# Single Technology Appraisal

# Dupilumab for treating severe chronic rhinosinusitis with nasal polyps [ID6480]

# Committee Papers

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Dupilumab for treating severe chronic rhinosinusitis with nasal polyps [ID6480]

**Contents:**

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# Dupilumab for treating severe chronic rhinosinusitis with nasal polyps [ID6480]

## Consultation on the draft guidance document

## Draft guidance comments from Sanofi. 15th August 2025.

| | |
|---|---|
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | **Aventis Pharma Limited, trading as Sanofi**<br>*Stakeholder* |
| **Disclosure**<br>Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | None |
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| **Name of commentator person completing form:** | [redacted]<br>[redacted] |

# Contents

# Executive summary

We thank the committee for their conclusions in the Draft Guidance that recognise the unmet need for CRSwNP patients and the benefits that dupilumab can bring. In this draft guidance response, we have addressed the key points of uncertainty identified by the committee.

## 1. Changes made to the population and quality of life data included in the economic modelling

In our original submission, severe disease was defined using the 2020 EPOS criteria and included patients with uncontrolled CRSwNP after at least one prior surgery. This population was accepted as appropriate by the EAG and committee.

However, at the committee meeting, clinicians noted that severity can also be assessed using SNOT-22 scores with SNOT-22 ≥50 commonly used to define severe CRSwNP.

In our original modelled population (uncontrolled disease + ≥1 surgery), the mean SNOT-22 score was 51.63 (SD: 20.19), with a median of 50. However, the score range (8–110) suggests some patients would not meet the specific SNOT-22 ≥50 severity threshold. This is important as it is likely to have impacted the utilities calculated from the EQ-5D data.

To better reflect clinical practice in England and ensure appropriate QoL capture, we have included the SNOT-22 ≥50 criterion in the population definition. The updated population is:

*"CRSwNP patients with severe, uncontrolled disease, ≥1 prior surgery, and SNOT-22 score ≥50."*

We continue to prefer SNOT-22 to describe quality of life changes in CRSwNP and believe that mapped data from SNOT-22 is likely to be more discriminating and address the limitations of EQ-5D.

However, following DSU 22 guidance and committee concerns, we have recalculated EQ-5D-5L utilities for the updated population with the expectation of more realistic QoL scores in this more severe group. For example, original EQ-5D values were implausibly high (e.g., 0.925 vs. 0.866 norm for controlled patients), but the updated observed values have more face validity (e.g., 0.881 for controlled disease).

The EAG previously applied a utility cap (0.937). Given the updated values for controlled disease align more closely with population norms, we do not apply a cap in the base case but present it in sensitivity analysis.

The updated deterministic base case produces an ICER of [redacted] per QALY gained for DUP+ECM versus ECM, with incremental costs of [redacted], incremental QALYs of [redacted], and incremental LYs of [redacted]. The probabilistic ICER is [redacted]. Sensitivity and scenario analyses confirm the robustness of these results, which remain within or close to the upper end of NICE's £20,000–£30,000/QALY range.

## 2. Long-term treatment effect of dupilumab: AROMA trial data

The assumption of a maintained treatment benefit for dupilumab beyond one year in the model is supported by its mechanism of action and long-term evidence from other Type 2 inflammatory diseases. By targeting IL-4 and IL-13 signalling, dupilumab addresses the underlying driver of nasal polyp formation in CRSwNP. This supports the expectation of a sustained benefit in NPS, NC and SNOT-22 for patients who remain on treatment.

Long-term studies in asthma and atopic dermatitis show that:

- **Clinical benefits are maintained or improve over time**
- **No waning of effect is observed over multiple years**

These trends suggest that the NPS, NC and SNOT-22 benefits seen in the first year would likely persist over the long term.

An exploratory Matching Adjusted Indirect Comparison (MAIC) was conducted using AROMA registry data to improve comparability with the pooled SINUS-24/52 ITT population. The analysis focused on patients with ≥1 prior sinus surgery, matching baseline characteristics to prior SCS use, NSAID-ERD, nasal congestion score, and SNOT-22 total score.

Using the matched AROMA population, weighted responder analyses were performed based on the updated response definition (SNOT-22 <50 or ≥8.9-point improvement plus ≥1-point NPS gain). The subgroup of patients of interest here with prior surgery and SNOT-22 ≥50 (n=185) showed consistently high responder rates to 24 months.

The results from these matched and weighted analyses demonstrate sustained high responder rates in real-world practice among patients with prior sinus surgery, particularly in those with severe baseline disease defined by SNOT-22 ≥50. These findings support the long-term effectiveness of dupilumab in the patient population modelled for this appraisal and have been incorporated into the economic model accordingly.

## 3. Transition probabilities from the post-op controlled to the uncontrolled health state: revision surgery rate and waiting time

Accurately estimating the rate of patients becoming uncontrolled after a second surgery is key to assessing cost-effectiveness. While the EAG confirmed that there is a lack of evidence to address this parameter and acknowledged that our base case uses the best available data, some confusion arose at the committee meeting regarding the derivation of this transition probability.

Importantly, relapse after surgery is distinct from revision surgery. In the UK, the average wait time for endoscopic sinus surgery (ESS) is around two to three years. In the absence of other evidence, we used Benson et al. (2023) as the source to calculate the rate of loss of control following surgery. Benson et al. reported that 17% of patients had a third surgery in their study. Given UK wait times, this implies relapse occurred within 0.4 years, suggesting a 43% relapse rate in year one. This was value used in the economic model and the derivation is described more fully in this document.

This estimate is supported by additional evidence (see Section 3.2), providing a clinically credible basis for the transition probability from controlled to uncontrolled post-surgery.

## Uncaptured benefits

The committee acknowledged that EQ-5D may not fully reflect the benefits of dupilumab in patients with severe CRSwNP, particularly those with ≥1 prior surgery and a baseline SNOT-22 score ≥50. One important but uncaptured benefit is the potential to reduce NHS surgery waiting lists, as dupilumab may reduce the need for repeat procedures compared to current standard care.

Another significant benefit is the reduction in repeated oral corticosteroid (OCS) use. Frequent OCS courses are associated with serious health risks—including osteoporosis, adrenal insufficiency, and

cardiovascular complications—which negatively affect patient outcomes and increase NHS resource use. Dupilumab supports the GIRFT initiative by enabling timely, high-quality treatment and reducing reliance on OCS, aligning with corticosteroid stewardship standards.

For patients with comorbid asthma, dupilumab offers further advantages, such as fewer exacerbations, reduced steroid use, and lower rates of emergency visits and hospital admissions. Although asthma-related costs are included in the model, they are conservatively estimated and may underrepresent the full-service impact.

System-level pressures further highlight the potential for dupilumab to be of value to the NHS. ENT UK reported nearly 700,000 patients awaiting ENT treatment as of March 2024, with ENT ranked third for longest wait times across specialties. Alongside the GIRFT programme and Elective Reform Plan prioritise ENT services, dupilumab could play a key role in alleviating these pressures and improving system efficiency.

## 4. Long-term compliance with dupilumab treatment

Adherence and compliance to treatment are lower in real-world settings compared with clinical trials, and this applies equally to biologics.

Current UK Sanofi homecare data indicate higher compliance for dupilumab than for biologics overall, with an average compliance rate of [redacted] across indications and a one-year persistence rate of [redacted] In the SINUS studies, compliance was 99.26%. For the CRSwNP indication, it is reasonable to expect real-world compliance rates to align with those observed in the other approved indications. Importantly, evidence suggests that small reductions in compliance are unlikely to significantly affect the long-term effectiveness of dupilumab in CRSwNP. In SINUS-52, some patients were re-randomised at week 24 to Q4W dosing. Changes from baseline in the primary outcomes showed little or no decline with similar stability in SNOT-22 scores.

Real-world studies further support the maintenance of efficacy with reduced dosing frequency once disease control is achieved, as described in section 3.1.

Taken together, these findings indicate that the therapeutic benefit of dupilumab is not dependent on perfect Q2W adherence once disease control is established without compromising long-term outcomes. In our base-case modelling, we have assumed a compliance rate of [redacted], consistent with UK homecare data for dupilumab, and have tested this assumption in sensitivity analyses in 2.5% increments down to 80% compliance.

## 5. CRSwNP willingness to pay

The Draft Guidance proposes a £25,000 per QALY threshold due to uncertainties, mainly around quality-of-life estimates from mapping SNOT-22 to EQ-5D using Crump's algorithm. We've addressed these uncertainties by refining the severity definition and submitting updated observed EQ-5D values from SINUS-24/52, which show face validity.

We've also aligned with the EAG on utility gains post-surgery and clarified how transition probabilities for patients becoming uncontrolled after a second surgery were calculated. These have been validated against published sources.

Real-world data shows high compliance with dupilumab in the UK. WE have incorporated an estimate of compliance into the model and supported the assumption of no reduction in

effectiveness with published evidence. Indeed clinical experts at committee confirmed that outcomes are likely to remain favourable even at lower dosing frequencies.

Given these resolved uncertainties and the lack of effective alternatives for some patients, it is appropriate to consider a willingness-to-pay threshold at the higher end of the £20,000–£30,000 range.

## 6. Updated economic modelling results

The updated Sanofi base case reflects all committee preferences except for capping utility values at the population norm. Key changes (see Table 13) include refining the population to patients with uncontrolled CRSwNP, ≥1 prior surgery, and SNOT-22 ≥50—aligning with the definition of severe disease eligible for biologics. Response criteria have also been updated to require a SNOT-22 score <50 or an improvement of ≥8.9 points plus ≥1-point improvement in NPS, ensuring consistency with the revised population.

The model now uses observed EQ-5D-5L data from SINUS-24/52, cross-walked to EQ-5D-3L via the Hernandez method, replacing the previous SNOT-22 to EQ-5D mapping (Crump et al.), in line with committee recommendations. Utility for inadequately controlled disease is now the average of baseline and Week 52 non-responder values rather than the Week 52 non-responder utility alone, better reflecting quality of life evolution over this time frame. Post-surgery utility gain has been updated to +0.0644 from Tashman et al. (2024), replacing the older Remenschneider estimate (+0.080), based on stronger and more recent data. Compliance has also been revised to [redacted] using UK homecare data, with evidence showing maintained effectiveness at this lower rate.

From Year 2 onwards, relapse rates have been recalculated using AROMA data matched to SINUS for the updated population, applying revised response criteria and censoring patients needing rescue therapy. Rates are now [redacted] in Year 2, [redacted] in Year 3, and [redacted] from Year 4 onwards - higher than in the original base case, which used unmatched AROMA data. For ECM, the transition from controlled to uncontrolled disease from Year 2 onwards now uses the post-surgery loss-of-response rate from Benson et al. (2023), estimated at 42.8%. This is a conservative real-world figure compared to the previously modelled [redacted] annualised rate from SINUS-24/52.

The updated base case for patients meeting the new population and response criteria produces a probabilistic ICER of [redacted] / QALY (deterministic: [redacted] /QALY) for DUP+ECM compared with ECM. Deterministic sensitivity analysis shows that, beyond the discount rate, the top three ICER drivers are the utility values for controlled and uncontrolled patients and compliance rates. Scenario analyses further test the impact of varying key assumptions, demonstrating that the updated base case is robust across a range of plausible parameter variations and remains within or close to the upper end of the £20,000–£30,000/QALY threshold range favoured by NICE.

## Conclusions

We have directed our responses to address the key points of uncertainty raised in the draft guidance and provided additional evidence that supports the validity and appropriate use of the modelling inputs and methodology applied in the company's base case.

# Responses in detail

## 1. Changes made to the economic modelling

### 1.1. Updated population definition

The SINUS studies included patients '*with bilateral sinonasal polyposis that persisted despite prior treatment with SCS within the past 2 years; and/or had a medical contraindication/ intolerance to SCS; and/or had prior sinonasal surgery for nasal polyps.'*

The population included in the scope for this appraisal is for '*People with previously treated severe chronic rhinosinusitis with nasal polyps'* (CRSwNP).

