–12.[5,6]
- **Consultation and ACM2 (July–September 2025):** the base case moved to prior surgery and 22-item Sinonasal Outcome Test (SNOT-22) ≥50 with a revised response definition (§3.8); AROMA was weighted to the SINUS prior-surgery population, and the EAG refitted the trend from month 12.[5,6]
- **Final guidance (TA1134; February 2026):** 'suitable for decision making' with the EAG refit (§3.10), but 'a potential waning of treatment effect could not be excluded' (§3.6); probabilistic incremental cost-effectiveness ratio £24,846/QALY (§3.18).[5]

Methods

- **Model:** 1-year decision tree, then lifetime Markov model; dupilumab + established clinical management (ECM) vs ECM; NHS and personal social services perspective.[2,5]
- **Population:** ≥1 prior sinus surgery and SNOT-22 ≥50.[5]
- **Response:** year 1 (SINUS prior-surgery responder rates, §3.9): ≥8.9-point SNOT-22 **and** ≥1-point nasal polyp score (NPS) improvement;[5,7] from year 2 (AROMA, no NPS): ≥8.9-point SNOT-22 improvement (as submitted: or SNOT-22 <50), 3-monthly; surgery or systemic corticosteroids = failure.[8,9]
- **AROMA (NCT04959448):** global phase 4 registry of adults starting dupilumab in routine care (691 recruited; up to 36 months).[8,10] Its 185 patients with ≥1 surgery and SNOT-22 ≥50 were weighted to the matching SINUS subgroup (Table 1; effective sample size [ESS] 106).[9]
- **Loss of control:** as in the NICE and SMC models,[2,5] loss of response plus all-cause study discontinuation (2.2%/year as submitted, unweighted; 1.9% here, weighted; Figure 2).[9]
- **Loss of response:** fitted from month 12 (Figure 1) as an exponential decay (Poisson log-link model; offset, previous responders), which handles the 0% intervals that prevented an exponential fit in the submission (§3.10).[5,9]

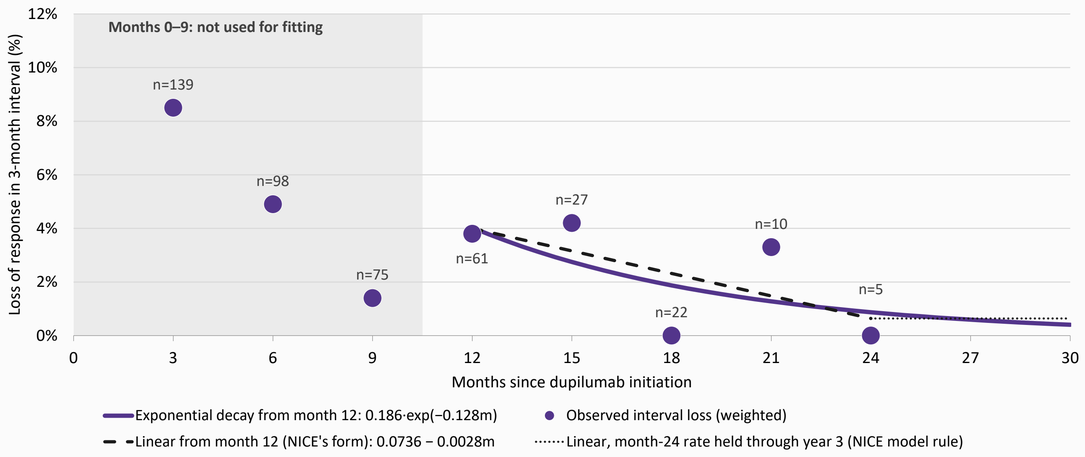
Table 1. Baseline characteristics (≥1 surgery, SNOT-22 ≥50): SINUS target and AROMA before and after weighting (weighting factors shaded)[9]