In our original submission, the definition of severe disease was based on the published 2020 EPOS criteria based on the level of disease control (pages 15-16 in the company submission) and furthermore included the expected positioning of dupilumab after at least one prior surgery. This was the '*patients who are inadequately controlled AND with at least one prior surgery'* subgroup of the pooled analysis of SINUS-24 & SINUS-52 and was confirmed by the EAG and committee as appropriate.

However, we heard from clinicians at the committee meeting that disease severity can also be graded by SNOT-22 score. Based on an English cohort with CRS, Toma and Hopkins published a statistically validated SNOT-22 stratification which described patients as mild (8-20), moderate (>20-50), or severe (>50).[1] As of 14 August 2025, the publication by Toma & Hopkins 2016, has been cited by over 60 peer-reviewed articles. In Europe, severe CRSwNP is generally classified with SNOT-22 ≥50[2-6]. Further, the phase IV multicentre real-world study, DUPIREAL, in patients with severe disease, utilised SNOT-22 score ≥50 as an inclusion criterion.[7]

For the originally modelled population (patients who are *inadequately controlled AND with at least one prior surgery'* the overall mean SNOT-22 score was 51.63 (SD: 20.19). The median score was 50, the interquartile range was 36:66 and the Min:Max was 8.0:110.0. When judged by SNOT-22 alone the range of these scores indicate that up to 50% of patients in the modelled population would not be classified with severe disease. This is also likely to have impacted the level of quality of life observed in the studies (see Section 1.2 below).

To ensure that the patients included in the updated model meet the requirement for severe disease and in particular, that quality of life is captured appropriately for patients categorised with severe disease we have included an additional criterion of SNOT-22 score ≥50 to align with expected clinical practice in England. The updated population in this DG response is therefore:

*'CRSwNP patients with severe, uncontrolled disease who have had at least 1 surgery and have a SNOT-22 score ≥50'.*

The updated population represents 50.1% of the originally submitted cohort (n = 230 vs n = 459). A side-by-side comparison of the baseline patient characteristics is presented in Table 20. Key outcomes for the updated population are provided in

Table 1 and Table 2.

*Table 1. Change from baseline in NPS score at Week 24: Updated base case: people with inadequately controlled CRSwNP AND ≥1 sinus surgery AND SNOT-22 ≥50*

| **Nasal polyps score** | **Placebo** | **Dupilumab 300mg q2w** |
|---|---|---|
| *Baseline* | | |
| Number | 100 | 128 |
| Mean (SD) | 5.885 (1.253) | 6.121 (1.256) |
| Median | 6.000 | 6.000 |
| *Week 24* | | |
| Number | 93 | 121 |
| Mean (SD) | 6.038 (1.143) | 3.822 (2.108) |
| Median | 6.000 | 4.000 |
| *Change from baseline* | | |
| Number | 93 | 121 |
| Mean (SD) | 0.188 (0.964) | −2.285 (1.793) |
| Median | 0.000 | −2.000 |
| LS Mean (SE) [a] | 0.359 (0.206) | −2.062 (0.193) |
| LS Mean (SE) placebo + q2w[a] | −0.852 (0.172) | |
| LS Mean Diff vs. placebo (95% CI) [a] | −2.421 (−2.818, −2.024) | |
| P-value vs. placebo[a] | <0.0001 | |

CI = confidence interval; CRSwNP = chronic rhinosinusitis with nasal polyps; ECM = established clinical management; LS = least square; NPS = nasal polyp score; Q2W = once very two weeks; SD = standard deviation; SE = standard error; SNOT-22 = 22-item Sino-Nasal Outcome Test

[a] Each of the imputed complete data was analysed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, regions and study as covariates. Note: Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis.

Source: Sanofi. Data on File, Post-hoc analyses.[8]

*Table 2. Change from baseline in SNOT-22 total score at Week 24: Updated base case: people with inadequately controlled CRSwNP AND ≥1 sinus surgery AND SNOT-22 ≥50*

| **SNOT-22 Total Score** | **Placebo** | **Dupilumab 300mg q2w** |
|---|---|---|
| *Baseline* | | |
| Number | 101 | 129 |
| Mean (SD) | 68.287 (13.865) | 67.829 (12.641) |
| Median | 67.000 | 65.000 |
| *Week 24* | | |
| Number | 94 | 125 |
| Mean (SD) | 53.234 (19.880) | 26.648 (19.380) |
| Median | 54.000 | 23.000 |
| *Change from baseline* | | |
| Number | 94 | 125 |
| Mean (SD) | -14.755 (19.561) | -41.320 (22.687) |
| Median | -13.000 | -40.000 |
| LS Mean (SE) [a] | -13.412 (2.695) | -40.517 (2.540) |
| LS Mean (SE) placebo + q2w[a] | -26.964 (2.257) | |
| LS Mean Diff vs. placebo (95% CI) [a] | -27.105 (-32.307, -21.903) | |
| P-value vs. placebo[a] | <.0001 | |

CI = confidence interval; CRSwNP = chronic rhinosinusitis with nasal polyps; ECM = established clinical management; LS = least square; NPS = nasal polyp score; Q2W = once very two weeks; SD = standard deviation; SE = standard error; SNOT-22 = 22-item Sino-Nasal Outcome Test

[a] Each of the imputed complete data was analysed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, regions and study as covariates. Note: Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis.

Source: Sanofi. Data on File, Post-hoc analyses.[8]

*Table 3. Change from baseline in NPS and SNOT-22 total score at Week 24: Original population: uncontrolled CRSwNP after at least one prior surgery compared to the updated population: people with inadequately controlled CRSwNP AND ≥1 sinus surgery AND SNOT-22 ≥50*

| | Original population | | New population | |
|---|---|---|---|---|
| | **Placebo (n=187)** | **Dupilumab (n=272)** | **Placebo (n=101)** | **Dupilumab (n=129)** |
| Change from baseline (responders at Week 24) | | | | |
| **NPS** | | | | |
| Mean (SD) | 0.133 (1.226) | -1.893 (1.881) | 0.188 (0.964) | −2.285 (1.793) |
| LS Mean Diff vs. placebo (95% CI) | -1.99 (-2.289, -1.683) | | −2.421 (−2.818, −2.024) | |
| P-value vs. placebo | <0.0001 | | <0.0001 | |
| **SNOT-22** | | | | |
| Mean (SD) | -9.932 (19.013) | -28.888 (21.847) | -14.755 (19.561) | -41.320 (22.687) |
| LS Mean Diff vs. placebo (95% CI) | -20.89 (-24.183, -17.600) | | -27.105 (-32.307, -21.903) | |
| P-value vs. placebo | <0.0001 | | <.0001 | |

CI = confidence interval; CRSwNP = chronic rhinosinusitis with nasal polyps; ECM = established clinical management; LS = least square; NPS = nasal polyp score; Q2W = once very two weeks; SD = standard deviation; SE = standard error; SNOT-22 = 22-item Sino-Nasal Outcome Test

[a] Each of the imputed complete data was analysed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, regions and study as covariates. Note: Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis.

Source: Sanofi. Data on File, Post-hoc analyses.[8]

## 1.2. Updated utility in the model

We note the committee agreed with the clinical experts and us that SNOT-22 is a sensitive tool to measure the key aspects of quality of life that hugely impact patients with CRSwNP. SNOT-22 can detect significant treatment-mediated changes in QoL, where EQ-5D may not. We continue to believe that the most appropriate way to capture CRSwNP QoL quality of life data for use in the model is via the SNOT-22 tool due to its disease specificity and sensitivity, allowing comprehensive QoL measurement.

However, we recognise the issues raised by the EAG and committee about the use of the CRUMP mapping algorithm and the guidance in DSU 22 which states that if EQ-5D is available in the studies then it is the preferred measure. Therefore, to satisfy the preference of the committee for the inclusion of directly observed EQ-5D in the model, we have recalculated the EQ-5D-5L utilities for the updated population (with SNOT-22 score ≥50). These data are provided in Table 4 below. The original and updated EQ-5D values are compared side-by-side. (see Section 1.2 below for a discussion about the updated response criteria).

*Table 4. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with ≥1 prior sinus surgery and baseline SNOT-22 total score ≥50 in SINUS-24 and SINUS-52 pooled ITT population vs. previous base-case population*

| | EQ-5D-5L Hernandez crosswalk – pooled SINUS data | | | |
|---|---|---|---|---|
| | Original EQ-5D values | | Updated EQ-5D values | |
| | DUP | ECM | DUP | ECM |
| **Decision tree** | | | | |
| W0 to W12 | 0.782 | | 0.698 | |
| W13 to W24* | 0.883 | 0.827 | 0.858 | 0.780 |
| W25 to W52 responders** | 0.915 | 0.888 | 0.891 | 0.831 |
| W25 to W52 non-responders*** | 0.845 | 0.814 | 0.820 | 0.781 |
| **Markov model** | | | | |
| Controlled disease (ALL responders utility at week 52) | 0.925 | | 0.881 | |
| Inadequately controlled disease**** | 0.793 | | 0.739 | |
| Uncontrolled disease | 0.782 | | 0.698 | |

DUP = dupilumab; ECM = established clinical management; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ITT = intention-to-treat; SNOT-22 = 22-item Sino-Nasal Outcome Test; UK = United Kingdom; W = week
Note: Utility values are adjusted to more appropriately reflect the expected midpoint of the time ranges represented by the health states.
*Utility at week 24. **Average of the utility for responder patients at week 24 and week 52. *** Average of the utility for non-responder patients at week 24 and week 52. **** Average of the utility for non-responder patients at week 52 and baseline utility.
Source: Sanofi. Data on File, Post-hoc analyses.[8]

The original EQ-5D values directly calculated for the population included in the model were implausibly high, with the responders having a score considerably higher than the population matched norm (controlled disease health state: 0.925 vs. 0.866 for population norm).

As a consequence of including the additional criterion of SNOT-22 score ≥50 in the population definition, the included population should more fully reflect patients with severe disease and the EQ-5D should be expected to somewhat reduce. This can be seen in the updated EQ-5D values in Table 4 occupy a more plausible range. For example, the EQ-5D value for the controlled disease health state is 0.881 (vs. 0.866 in the matched population norm and vs. 0.925 in the original submission) and the baseline is 0.698 vs. an implausibly high baseline of 0.782 in the original population.

The EAG and committee preferred to mitigate the issue of overly high utilities by capping the data using a factor derived by dividing the matched general population utility by the utility at week 52 for sustained responders between week 24 and 52 (0.925/0.866 = 0.937).

Given the updated utility values for the population with SNOT-22 ≥50 are not substantively different to a matched population norm, we have not included a cap in our updated base case. However, for completeness, we have recalculated the cap for the updated EQ-5D values (0.881/0.866 = 0.983) and applied according to the EAG precedent to the values in Table 4 above. The updated capped values are tabulated below (Table 5). These are applied in sensitively analyses.

*Table 5. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with ≥1 prior sinus surgery and baseline SNOT-22 total score ≥50 in SINUS-24 and SINUS-52 pooled ITT population vs. previous base-case population (Capped according to 0.937)*

| | EQ-5D-5L Hernandez crosswalk – pooled SINUS data | | | |
|---|---|---|---|---|
| | Original EQ-5D values | | Updated EQ-5D values | |
| | DUP | ECM | DUP | ECM |

| | | | | |
|---|---|---|---|---|
| *Decision tree* | | | | |
| W0 to W12 | 0.782 | | 0.698 | |
| W13 to W24* | 0.827 | 0.775 | 0.843 | 0.767 |
| W25 to W52 responders** | 0.856 | 0.832 | 0.876 | 0.816 |
| W25 to W52 non-responders*** | 0.791 | 0.762 | 0.806 | 0.768 |
| *Markov model* | | | | |
| Controlled disease (Population norm) | 0.866 | | 0.866 | |
| Inadequately controlled disease**** | 0.767 | | 0.732 | |
| Uncontrolled disease | 0.732 | | 0.686 | |

DUP = dupilumab; ECM = established clinical management; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ITT = intention-to-treat; SNOT-22 = 22-item Sino-Nasal Outcome Test; UK = United Kingdom; W = week
Note: Utility values are adjusted to more appropriately reflect the expected midpoint of the time ranges represented by the health states.
*Utility at week 24. **Average of the utility for responder patients at week 24 and week 52. *** Average of the utility for non-responder patients at week 24 and week 52. **** Average of the utility for non-responder patients at week 52 and baseline utility.

## 1.3.New response criteria

To align with the severe CRSwNP criterion of SNOT-22 score ≥50 as a definition of severity, the response criteria have also been updated to: SNOT-22 <50 or improvement in SNOT-22 ≥8.9 and NPS improvement ≥1.

A side-by-side comparison of response for the updated base case population compared to the original base case population is presented in Table 6 below.

*Table 6. Comparison of response for the ITT population and base case population with inadequately controlled CRSwNP AND ≥1 NP surgery according to the response criteria of SNOT-22 <50 or improvement in SNOT-22 ≥8.9 and NPS improvement ≥1*

| | **Original base case: people with inadequately controlled CRSwNP AND ≥1 sinus surgery** | | **Updated base case: people with inadequately controlled CRSwNP AND ≥1 sinus surgery AND SNOT-22 ≥50** | |
|---|---|---|---|---|
| | **ECM** | **Dupilumab 300 mg Q2W** | **ECM** | **Dupilumab 300 mg Q2W** |
| *Overall population response at Week 24* | | | | |
| | N=187 | N=272 | N=101 | N=129 |
| Responders | [redacted] | [redacted] | [redacted] | [redacted] |
| Non-responders | [redacted] | [redacted] | [redacted] | [redacted] |
| OR vs placebo (95% CI)[a] | [redacted] | | [redacted] | |
| P value vs placebo[b] | <0.0001 | | <0.0001 | |
| *Overall population: Response at Week 52* | | | | |
| | N=88 | N=88 | N=49 | N=40 |
| Responders | [redacted] | [redacted] | [redacted] | [redacted] |
| Non-responders | [redacted] | [redacted] | [redacted] | [redacted] |
| OR vs placebo (95% CI)[a] | [redacted] | | [redacted] | |
| P value vs placebo[b] | <0.0001 | | <0.0001 | |
| *Subpopulation: Responders at Week 24 - Response at Week 52* | | | | |
| | N=5 | N=46 | N=1 | N=26 |
| Responders | [redacted] | [redacted] | [redacted] | [redacted] |
| Non-responders | [redacted] | [redacted] | [redacted] | [redacted] |

| | Original base case: people with inadequately controlled CRSwNP AND ≥1 sinus surgery | | Updated base case: people with inadequately controlled CRSwNP AND ≥1 sinus surgery AND SNOT-22 ≥50 | |
|---|---|---|---|---|
| | **ECM** | **Dupilumab 300 mg Q2W** | **ECM** | **Dupilumab 300 mg Q2W** |
| OR, 95% CI vs placebo[a] | NE (NE, NE) | | NE (NE, NE) | |
| P-value vs placebo[b] | <0.0001 | | <0.0001 | |

CI = confidence interval; CRSwNP = chronic rhinosinusitis with nasal polyps; ECM = established clinical management; ITT = intent-to-treat; NE = not evaluable; OR = odds ratio; Q2W = every 2 weeks; SNOT-22 = 22-item Sino-Nasal Outcome Test
[a] OR: odds ratio, derived from Mantel-Haenszel estimator.
[b] CMH test was performed on the association between the responder status and treatment group (dupilumab vs placebo), stratified by asthma/NSAID-ERD status, prior surgery history, and region.
Source: Sanofi data on file, 2019

We note the number of patients in the Responders at Week 24 - Response at Week 52 category remains very small in the updated population. However, it is important to note that these data do not inform transition probabilities in the longer term Markov portion of the model because the committee has taken the decision to endorse the real world data from AROMA for this purpose.

Response data inputs used in the model for the original base case (Table 6 above) and new base case with the updated population are presented in Table 7 below.

*Table 7. Response data inputs used in the economic model according to the response criteria of SNOT-22 <50 or improvement in SNOT-22 ≥8.9 and NPS improvement ≥1*

| **Response criteria and timepoint** | **Original base case: people with inadequately controlled CRSwNP AND ≥1 sinus surgery** | | **Updated base case: people with inadequately controlled CRSwNP AND ≥1 sinus surgery AND SNOT-22 ≥50** | |
|---|---|---|---|---|
| | **ECM** | **DUP + ECM** | **ECM** | **DUP +ECM** |
| *Proportion achieving SNOT-22 <50 or SNOT-22 change from BL ≥8.9 and NPS change from BL ≥1* | | | | |
| Week 24, % | [redacted] | [redacted] | [redacted] | [redacted] |
| Week 52, % | [redacted] | [redacted] | [redacted] | [redacted] |

BL = baseline; CRSwNP = chronic rhinosinusitis with nasal polyps; DUP = dupilumab; ECM = established clinical management; NP = nasal polyp; NPS = nasal polyp score; SNOT-22 = Sinonasal Outcomes Test-22.
Source: Sanofi data on file, 2019

## 1.4. Updated source of utility gain after surgery

In section 3.11 of the Draft Guidance, the committee expressed a preference for Remenschneider et al. (2015)[10] over Soler et al. (2011)[11] to describe utility gain following surgery because it used the EQ-5D in line with NICE's reference case, was based on more recent data (2011–2012), and reported a larger, statistically significant gain (+0.08) after endoscopic sinus surgery (ESS). We agree with this rationale and have discontinued use of SF-12 values from Soler et al. (2011).

However, we have identified an even more recent and methodologically stronger study – Tashman et al. (2024)[12] – which meets all the above criteria and further strengthens the evidence base. Compared with Remenschneider, Tashman:

- Includes a larger cohort (n = 1,296 vs 242)
- Extends follow-up to 5 years (vs 2 years)
- Applies the CRS-specific MCID (0.04 HUV) rather than generic thresholds

- Uses multivariable mixed-effects modelling adjusting for key prognostic factors, including prior ESS, comorbidities, and baseline disease severity
- Reports both domain-level outcomes and long-term durability of benefit.[12]

These features make Tashman et al. more robust for estimating the utility gain after ESS.

**Tashman et al. (2024)[12]**

Tashman et al. measured EQ-5D-5L health utility values (HUVs) at baseline, 3 months, and annually to 5 years, converting responses to utilities using the US EQ-5D-5L value set.[12]

The mixed-effects model included timepoint as a fixed effect and patient as a random effect, with the following covariates: age, sex, race, baseline SNOT-22 score, polyp status, Lund–Mackay score, history of prior ESS (primary vs revision) and comorbidities (diabetes, hypertension, asthma, allergic rhinitis, tobacco use, migraine/headaches).

From this model, the predicted change in HUV from baseline to year 1 was +0.0644 (SE 0.0049, $p<0.001$), exceeding the CRS-specific MCID of 0.04. Prior ESS status was a statistically significant predictor of lower absolute HUV across all timepoints (coefficient = –0.0211, $p = 0.010$), but there was no significant interaction between prior ESS and time, indicating that the magnitude of improvement from baseline to year 1 was the same for revision and primary surgeries.[12]

Although the Tashman cohort included both primary and revision ESS and patients with and without nasal polyps, the fully adjusted model accounts for these differences unlike Remenschneider where crude estimates may be influenced by the case-mix.

Accordingly, we have applied a utility gain of +0.0644 for patients entering the post-op controlled HS. This value is based on the largest EQ-5D data for ESS, meets NICE's reference case requirements, and is methodologically more robust than unadjusted estimates.

# 2. Evidence to support the long-term effectiveness of dupilumab treatment used in the company's model (Section 3.5 in the Draft Guidance)

## 2.1. AROMA data formally matched to the SINUS trials accounting for differences in responder classification

To match the AROMA registry data with the SINUS Dupixent trial for CRSwNP patients, we employed a weighting approach similar to that applied to unanchored matching adjusted indirect treatment comparisons (MAIC). We applied weights to patients in the AROMA registry to match the characteristics of patients in the SINUS trial. This adjusted AROMA population was used to calculate weighted long term discontinuation rates for real-world Dupixent use. This approach is similar to propensity score weighting and was performed simultaneously for all selected matching criteria. Essentially, patients in the AROMA registry were reweighted to match the baseline characteristics of those in the SINUS trial. This process allowed us to create a more comparable population between the real-world registry and the clinical trial, enabling a more accurate assessment of Dupixent's real-world discontinuation rates from AROMA. To ensure comparability of patients with ≥1 previous sinus surgery in the SINUS-24 and SINUS-52 pooled ITT population and AROMA Registry Analysis Set (RAS) population at baseline (**Error! Reference source not found.**), rate of prior SCS use, rate of comorbid NSAID-ERD, mean NC score and mean SNOT-22 total scores were weighted in the AROMA population to match the baseline characteristics of the SINUS-24 and SINUS-52 pooled ITT population. A total of

691 patients were enrolled in AROMA and 639 patients remained in the study for over 24 months. The effective sample size for the matched population of patients with ≥1 previous sinus surgery was 512.

*Table 8. Baseline characteristics of matched patents in the pooled ITT population of SINUS-24/52 and in the RAS of AROMA (patients with ≥1 previous nasal polyp/sinonasal surgery*)*

| | **Patients with ≥1 sinus surgery in pooled SINUS-24/SINUS-52 ITT population** | **Matched patients with ≥1 nasal polyp surgery in AROMA registry** RAS (ESS)** |
|---|---|---|
| N | 459 | 512 |
| *Matching on:* | | |
| SCS use in the past 2 years, n (%) | 292 (63.6) | 63.6% |
| NSAID-ERD, n (%) | 159 (34.6) | 34.6% |
| NC score (scale 0-3), mean (SD) | 2.44 (0.56) | 2.44 (0.03) |
| SNOT-22 total score (scale 0-110), mean (SD) | 51.63 (20.19) | 51.63 (0.98) |
| *Comparison of unmatched characteristics* | | |
| Male, n (%) | 268 (58.4) | 54.9% |
| Age, mean (SD) | 51.4 (12.6) | 52.3 (0.7) |
| Race, n (%)<br>White<br>Black or African American<br>Asian<br>American Indian or Alaska Native<br>Multiple<br>Not reported<br>Unknown | <br>409 (89.1)<br>7 (1.5)<br>37 (8.1)<br>5 (1.1)<br>1 (0.2)<br>0<br>0 | <br>72.2%<br>6.7%<br>6.9%<br>0.1%<br>5.0%<br>4.0%<br>3.7% |
| Ethnicity, n (%)<br>Hispanic or Latino<br>Not Hispanic or Latino<br>Not reported<br>Unknown | <br>47 (10.2)<br>409 (89.1)<br>2 (0.4)<br>1 (0.2) | <br>5.9%<br>78.2%<br>15.9%<br>NA |
| Time since first diagnosis of nasal polyps* (years), mean (SD) | 14.20 (9.62) | 11.58 (0.54) |
| ≥3 previous surgeries for nasal polyps*, n (%) | 111 (24.2) | 25.0% |
| Time since most recent surgery for nasal polyps* (years), mean (SD) | 7.16 (6.44) | 7.80 (0.40) |
| NPS (scale 0-8), mean (SD) | 5.86 (1.26) | NA |
| Smell test (UPSIT) score (scale 0-40), mean (SD) | 12.80 (7.52) | 19.62 (0.48) |
| LoS score (scale 0-3), mean (SD) | 2.79 (0.52) | 2.60 (0.04) |
| LMK-CT total score (scale 0-24), mean (SD) | 19.07 (3.97) | 16.80 (0.28) |
| VAS (0-10) for overall rhinosinusitis, mean (SD) | 8.00 (2.00) | NA |
| NPIF (L/min), mean (SD) | 89.32 (57.37) | 98.71 (2.56) |
| Age of asthma onset in patients with comorbid asthma (years), mean (SD) | 33.98 (15.28) | 36.96 (0.87) |
| Baseline ACQ-6 score (0-6) in patients with comorbid asthma, n, (%)<br><1<br>≥1 to <1.5<br>≥1.5 | <br>105 (22.9)<br>42 (9.2)<br>143 (31.2) | <br>24.1%<br>12.2%<br>31.8% |

ACQ-6 = 6-item Asthma Control Questionnaire; BMI = body mass index; ERD = exacerbated respiratory disease; ITT = intention-to-treat; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; NA = not applicable; NC = nasal congestion/obstruction; NPIF = peak nasal inspiratory flow; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = every 2 weeks; RAS = registry analysis set; SCS = systemic corticosteroid use; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale
* **N**asal polyp surgery for SNIUS24/52, sinonasal surgery for AROMA.
** AROMA registry results reflect weighted analyses
† North America: Canada and USA; European Union: Belgium, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Poland, Portugal, Romania, Spain, Sweden, and United Kingdom; Rest of World: Argentina, Australia, Chile, Israel, Japan, Mexico, Russia, Turkey, and Ukraine
Source: Regeneron. Data on File, AROMA and SINUS-24/SINUS-52 MAIC.[13]

Using the matched AROMA RAS population, weighted responder analyses based on SNOT-22 (total score <50 or cfb >8.9) were carried out (Table 9 & Table 10). The weighted responder analysis for patients ≥1 prior sinonasal surgery and baseline SNOT-22 total score ≥50 has been included in the model.