Characteristic	SINUS (n=230)	AROMA unweighted (n=185)	AROMA weighted (n=174; ESS 106)
Age, years, mean	51.1	–	52.1
≥3 prior surgeries, %	26.1	–	29.1
Comorbid asthma, %	75.2	70.3	72.6
Non-steroidal anti-inflammatory drug-exacerbated respiratory disease, %	38.3	22.7	38.3
Systemic corticosteroids, past 2 years, %	71.3	71.9	71.3
Nasal congestion score, 0–3, mean	2.66	2.23	2.66
SNOT-22, 0–110, mean	68.0	65.9	68.0
Nasal polyp score, 0–8, mean	6.02	not collected	not collected

SINUS: pooled intention-to-treat subgroup. Unweighted AROMA from the weighting dataset (nasal congestion score n=174; the 11 without it have no weight; age and surgery count not included). Not weighted: age, ≥3 surgeries and asthma (similar after weighting); smell test (n=12), Lund–Mackay (n=56) and years since surgery (AROMA vs SINUS: 20.4 vs 11.5; 16.6 vs 19.7; 8.4 vs 6.8) suggest less severe objective disease in AROMA, on sparse data.[6,9]

Results

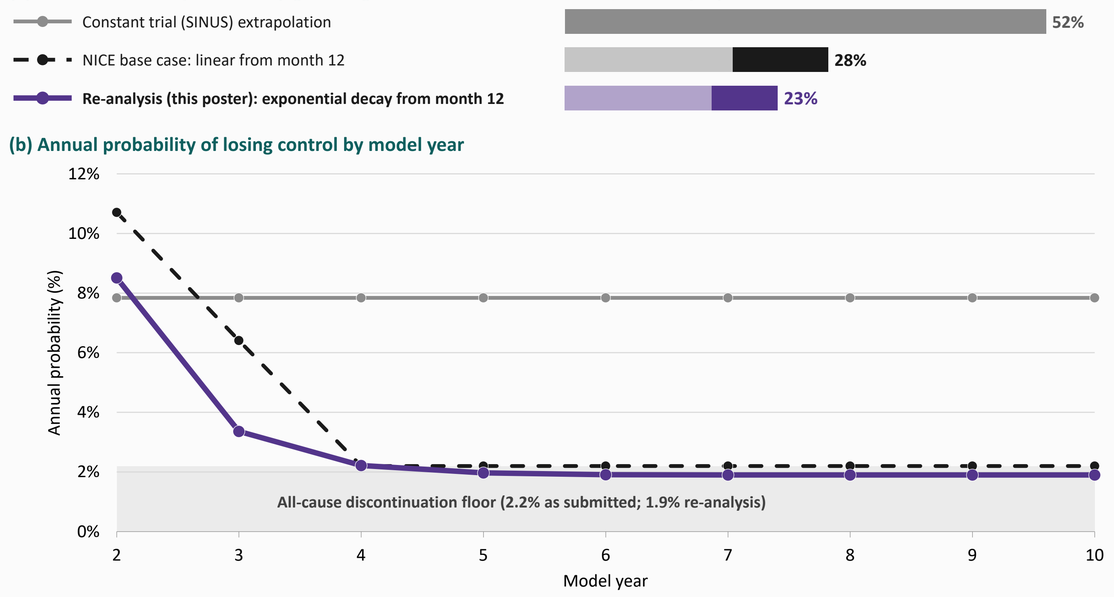
Figure 1. Weighted AROMA loss of response by 3-month interval, with trends fitted from month 12 (≥1 surgery, SNOT-22 ≥50; n=185)[9]



Labels: previous responders assessed at each visit; numbers fall because later visits had not been reached at the interim data cut (May 2024). Fits start at the month-12 point (months 9–12), as in the EAG refit; m, months. Interval losses as submitted differed by ≤1.2 percentage points at every visit.[6] Weighted mean change: SNOT-22 −46, −49 to −52 and −44 at months 6, 12–21 and 24 (n=113, 70 to 14, 8); nasal congestion −1.8, −1.9, −2.1 and loss of smell −1.7, −1.8, −2.4 (0–3) at months 6, 12 and 24 (n=131, 94, 14).[9]

Results (continued)