*Table 9. Weighted responder analysis based on SNOT-22 total score <50 or ≥8.9-point improvement (AROMA RAS with ≥1 prior sinonasal surgery)*

| **Visit** | **Endpoint** | **Total (N=512)*** |
|---|---|---|
| Visit 2 (Baseline) | Number of patients who had baseline SNOT-22, n/N | 413/512 |
| Visit 4 (Month 6) | SNOT-22 total score <50 or change from baseline ≥8.9-point improvement, n/N1 (%) | 284 (89.4) |
| Visit 6 (Month 12) | | 150 (94.7) |
| Visit 8 (Month 18) | | 53 (99.2) |
| Visit 10 (Month 24) | | 15 (98.0) |
| Visit 12 EOS (Month 36) | | 0 (0) |

EOS = end of study; SNOT-22 = Sino-Nasal Outcome Test-22.
N1 refers to the number of patients with baseline and post-baseline SNOT-22 values at specified visits (Month 6, 12, 18, 24, 36) excluding non-responders from any prior visit. Exclusion criteria are applied cumulatively: Month 6: No exclusions, N1=Patients with SNOT-22 values at baseline and Month 6. Month 12: Excludes patients non-responsive at Month 6. Month 18: Excludes patients non-responsive at month 6 or 12. Month 24: Excludes patients non-responsive at month 6, 12, or 18. Month 36: Excludes patients non-responsive at month 6, 12, 18, or 24. n refers to the number of patients meeting the endpoint criterion (SNOT-22 <50 or improvement ≥8.9) at the visit after 1st sinonasal surgery data/SCS start date are considered as non-responders. 1st sinonasal surgery date/SCS records start date is the first date after/on the first treatment start date.
* Responder status is first derived using original scale of SNOT-22. After that, the responder status is weighted.
Source: Regeneron. Data on File, AROMA and SINUS-24/SINUS-52 MAIC.[13]

*Table 10. Weighted responder analysis based on SNOT-22 total score <50 or ≥8.9-point improvement (AROMA RAS with ≥1 prior sinonasal surgery and baseline SNOT-22 total score ≥50)*

| **Visit** | **Endpoint** | **Total (N=185)*** |
|---|---|---|
| Visit 2 (Baseline) | Number of patients who had baseline SNOT-22, n/N | 185/185 |
| Visit 3 (Month 3) | SNOT-22 <50 or change from baseline in SNOT-22 ≥8.9-point improvement, n/N1 (%) | 147 (90.7) |
| Visit 4 (Month 6) | | 106 (96.3) |
| Visit 5 (Month 9) | | 80 (97.6) |
| Visit 6 (Month 12) | | 64 (96.8) |
| Visit 7 (Month 15) | | 29 (94.7) |
| Visit 8 (Month 18) | | 23 (100) |
| Visit 9 (Month 21) | | 10 (95.9) |
| Visit 10 (Month 24) | | 6 (100) |

| Visit | Endpoint | Total (N=185)* |
|---|---|---|
| Visit 11 (Month 30) | | 0 (0) |
| Visit 12 EOS (Month 36) | | 0 (0) |

EOS = end of study; SNOT-22 = Sino-Nasal Outcome Test-22.
N1 refers to the number of patients with baseline and post-baseline SNOT-22 values at specific visit excluding patients who are non-responder at any prior visits. n refers to patients meeting the endpoint criterion (SNOT-22 <50 or improvement ≥ 8.9) at the visit after 1st sinonasal surgery data/SCS start date are considered as non-responders. 1st sinonasal surgery date/SCS records start date is the first date after/on the first treatment start date
* Responder status is first derived using original scale of SNOT-22. After that, the responder status is weighted.
Source: Regeneron. Data on File, AROMA and SINUS-24/SINUS-52 MAIC.[13]

*Figure 1 AROMA long-term response (cfb SNOT-22 > 8.9) – RAS with prior surgery and SNOT-22>50 at baseline*

# 3. Evidence to support the transition probabilities used in the company's model (Section 3.9 in the Draft Guidance)

## 3.1. Additional details on the equation used to calculate the transition probability from the post-op controlled to the uncontrolled health state

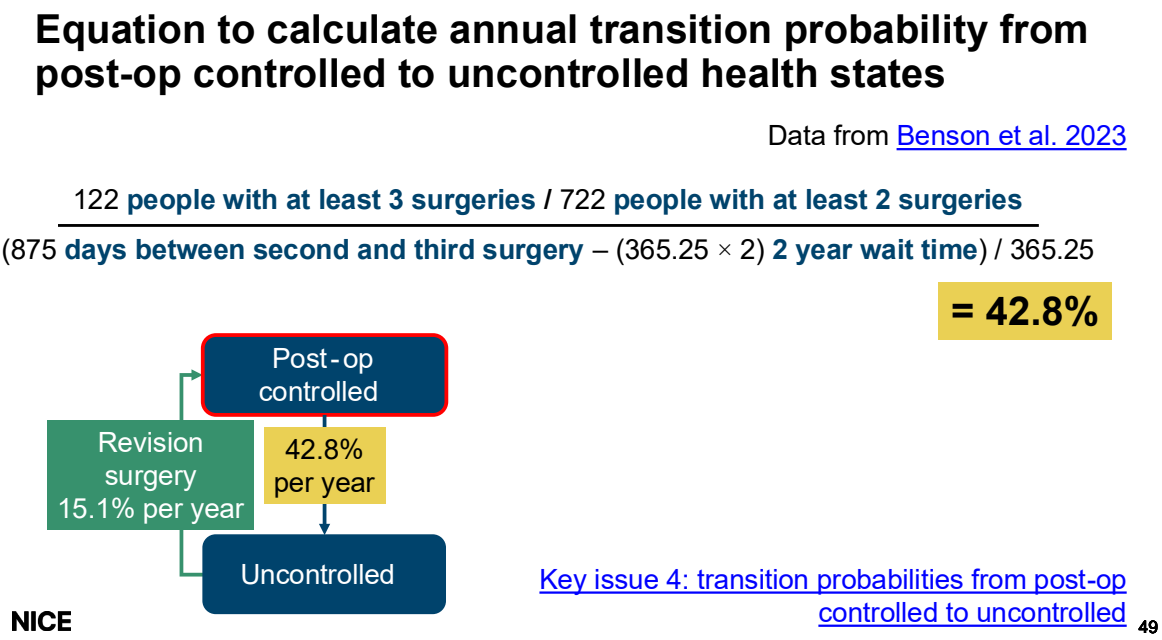
*Background*

We agree with the EAG that to evaluate the cost-effectiveness of dupilumab for treating CRSwNP, it is critical to accurately determine the rate at which patients become uncontrolled after their second surgery. We also note that the EAG confirmed there is a paucity of evidence to address this parameter and that we used the best available evidence in our base case. They did not raise concerns about the methodology for the calculation of the transition probability, but we recognise that this caused some confusion at the committee meeting. Therefore, we have provided a detailed explanation of the rationale behind our calculations. We also provide the findings from a pragmatic literature search to address this evidence gap

(reproduced from ACM 1 slide deck).

Figure 2 below outlines how the transition probabilities were calculated for patients entering the uncontrolled health state after their second surgery in the model (reproduced from ACM 1 slide deck).

*Figure 2. Calculation of the transition probability from post-op controlled to uncontrolled health state*



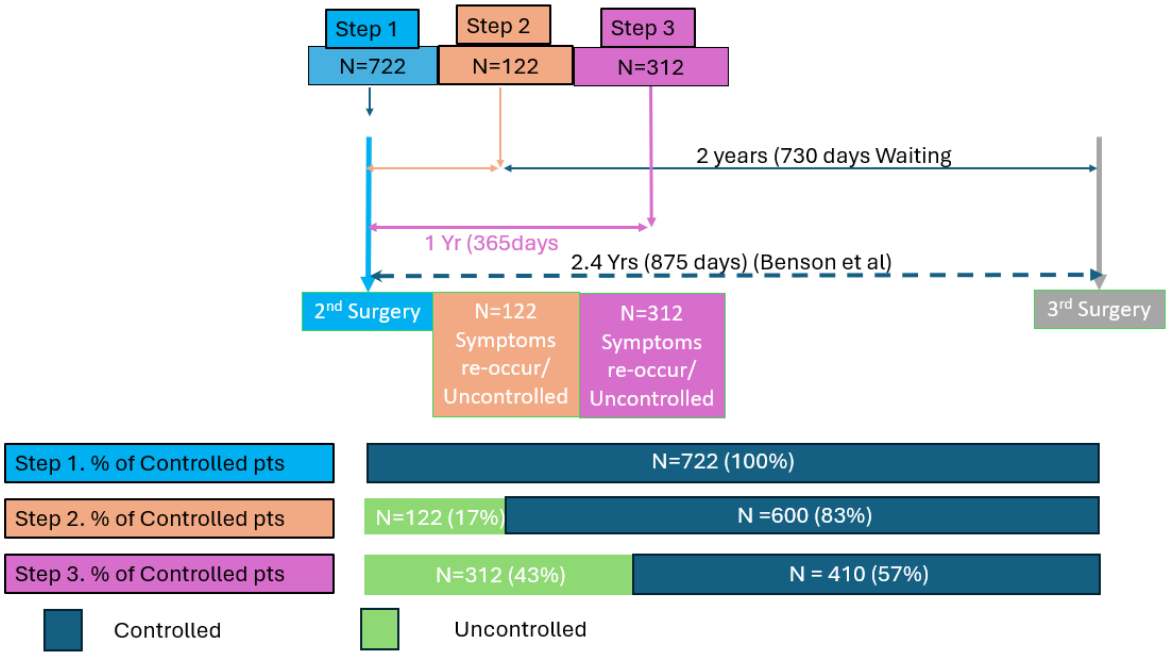

The transition probability of 42.8% was calculated using Benson et al, 2023. This was chosen as the most appropriate source because it is a recent, UK-based retrospective study that is reflective of the population in question.[14]

The loss of response or control after surgery for CRSwNP is different from the revision surgery rate, as reported in Benson et al 2023.[14] In practice, patients do not undergo surgery immediately after losing disease control but are put on a surgery waiting list whilst still experiencing disease symptoms. This is particularly relevant in the UK, where the average wait time for ESS is 2 to 3 years (as stated during the advisory board held in June 2024 and the following HCP consultancy meetings held in November 2024), delaying surgical intervention even for those with recurrent or uncontrolled disease. This was confirmed at the committee meeting by the clinical experts.

Benson et al 2023 do not directly report the rate at which subjects became uncontrolled or for whom symptoms returned after the second surgery; however, they do report the number of subjects who underwent a third surgery and the average time between these surgeries.[14] This information coupled with a known waiting list of at least 2 years is used to calculate the transition probability of moving from the post-operative controlled health state to the post-operative uncontrolled health state.[14]

Figure 3 and the accompanying stepwise description explain how the transition probability of 43% is arrived at.

*Figure 3. Illustration of how the transition probability of moving from post-operative controlled to the post-operative uncontrolled health states is calculated using data from Benson et al. 2023*




**Step 1.** Benson et al reported that during their observation period, 722 underwent a second surgery.[14]

**Step 2**. Benson et al also report that over the observation period, 122 subjects of the 722 subjects (17%) underwent a third surgery. The time between surgeries was 875 days or 2.40 years.[14]

Expert clinical opinion obtained by us suggests that the waiting time for endoscopic surgery in the UK is at least 2 years (730 days),[15] therefore, to have the opportunity to undergo a third surgery within the observation period, the 122 subjects (17%) will have had to relapse within 145 days (875 days - 730 days) post-operatively.

**Step 3.** Assuming this relapse rate over the first 0.4 years (145 days) is constant, then during the first year, we can calculate that (N=312) 43% of patients are likely to relapse.

- 17% = 0.4 Years (145 days)
- 43% = 1 year (365 days)

### *Validation from literature*

In the LANDMARK study in which 234 patients with CRSwNP were randomly assigned to a strategy of medical treatment or ESS and medical treatment (n=142; 61%), it was reported that that a large proportion of patients in both groups were considered to have uncontrolled disease according to EPOS 2020 criteria at 12 months (46% in the ESS plus medical therapy group vs 63% in the medical therapy group).[16]

In a single-centre retrospective observational study, Pirola et al. (2022) reported that among patients who had undergone an average of 2.4 to 3.3 surgical procedures prior to a reboot procedure, 26 patients (86.6%) experienced a relapse by the three-year follow-up after their first surgery. The mean time to recurrence was 8.08 months (± 2.83) after each procedure.[17]

In an American prospective, multi-centre cohort of adult patients undergoing an ESS trial, DeConde et al. 2017 reported that the recurrence of nasal polyposis 6 months after ESS was 35%.[18]

## 3.2. Additional details on the proportions of different types of patients in the uncontrolled health state used to inform the annual rate of revision surgery

We note that there was concern raised at committee and by the EAG about both the calculation and the magnitude for the annual probability of moving from uncontrolled to next surgery. We have examined this parameter and provide an updated calculation and explanation below.

As requested by the committee, using data from Benson et al. (CPRD/HES retrospective study - 2023), we examined the spread of patients in England who required surgery, by the number of prior surgeries. The figures below represent the share of all patients in each number of surgery category. They are not the proportion of each subgroup that will go on to require another surgery (this is calculated separately).

*Table 11. Spread of patients according to the number of surgery during the observation period (Benson et al. 2023)*

| Number of surgery(ies) | Patient count | **Share including 0 surgery (%)** | **Share excluding 0 surgery (%)** |
|---|---|---|---|
| No surgery during follow-up | 25,314 | 76.5 | – |
| Exactly 1 surgery | 6,935 | 20.9 | 89.0 |
| Exactly 2 surgeries (incl. failure) | 700 | 2.1 | 9.0 |
| Exactly 3 surgeries (incl. failure) | 114 | 0.3 | 1.5 |
| 4 or more surgeries (incl. failure) | 44 | 0.1 | 0.6 |
| Total | *33,107* | *100* | *100* |

In our cost-effectiveness model, uncontrolled patients after ≥1 surgery can either remain in the uncontrolled state (receiving medical management only), or transition to the next surgery after an average wait of ~2 years.

Because surgery rates are constrained by NHS capacity and waiting times, the waiting list remains relatively stable:

- New uncontrolled patients enter the list each year (e.g., following loss of control at 42.8% after surgery 2);
- Patients leave the list either by undergoing surgery or being lost to follow-up (e.g., due to declining surgery, comorbidity, lack of treatment options).

The rates calculated above are therefore realised surgical transition rates, not theoretical demand. They reflect the proportion of patients who reach their next surgery under current NHS conditions. This aligns the model with the real-world pathway observed in England, where time-to-surgery acts as a natural bottleneck.

To align with our base case population (people with at least one prior surgery), transitions from the “post-operative controlled” health state to the “uncontrolled” health state should only occur following a second (or subsequent) surgery. Accordingly, the relevant subgroup from this study is peopls with at least two prior surgeries who subsequently undergo a third surgery.

**Direct inputs from Benson et al. 2023**

- Denominator ($n_2$): 722 patients with ≥2 during observation.
- Numerator ($n_3$): 122 with ≥3 during observation.

- Mean interval between 2nd and 3rd surgery (875 days): S = 875 / 365.25 = **2.40 years** (2 years and 5 months)
- Proportion: P = 122 / 722 = 0.17 = **17%**
- Annual observed surgery rate (2 → 3): 0.17 / 2.40 = 0.071 = **7.1%**

This calculation demonstrates that, for an average year, **7.1%** of patients who have had a second operation go on to receive a third operation under current NHS conditions.

This is the rate based on observed, capacity-constrained data from Benson et al 2023.

**Calculation of disease recurrence**

- Mean interval between 2nd and 3rd surgery = **2.40 years**
- NHS average waiting time for ESS (UK advisory board, validated by clinical experts): 730 days = **2.00 years**

As the current waiting list for ESS in England is 2.00 years in average, it is a sensible assumption to assume that the 122 patients referred for a third surgery during observation would have been so within 0.40 years after their second surgery (as their third surgery took place 2.40 year after their second surgery in average). This average time to referral helps us estimate the average time to relapse (assumed equal).

- Time for patients to be referred to third surgery: 2.40 – 2.00 = **0.40 years** (5 months)
- Annualised relapse rate = P / time to relapse = 0.17 / 0.40 = 0.43 = **43%**

If 17% of patients received a third surgery within 2 years and 5 months, relapse must have occurred within 5 months, accounting for the current NHS constraints to access surgery. Therefore, our calculated annual rate of relapse is 43%, as previously explained in our draft guidance consultation response.

In the Draft Guidance for Dupilumab for treating severe chronic rhinosinusitis with nasal polyps (ID6480), NICE reported that “the clinical experts said it would be almost impossible to wait only 1 year for revision surgery, and at least 2 years was more likely. They also said that a rate of 42.8% per year for CRSwNP to become uncontrolled again after surgery was reasonable, noting that 10% of people still have severe symptoms despite surgery. SINUS UK provided evidence from a survey of 51 people that showed that half had their symptoms return with 6 months of surgery. The clinical experts also noted that the polyps regrow within 6 months in about a third of people.”

Thus, the probabilities applied to our model are:

- Post-op controlled → uncontrolled: 42.8% per year.
- Uncontrolled → next post-op controlled: 7.1% per year.

## 4. Uncaptured benefits (Section 3.14 in the Draft Guidance)

The committee acknowledged that not all benefits of dupilumab have been completely captured in the QALY calculation given the likely poor performance of EQ-5D to calculate utility values.

It is likely that the introduction of dupilumab for treating severe CRSwNP in those who have had ≥1 sinus surgery and present with a SNOT-22 score ≥50 will reduce the current NHS surgery waiting list compared to current established clinical management which consists of cycling through ESS, oral corticosteroids (OCS) and inhaled nasal corticosteroids. In the prespecified pooled analysis of SINUS

the proportion of patients who required surgery decreased by 82.6% with dupilumab versus placebo (HR: 0.17; 95% CI: 0.07, 0.46; p=0.0005).

Repeated cycling through OCS increases the likelihood of developing other serious conditions which in turn negatively impact patients' quality of life, prognostic outcomes and burden on NHS resources. For example, osteoporosis, Cushing's syndrome, adrenal insufficiency and significant cardiovascular complications are all issues associated with prolonged OCS use. Reduction of steroid use (the proportion of patients who required systemic corticosteroids decreased by 73.9% with dupilumab vs. placebo HR: 0.26; 95% CI: 0.18, 0.38; p<0.0001) aligns with the 'Get It Right First Time' (GIRFT) principle, advocating for timely, appropriate and high standard of treatment decision-making for severe CRSwNP patients, preventing the repeated cycle of surgery and prolonged OCS use which deviates from corticosteroid stewardship standards.

Additionally, severe CRSwNP patients typically also present with other type 2 inflammatory conditions, with up to 60% of patients suffering from comorbid asthma. For these patients, treatment with dupilumab represents significant uncaptured benefits, specifically the reduction in exacerbations, steroid-sparing benefit, accident and emergency resource savings and hospital bed day impact. Whilst we note the committee has agreed to incorporate asthma related costs into their preferred assumptions it is at a very conservative level and the positive service impact of this should not be underestimated.

ENT waiting lists have reached a critical milestone, with ENT UK (2024)[19] reporting nearly 700,000 patients awaiting treatment as of March 2024.[19] Notably, 60% of these patients are adults, underscoring the widespread impact across age groups.[19] The GIRFT programme report by Andrew Marshall (2019)[20] highlighted the scale of ENT services, documenting 2.8 million outpatient attendances annually, including 960,000 outpatient procedures.[20] Recent research by Neito et al. (2024)[21] places ENT as the third-highest ranking specialty in waiting times across all medical disciplines, emphasising the urgent need for attention to this critical area of healthcare.[21] It is clear there is significant pressures to reduce the current strain on the healthcare system, specifically with the introduction of the Elective Reform Plan and commitment to current services, drive efficiencies across the system, with ENT is a priority specialty.[22] Nonetheless further action must be taken to support the taskforce. Hereby, the introduction of dupilumab can play a critical role in.

Here are two proposed scenarios to illustrate potential impact on the current surgery waiting list.

**Scenario 1:**

50% of patients with CRSwNP who are about to undergo surgery are initiated on dupilumab. The current rate of surgery is maintained until the waiting lists have effectively been eradicated.

Calculation steps:

1. Based on Hopkins et al 2022 and inflated in line with population growth to 2024 there were 10,350 endoscopic nasal surgeries (ESS) in the UK in 2024.[16]
2. Feedback from the advisory board meeting and expert opinion advise us that there is at least a 2-year waiting list for ESS in the UK.[15]
3. Feedback from the same advisory board and experts also informs us that at least 50% of the operations performed are revision surgeries.[15]

Scenario parameters:

1. Based on the assumptions and calculations outlined above, we expect there to be 10,350 surgeries in 2024. Feedback from experts indicate that of these patients who are about to undergo surgery, 50% of these surgeries will be primary surgeries (N=5,175), while the remaining 50% will be for patients who have previously undergone surgery but are experiencing a return of symptoms (revision surgeries; N=5,175).[15]
2. Experts also advise that there is a two-year waiting list for surgery; using this information, it is calculated that there are 20,702 patients on the waiting list.[15]
3. As the ratio of primary and revision surgery is 1:1, it is calculated that there are 10,350 patients awaiting primary surgery and 10,350 awaiting revision surgery on the waiting lists.
4. In scenario 1, in accordance with its indication, if dupilumab were initiated in 50% of those who had already undergone surgery, and the current number of surgeries were continued until the waiting list had been eradicated, then the following outcomes would be achieved as presented in Table 12.