Figure 2. Losing control on dupilumab over years 2–10: 23% in the re-analysis, 28% in NICE's base case and 52% with constant trial extrapolation[9]



Each year compounds four fitted quarterly losses and adds annual discontinuation, as in NICE's model; discontinuation alone gives 18% (as submitted) and 16% (re-analysis). A linear fit weighted by numbers at risk gives 22%.[5,9]

- From 28% to 23% (changes applied in turn): weighting target and response definition about 2 points; the subset's weighted discontinuation (2.2% to 1.9%) about 2; fitting method about 1 (exponential decay on the as-submitted data: 29%).[5,9]

Implications for registry-informed models

- Match registry data to the decision population; report balance on unweighted prognostic factors and effect modifiers, and ESS.[4,11]
- Where the registry lacks a trial measure (here NPS), agree a bridging definition with the health technology assessment body early.[5]
- Estimate loss of response and discontinuation as time to event, censored at the data cut, with models that handle 0% intervals; report sensitivity to trend shape.
- NICE methods give limited guidance on effect waning;[12] later data cuts and competing-risk models could reduce uncertainty.[5]

Limitations

- About 4 weighted late events (5 at risk in the final interval): log-rate slope −0.128/month (Wald 95% confidence interval −0.50 to 0.25, not adjusted for weights).[9]
- Discontinuation (16 of the 23 points) is the all-cause rate in the current data cut, with follow-up counted to month 24 for patients still in the study; counting every exit as loss of control is conservative, as leaving the registry need not mean losing response or stopping dupilumab (months 12–24: 2 patient decisions, 1 sponsor request, 1 adverse event).[9]
- AROMA lacks NPS (response from year 2 is probably easier to maintain) and has no UK patients (prior-surgery set: USA 46%, Italy 24%, four other countries 30%); weighting cannot adjust for NPS or unmeasured confounders (ESS 106).[9,10]
- ECM responders' loss of control follows the post-surgery rate (§3.10), set at 46% a year from a randomised trial (46% uncontrolled 12 months after surgery vs 64% with medical therapy alone)[13]; NICE judged it likely an overestimate, as the rate is not constant (§3.11).[5]

ACM, appraisal committee meeting; CRSwNP, chronic rhinosinusitis with nasal polyps; EAG, external assessment group; ECM, established clinical management; ESS, effective sample size; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NPS, nasal polyp score; QALY, quality-adjusted life year; SMC, Scottish Medicines Consortium; SNOT-22, 22-item Sinonasal Outcome Test; UK, United Kingdom.

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Generative AI (Claude, Anthropic) was used to draft and edit text, check references, build the figures and layout, and write code for the trend re-fits and the annual and cumulative probabilities. The authors checked all outputs against the source analyses and take full responsibility for the content.

Disclosures:
Halin C, Msihid J, Gandhi A: Sanofi – employees, may hold stock or stock options in the company. Xia C: Regeneron Pharmaceuticals Inc. – employee, may hold stock or stock options in the company. Dreyfus L: Aixial – employee at the time of the analysis (Aixial received funding from Sanofi and Regeneron Pharmaceuticals Inc. for this work); now runs an independent consultancy. Philpott C: National Institute for Health and Care Research, Engineering and Physical Sciences Research Council – grants; GSK, Sanofi, Medtronic, Stryker – consultancy fees and advisory board honoraria; Thieme – royalties; trustee of the charity SmellTaste; President of the UK Semiochemistry Network. Hopkins C: AstraZeneca, Dianosic, GSK, Medtronic, Mylan, Olympus, Sanofi – advisory board or consultancy fees, or speaker honoraria; Secretary General of the European Rhinologic Society; clinical expert nominated by AstraZeneca in the NICE appraisal of tezepelumab for chronic rhinosinusitis with nasal polyps (ID6379). Philpott C, Hopkins C: clinical experts at the NICE committee meetings for dupilumab (TA1134; both nominated by Sanofi and by patient and professional organisations); external advisers to the British Rhinological Society 2026 biologics consensus statement. No author received honoraria for the development of this poster. Contact: Clement.Halin@sanofi.com

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