*Table 12. Scenario 1, adopting the use of dupilumab in 50% of patients who have undergone ESS whilst maintaining current surgery rates will affect the surgery waiting time and resource availability across UK hospitals*

| | **Surgical Intervention** | | **Surgery Waiting List** | |
|---|---|---|---|---|
| | **Surgery conducted** | | **Total Waiting List** | |
| | **Current predication** | **Scenario prediction** | **Current predication** | **Scenario prediction** |
| Year 1 | 10,351 | 10,351 | 20,702 | 12,939 |
| Year 2 | 10,602 | 10,602 | 21,205 | 7,700 |
| Year 3 | 10,860 | 10,860 | 21,720 | 3,691 |
| Year 4 | 11,124 | 8,343 | 22,247 | 647 |
| Year 5 | 11,394 | 8,545 | 22,788 | 323 |
| | Free surgery slots | 5,630 | | |

Calculated from UK Sanofi homecare data

Key findings:

Adopting the use of dupilumab in half of the patients who had previously experienced an ESS whilst maintaining current surgery rates would:

1) Effectively eliminate waiting lists within three years,
2) Would potentially free up over 5,500 theatre/surgery slots for five years or 20,000 over ten years, thereby enabling other patients with different conditions to access these resources.

This does not take into account the clinical and quality of life benefits that patients suffering from CRSwNP would experience if they were initiated on dupilumab.

**Scenario 2:**

50% of patients with CRSwNP who are about to undergo or are awaiting revision surgery are initiated on dupilumab. The rate of surgery is decreased by the number of patients who are about to undergo surgery in the next year but are initiated on dupilumab instead.

Calculation steps:

1. Based on Hopkins et al 2022 and inflated in line with population growth to 2024 there were 10,350 ESS in the UK in 2024.[16]
2. Feedback from the advisory board meeting and expert opinion advises us that there is at least a 2-year waiting list for ESS in the UK.[15]
3. Feedback from the same advisory board and experts also informs us that at least 50% of the operations performed are revision surgeries.[15]

Scenario parameters:

1. Based on the assumptions and calculations outlined above, we expect there to be 10,350 surgeries in 2024. Feedback from experts indicates that 50% of these surgeries will be for primary surgery patients, while the remaining 50% will be for patients who have previously undergone surgery but are experiencing a return of symptoms.[15]
2. Experts also advise that there is a two-year waiting list; it is calculated that there are 20,702 patients on the waiting list.[15]
3. As the ratio of primary and revision surgery is 1:1, it is calculated that there are 10,350 patients awaiting primary surgery and 10,350 awaiting revision surgery.
4. In scenario 2, in accordance with its indication, if dupilumab were initiated in 50% of those who had already undergone surgery and if the current number of surgeries were reduced by the number of patients who were about to undergo surgery within the next year, but we initiated on dupilumab instead, as presented in Table 13.

*Table 13. Scenario 2 results on adopting the use of dupilumab in 50% of patients who have already undergone ESS and reducing the surgery rate will affect the surgery waiting time and resource availability in UK hospitals.*

| | **Surgical Intervention** | |
|---|---|---|
| | **Surgery conducted** | |
| | **Current predication** | **Scenario prediction** |
| Year 1 | 10,351 | 10,351 |

Calculated from UK Sanofi homecare data

Key findings:

Adopting the use of dupilumab in half of the patients who had previously experienced an ESS and reducing the surgery rate by the number of patients who were about to undergo surgery in the next year would

1. Reduce the waiting list by 33% to about 16 months
2. Would free up over 13,500 theatre/surgery slots for five years, thereby enabling other patients with different conditions to access these resources.

This does not take into account the clinical and quality of life benefits that patients suffering from CRSwNP would experience if they were initiated on dupilumab.

# 5. Long-term compliance with dupilumab treatment

## 5.1. Compliance to dupilumab in the real world

It is generally recognised that adherence and compliance to treatment is universally lower in the real world than in clinical studies. This is as true of biologics as for any other treatment. For example, a recent metanalysis on fifty-five studies in psoriasis found that adherence rates ranged between 72% for ustekinumab, followed by 63% for infliximab, 62% for adalimumab, 52% for secukinumab, 50% for etanercept and 46% for ixekizumab.[23]

A good way to accurately assess adherence to biologics is via homecare delivery services. These have become increasingly common in the management of chronic conditions such as rheumatoid arthritis, psoriasis and inflammatory bowel diseases. These services not only improve patient convenience but also offer a unique opportunity to indirectly measure treatment compliance.

For example, a study conducted in the NHS Greater Glasgow and Clyde health board focused on subcutaneous biologic options over a three-year data collection period utilising homecare delivery services data observed mean adherence at 79.73%.[24]

Overall, though, the most up to date UK Sanofi homecare data for dupilumab suggest a much higher compliance rate of [redacted]. Adherence to dupilumab may be higher than biologics in general because the dupilumab homecare program seeks to identify patients with adherence issues using a prediction tool based on behavioural science, demographics and how the patient interacts with homecare in the first 12 weeks of treatment. This suggests a low, medium or high risk of adherence and ongoing support is tailored to them with increased contacts via various channels to ensure as much as possible optimal use of their medication and maintenance of effectiveness similar to trail based outcomes.

*Table 14, UK Sanofi Dupilumab homecare average compliance rates across current indications.*

| | Average Compliance Rate (%) | Average 1 Year Persistence (%) |
|---|---|---|
| All | [redacted] | [redacted] |
| Atopic Dermatitis | [redacted] | |
| Asthma | [redacted] | |

Calculated from UK Sanofi homecare data in an adult patient population aged 18 years and above and have been utilising homecare service for at least 42 months, collected from 4,522 active patients whereby 8,881 patients started for atopic dermatitis and asthma.

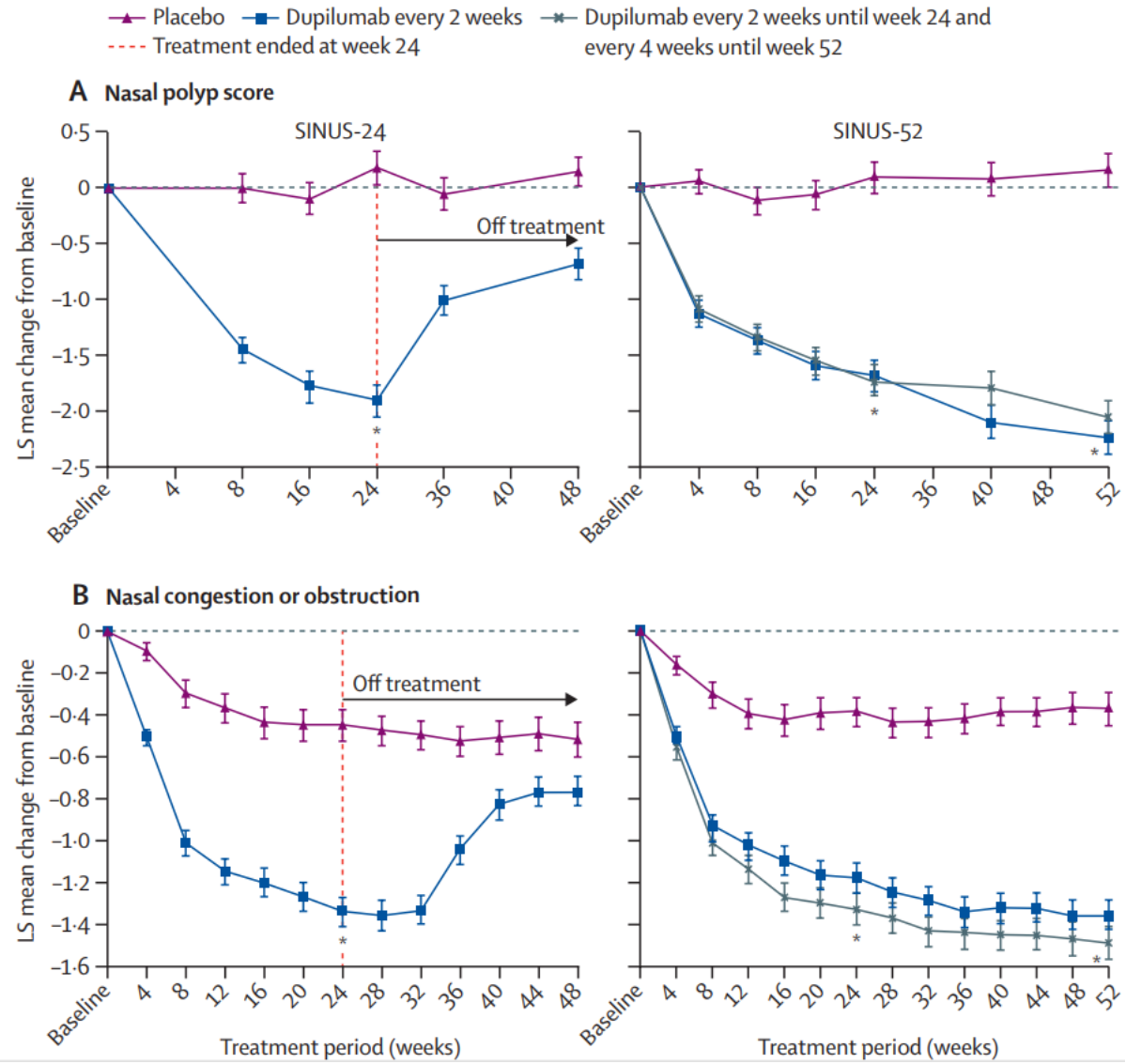
## 5.2. Modelling compliance

The compliance rate in the SINUS studies was 99.26%, however it is not unreasonable that the likely compliance rate for dupilumab in the real world for CRSwNP would be like the observed rates for the current asthma indication. A key consideration then, is the expected effectiveness of treatment at lower than trial compliance rates. There is considerable evidence to suggest that for the CRSwNP indication, effectiveness of dupilumab could be maintained if there was to be a small drop off in compliance amongst some patients.

### 5.2.1. Evidence from the SINUS studies

In the SINUS 52 study patients were re-randomized to receive Q2W or Q4W at 24 weeks. The coprimary endpoints in both studies were change from baseline in both endoscopic NPS and nasal congestion severity (based on monthly average of daily score recorded by patients) at week 24. The results for both the SINUS 24 and SINUS 52 studies are shown in Figure 4 below reproduced from Bachert et al. 2019.[25]

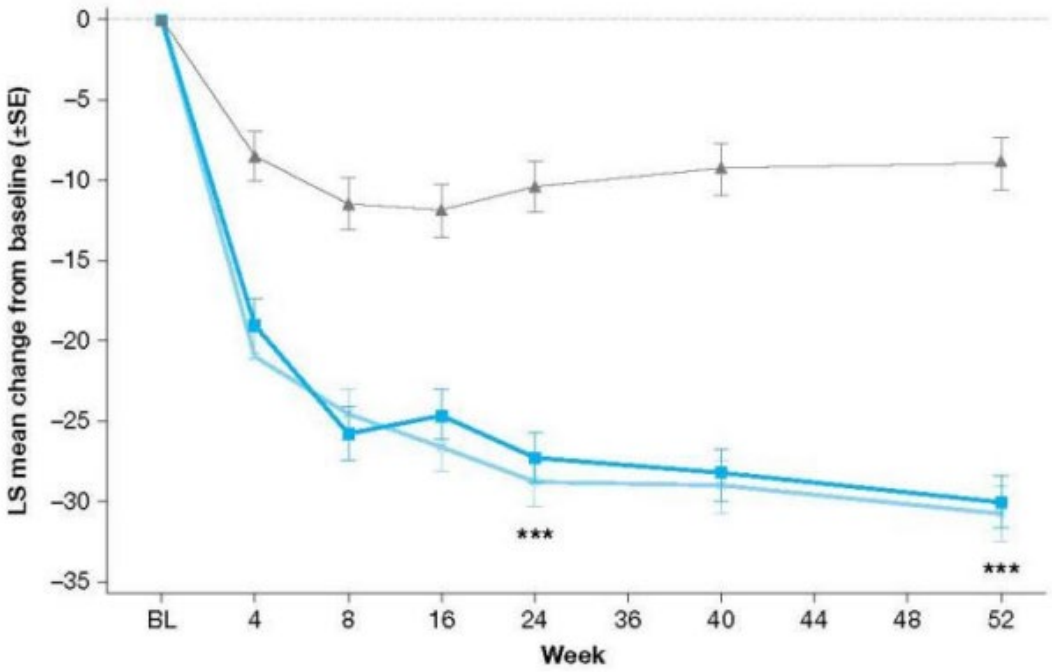
*Figure 4. Change from baseline over time in nasal polyp score (A) and nasal congestion or obstruction (B) in SINUS-24 and SINUS-52.*




Source: Reproduced from Bachert et al 2019.[25]

As can be seen in the above figures, the Q2W-Q4W groups show little or no decline in the key primary outcomes after the switch at week 24. SNOT-22 follows a similar trajectory (Figure 5 reproduced from Bachert et al 2019, supplementary material Figure S3).

*Figure 5. Change from baseline over time in SNOT-22. Reproduced from Bachert et al 2019.*




Source: Reproduced from Bachert et al 2019.[25]. *** p<0.0001

### 5.2.2. Overview of key real-world studies

In pivotal trials, dupilumab for severe uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP) was administered as a fixed 300 mg subcutaneous dose every two weeks (Q2W). As we have discussed above in real-world clinical practice, patient adherence to this dosing frequency is imperfect, either because of adverse events, patient preference, comorbidity management or logistical issues. To provide further reassurance that effectiveness would remain unchanged from the observed study data used in the model, we reviewed three recent real-world studies that evaluated long-term outcomes with dupilumab in CRSwNP.

Across three independent, prospective real-world cohorts totalling >900 patients (2023 to 2025), the evidence consistently shows early, substantial improvements in key disease measures (NPS, SNOT-22, olfaction, asthma control) are achieved within the first 6 months of Q2W dupilumab treatment. Sustained efficacy is observed for at least 2 years, even when a substantial proportion of patients deviate substantially in compliance. No clinically meaningful differences in long-term outcomes are detected between patients maintaining strict Q2W dosing and those extending intervals once stable. These findings are robust across patient subgroups, including those with more severe type-2 inflammation (NSAID-ERD), and have been replicated in different European healthcare settings.

These data provide high-quality real-world confirmation that the therapeutic benefit of dupilumab is not contingent upon perfect adherence once disease control is established. These findings support sensitivity analyses in which reduced-frequency dosing is assumed after the initial disease-control period, without modelling a decrement in health outcomes.

### 5.2.3. Modelling compliance

We have shown that the best estimated for compliance to dupilumab is currently [redacted] in UK clinical practice for patients with 42 or more months follow-up (Table 14). With the evidence above in mind, it is not unreasonable to assume that effectiveness may be maintained overall if compliance rates are slightly reduced from trial levels to match those seen in the real world for dupilumab. Our base case modelling uses an estimate for compliance of [redacted] and we have tested this assumption in sensitivity analyses at increments of 2.5% with values as low as 80.0%.

## 6. Valuing CRSwNP: Willingness to pay

A willingness to pay of £25,000 / QALY has been suggested in the Draft Guidance due to the uncertainties identified by the committee.

The key uncertainty was for the quality of life estimates derived from mapping of SNOT-22 to EQ-5D using the published Crump algorithms. We have resolved this uncertainty by improving the definition of severity in the population of interest and re-calculating the EQ-5D data for this patient group. The utility values obtained for this new cohort do not lack face validity and so provide good a basis for decision making.

Similarly, we have re-examined the utility gain following surgery and aligned with the EAG on the most appropriate value to use.

We have described how the estimates for the transition probabilities were calculated for patients entering the uncontrolled health state after their second surgery in the model and validated this against additional sources.

Finally, we have shown that current compliance in the real world for dupilumab in the UK is high compared to other biologics and provided evidence to suggest that incorporating an estimate for compliance aligned with homecare data into the model should not be expected to result in a decrease in effectiveness. This was confirmed at the first committee meeting by the clinical expert who described outcomes for CRSwNP patients treated with dupilumab at lower dosing rates.

Having addressed all the key points of uncertainty in a disease for whom some patients have no other options, a more suitable WTP threshold is towards the higher end of the £20,000 to £30,000 / QALY range.

## 7. Results from the updated economic modelling

The updated Sanofi base case includes all the committee preferences in their base case, except for the capping of utility values at population norm. The key changes are presented in Table .15 below.

*Table .15 Updated Sanofi economic modelling parameters*

| **Parameter** | **Updated parameter estimate** | **Change from original Sanofi base case** | **Justification** |
|---|---|---|---|
| Patient population | Patients with prior surgery AND SNOT-22>50 at baseline<br><br>Base case population is people with uncontrolled | Patients with prior surgery<br><br>Base case population is people with uncontrolled disease | New population aligned with the severe uncontrolled population eligible for a biologic |

| | | | |
|---|---|---|---|
| | disease following one (or more) surgeries **with SNOT-22 score ≥50 at baseline** | following one (or more) surgeries. | |
| Response criteria | SNOT-22 total score (**total score <50 or** ≥8.9-point improvement) and NPS (≥1-point improvement): | SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement): | New response criteria to align with the new population definition. |
| Source for utility values | **Observed EQ-5D-5L in the pooled SINUS-24/52 studies, cross walked to EQ-5D-3L using the Hernandez et al. crosswalk method.** | Observed SNOT-22 in the pooled SINUS-24/52 studies, mapped to expected EQ-5D-3L utility values using the published peer-reviewed mapping algorithm from **Crump et al. 2017**. | Following the recommendation from the committee to not use the mapping algorithm, we have decided to provide the NICE preferred utility instrument, in a refined patient population (described in section 1.1). |
| Probability of moving to the inadequately controlled state from controlled disease Years 2 and on<br><br>DUP + ECM - RW-based discontinuation | Rate calculated from the new patient population in AROMA matched to SINUS<br><br>**Year 2:** [redacted]<br>**Year 3:**<br>**Year 4:**<br>**Year 5+:** | Rates calculated based on the AROMA population (RAS and at least one surgery) without matching to SINUS and without censoring rescue therapy from the response analysis<br><br>Year 2: [redacted]<br>Year 3:<br>Year 4:<br>Year 5+: | As requested by the committee and described in section 2.1, we have carried out the analysis of long-term response on AROMA data in the new patient population matched to SINUS, considering the new response criteria and applying the same methodology (censoring patients requiring rescue therapy). |
| Probability of moving to the inadequately controlled state from controlled disease Years 2 and on<br><br>ECM - RW-based discontinuation | Aligned with the transition probability for patients in Post-op Controlled to move to uncontrolled HS (calculated from Benson et al. 2023)<br><br>**42.8%** | Extrapolation of the rate of ECM W52 responders amongst W24 responders, annualised<br><br>[redacted] | To align with the EAG recommendation, we have decided to apply a real-world transition probability. We have selected the rate of loss of response following surgery, which is a conservative estimate for this long-term discontinuation rate. |
| Probability of receiving surgery and moving to Post-op Controlled HS from both Controlled, Uncontrolled and Inadequately controlled HS | Updated extrapolation of the mean rate of surgery from Benson et al. 2023<br><br>**7.1%** | Extrapolation of the mean rate of surgery from Benson et al. 2023<br><br>14.8% | To align with the EAG recommendations (lower rate of surgery), we have updated our analysis of the data to take account of the spread of prior surgeries in Benson et al. 2023 |
| Inadequately controlled disease utility value | **Average between baseline utility weight and** utility weight of non-responders at W52 | Utility weight of non-responders at W52 | As there is no evidence that the efficacy remains for a whole year after W52, and considering the model applies a half-cycle correction, it is |

| | | | |
|---|---|---|---|
| | | | appropriate to apply an average of the starting and ending utility weights. |
| Utility gain following revision surgery | Source: Tashman 2024<br><br>**+0.0644** | Source: Riemenschneider 2015<br><br>+0.080 | More recent and methodology strong source of EQ-5D utility values post-surgery (As described in section 1.4) |
| Percentage of scheduled doses given to patients (compliance) | Extrapolated from the real-world compliance to dupilumab in England (Homecare data)<br><br>[redacted] | Extrapolated from the compliance reported in a pooled analysis of SINUS-24/52<br><br>99.26% | As described in section 5.1, compliance to dupilumab in the real-world is 88.1%, whilst literature suggests a maintained efficacy. |

## 7.1. Updated deterministic base-case results

*Table 16. Updated results for patients with ≥1 prior sinus surgery and baseline SNOT-22 total score ≥50, according to the response criteria of SNOT-22 total score (total score <50 or ≥8.9-point improvement) and NPS (≥1-point improvement): Deterministic*

| Treatments | TOTAL costs | TOTAL LYs | TOTAL QALYs | Incr. costs | Incr. LYs | Incr. QALYs | ICER |
|---|---|---|---|---|---|---|---|
| Dupilumab + ECM | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ECM | [redacted] | [redacted] | [redacted] | | | | |

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

## 7.2. Deterministic sensitivity analysis

Model inputs used for the updated base case analysis are varied in a one-way deterministic sensitivity analysis (DSA). As shown in the tornado chart (Figure 6) and Table 17 beyond the impact of the discount rate, the top three drivers of the results are as expected and are the utility values for controlled patients and uncontrolled patients, and compliance.

*Figure 6. Tornado diagram of ICER of DUP + ECM vs. ECM – updated base case*

[redacted]

DUP = dupilumab; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

*Table 17. Top 10 drivers of the ICER results – updated*

| Rank | Parameter | ICER - Lower Bound | ICER - Upper Bound | Difference |
|---|---|---|---|---|
| **Base case ICER (Deterministic)** | | | | |
| 1 | Utility for patients in controlled HS | [redacted] | [redacted] | [redacted] |
| 2 | Utility for patients in uncontrolled HS | [redacted] | [redacted] | [redacted] |

| Rank | Parameter | ICER - Lower Bound | ICER - Upper Bound | Difference |
|---|---|---|---|---|
| 3 | DUP+ECM compliance - rest of model time | [redacted] | [redacted] | [redacted] |
| 4 | Discount rate - outcomes | [redacted] | [redacted] | [redacted] |
| 5 | Discount rate - costs | [redacted] | [redacted] | [redacted] |
| 6 | Utility for patients in Post-op controlled HS | [redacted] | [redacted] | [redacted] |
| 7 | Utility for patients in inadequately HS | [redacted] | [redacted] | [redacted] |
| 8 | Mortality increase for patients with asthma | [redacted] | [redacted] | [redacted] |
| 9 | Rate of uncontrolled ECM | [redacted] | [redacted] | [redacted] |
| 10 | % of ECM patients achieve response at W24 | [redacted] | [redacted] | [redacted] |

DUP = dupilumab; ECM = established clinical management; HS = health state; ICER = incremental cost-effectiveness ratio; W24 = week 24

## 7.3. Updated probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) has been conducted to assess the parametric uncertainty associated with the new model results. All key parameters were assigned probability distributions from which random sampling was done over 1,000 simulations. Where uncertainty data were not available for an input, standard errors (SE) of 10% of the mean values were assumed. The PSA results are presented in Table 18. The results align with the deterministic results.

*Table 18. Updated results for patients with ≥1 prior sinus surgery and baseline SNOT-22 total score ≥50, according to the response criteria of SNOT-22 total score (total score <50 or ≥8.9-point improvement) and NPS (≥1-point improvement): Probabilistic*

| Treatments | TOTAL costs | TOTAL LYs | TOTAL QALYs | Incr. costs | Incr. LYs | Incr. QALYs | ICER |
|---|---|---|---|---|---|---|---|
| Dupilumab + ECM | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ECM | [redacted] | [redacted] | [redacted] | | | | |

ECM = established clinical management; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

In addition, the incremental PSA results and cost-effectiveness acceptability curve (CEAC) are presented in Figure 7 and Figure 8, respectively.

*Figure 7. Scatter plot for incremental cost-effectiveness results (1,000 iterations) – updated base case*

DUP = dupilumab; ECM = established clinical management; QALY = quality-adjusted life-year; WTP = willingness-to-pay

*Figure 8. Cost-effectiveness acceptability curve (1,000 iterations) – updated base case*

DUP = dupilumab; ECM = established clinical management

*Figure 9. Convergence ICER plot for the PSA*

ICER = incremental cost-effectiveness ratio

*Figure 10. Convergence plot for the PSA (detail).*

ICER = incremental cost-effectiveness ratio

## 7.4. Updated sensitivity results and scenario analyses

To test the sensitivity of the cost-effectiveness results due to the modifications of some parameters and assumptions (following the conclusions of the draft guidance), various analyses have been explored (Table 19).

*Table 19. Sensitivity analysis results – PAS price (Deterministic ICERs)*

| Updated parameter | Scenario | Incr. costs | Incr. LYs | Incr. QALYs | ICER* |
|---|---|---|---|---|---|
| Percentage of scheduled doses given to patients after W24 | 99.3% | [redacted] | [redacted] | [redacted] | [redacted] |
| | 97.5% | [redacted] | [redacted] | [redacted] | [redacted] |
| | 95.0% | [redacted] | [redacted] | [redacted] | [redacted] |
| | 93.7% | [redacted] | [redacted] | [redacted] | [redacted] |
| | 90.0% | [redacted] | [redacted] | [redacted] | [redacted] |
| | 85.0% | [redacted] | [redacted] | [redacted] | [redacted] |
| | 82.5% | [redacted] | [redacted] | [redacted] | [redacted] |
| | 80.0% | [redacted] | [redacted] | [redacted] | [redacted] |
| Source for Probability of Moving to Inadequately Controlled HS after year 1 | Extrapolated from SINUS ("CT-based") | [redacted] | [redacted] | [redacted] | [redacted] |
| Population | Patients with asthma AND SNOT-22>50 at baseline | [redacted] | [redacted] | [redacted] | [redacted] |
| Utility values capped at population norm (+ multiplier applied) | Yes | [redacted] | [redacted] | [redacted] | [redacted] |

CT = clinical trial; HS = health state; ICER = incremental cost-effectiveness ratio; LY = life year; N/A= not applicable; QALY = quality-adjusted life year; W24 = week 24

* Deterministic ICERs.

# References


1. Toma S, Hopkins C. Stratification of SNOT-22 scores into mild, moderate or severe and relationship with other subjective instruments. *Rhinology*. Jun 2016;54(2):129-33. doi:10.4193/Rhino15.072

2. Cantone E, Cassiano B, Pezzella P, Russo MB, Detoraki A. The Effects of Mepolizumab on CRSwNP: Real-Life Evidence. *J Pers Med*. Nov 20 2024;14(11)doi:10.3390/jpm14111112

3. Cavaliere C, Loperfido A, Ciofalo A, et al. Real-Life Evidence of Mepolizumab Treatment in Chronic Rhinosinusitis with Nasal Polyps: A Multicentric Study. *J Clin Med*. Jun 18 2024;13(12)doi:10.3390/jcm13123575

4. Galletti C, Ragusa M, Sireci F, et al. Dupilumab in chronic rhinosinusitis with nasal polyps: Real life data in a multicentric Sicilian experience. *Am J Otolaryngol*. Jan-Feb 2024;45(1):104106. doi:10.1016/j.amjoto.2023.104106

5. Lombardo N, Piazzetta G, Lobello N, et al. Real-Life Effects of Omalizumab on Chronic Rhinosinusitis with Nasal Polyposis. *Journal of Personalized Medicine*. 12/19 2023;14:3. doi:10.3390/jpm14010003

6. Moffa A, Iafrati F, Giorgi L, et al. Clinical Evidence of the Use of Mepolizumab in the Treatment of Chronic Rhinosinusitis with Nasal Polyps: A Prospective Observational Study. *Healthcare (Basel)*. Feb 15 2025;13(4)doi:10.3390/healthcare13040419

7. De Corso E, Pasquini E, Trimarchi M, et al. Dupilumab in the treatment of severe uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP): A multicentric observational Phase IV real-life study (DUPIREAL). *Allergy*. Oct 2023;78(10):2669-2683. doi:10.1111/all.15772

8. Sanofi. *Data on file. SINUS-24 and SINUS-52 Post-hoc analyses*. 2025. July.

9. Crump RT, Lai E, Liu G, Janjua A, Sutherland JM. Establishing utility values for the 22-item Sino-Nasal Outcome Test (SNOT-22) using a crosswalk to the EuroQol-five-dimensional questionnaire-three-level version (EQ-5D-3L). *Int Forum Allergy Rhinol*. 2017/05// 2017;7(5):480-487. doi:10.1002/alr.21917

10. Remenschneider AK, Scangas G, Meier JC, et al. EQ-5D-derived health utility values in patients undergoing surgery for chronic rhinosinusitis. *Laryngoscope*. May 2015;125(5):1056-61. doi:10.1002/lary.25054

11. Soler ZM, Wittenberg E, Schlosser RJ, Mace JC, Smith TL. Health state utility values in patients undergoing endoscopic sinus surgery. *Laryngoscope*. Dec 2011;121(12):2672-8. doi:10.1002/lary.21847

12. Tashman K, Adams D, Vickery TW, et al. Five-year EuroQol 5-Dimension Outcomes After Endoscopic Sinus Surgery. *Laryngoscope*. Jun 2024;134(6):2592-2601. doi:10.1002/lary.31206

13. Regeneron Pharmaceuticals. *Data on file. AROMA Registry and SINUS-24/SINUS-52 MAIC*. 2025.

14. Benson VS, Fu Q, Yang S, et al. Real-world characterisation of patients with chronic rhinosinusitis with nasal polyps with and without surgery in England. *Clin Otolaryngol*. Jul 2023;48(4):680-688. doi:10.1111/coa.14070

15. Sanofi. *Data on file. UK Health Technology Assessment Advisory Board for Chronic Rhinosinusitis with Nasal Polyposis in the Devolved Nations. Full Confidential Report*. 2024. 26 June.

16. Hopkins C, Conlon S, Chavda S, Hudson R, Rout R. Investigating the secondary care system burden of CRSwNP in sinus surgery patients with clinically relevant comorbidities using the HES database. *Rhinology*. Aug 1 2022;60(4):252-260. doi:10.4193/Rhin21.264

17. Pirola F, Pace GM, Giombi F, et al. Outcomes of Non-Mucosa Sparing Endoscopic Sinus Surgery (Partial Reboot) in Refractory Chronic Rhinosinusitis with Nasal Polyposis: An Academic Hospital Experience. *The Laryngoscope*. 2023;133(7):1584-1589. doi:https://doi.org/10.1002/lary.30422

18. DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *Laryngoscope*. Mar 2017;127(3):550-555. doi:10.1002/lary.26391

19. ENT UK. ENT Waiting Lists. Updated 15 March 2024. Accessed 12 August, 2025. https://www.entuk.org/news_and_events/news/351/ent_waiting_lists

20. Marshall A. Getting It Right First Time in ENT. *ENT & Audiology News*. 14 January 2020;

21. Nieto H, Lee J, Hall C, McDermott AL. The Otolaryngology Consultant Workforce in England: A Survey Update and Future Repercussions. *Clin Otolaryngol*. Sep 2024;49(5):682-686. doi:10.1111/coa.14190

22. UK Parliament. Written questions, answers and statements - Ear, Nose and Throat Conditions: Surgery - Question for Department of Health and Social Care. Updated 16 January 2025. Accessed 12 August, 2025. https://questions-statements.parliament.uk/written-questions/detail/2025-01-16/24559/

23. Piragine E, Petri D, Martelli A, et al. Adherence and Persistence to Biological Drugs for Psoriasis: Systematic Review with Meta-Analysis. *J Clin Med*. Mar 9 2022;11(6)doi:10.3390/jcm11061506

24. Alvarez-Madrazo S, Kavanagh K, Semple Y, et al. Adherence and persistence of subcutaneous biologics delivered through homecare services to a cohort of patients with rheumatoid arthritis: IJPDS (2017) Issue 1, Vol 1:228 Proceedings of the IPDLN Conference (August 2016). *International Journal of Population Data Science*. 04/18 2017;1(1)doi:10.23889/ijpds.v1i1.248

25. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. Nov 2 2019;394(10209):1638-1650. doi:10.1016/s0140-6736(19)31881-1

# Baseline characteristics and utilities used in the updated base case and sensitivity analyses

## Patients with ≥1 prior sinus surgery and SNOT-22 total score ≥50

### Baseline characteristics

Baseline demographics of the updated population (i.e., patients with ≥1 prior sinus surgery and baseline SNOT-22 total score ≥50) were consistent with those of the previous population (i.e., patients with ≥1 prior sinus surgery), with a majority of male, Caucasian and non-Latino individuals and a mean age ~50 years (Table 20). Baseline disease characteristics of the updated population were representative of a population with slightly more severe disease compared with those of the previous population, with a longer disease duration, higher rate of SCS use in the past 2 years, generally worse disease measures and a higher proportion of Type 2 comorbidities.

*Table 20. Baseline characteristics of patients with ≥1 prior sinus surgery and baseline SNOT-22 total score ≥50 in SINUS-24 and SINUS-52 pooled ITT population vs. previous base-case population*

| | **Updated population: Patients with ≥1 prior sinus surgery and SNOT-22 ≥50** | | **Previous population: Patients with ≥1 prior sinus surgery** | |
|---|---|---|---|---|
| | **Placebo** | **Dupilumab pooled doses** | **Placebo** | **Dupilumab pooled doses** |
| N | 101 | 129 | 187 | 272 |
| Male, n (%) | 53 (52.5) | 68 (52.7) | 103 (55.1) | 165 (60.7) |
| Age, mean (SD) | 49.98 (12.40) | 51.98 (11.29) | 50.97 (13.16) | 51.66 (12.23) |
| Race, n (%) | | | | |
| Caucasian/White | 94 (93.1) | 115 (89.1) | 170 (90.9) | 239 (87.9) |
| Black/African decent | 2 (2.0) | 2 (1.6) | 4 (2.1) | 3 (1.1) |
| Asian/Oriental | 4 (4.0) | 8 (6.2) | 12 (6.4) | 25 (9.2) |
| American Indian/Alaska Native | 1 (1.0) | 3 (2.3) | 1 (0.5) | 4 (1.5) |
| Native Hawaiian/Other Pacific Islander | 0 | 0 | 0 | 0 |
| Multiple | 0 | 1 (0.8) | 0 | 1 (0.4) |
| Unknown | 0 | 0 | 0 | 0 |
| Ethnicity | | | | |
| Hispanic or Latino | 13 (13.0) | 21 (16.4) | 14 (7.6) | 33 (12.2) |
| Not Hispanic or Latino | 87 (87.0) | 107 (83.6) | 171 (92.4) | 238 (87.8) |
| Territory | | | | |
| North America | 15 (14.9) | 23 (17.8) | 27 (14.4) | 53 (19.5) |
| European Union | 43 (42.6) | 45 (34.9) | 82 (43.9) | 100 (36.8) |
| Rest of the World | 43 (42.6) | 61 (47.3) | 78 (41.7) | 119 (43.8) |
| BMI ($kg/m^2$), mean (SD) | 27.83 (5.49) | 27.90 (5.58) | 27.70 (5.46) | 27.54 (5.20) |
| Time since first diagnosis of nasal polyps (years), mean (SD) | 12.94 (8.85) | 13.20 (9.07) | 13.75 (9.16) | 14.51 (9.93) |
| ≥3 previous surgeries for nasal polyps, n (%) | 27 (26.7) | 33 (25.6) | 47 (25.1) | 64 (23.5) |
| Time since most recent surgery for nasal polyps (years), mean (SD) | 6.82 (5.93) | 6.80 (5.67) | 7.06 (6.33) | 7.22 (6.52) |
| SCS use in the past 2 years, n (%) | 73 (72.3) | 91 (70.5) | 118 (63.1) | 174 (64.0) |
| Bilateral endoscopic NPS* (scale 0-8), mean (SD) | 5.89 (1.25) | 6.12 (1.26) | 5.74 (1.27) | 5.94 (1.26) |
| NC score* (scale 0-3), mean (SD) | 2.66 (0.45) | 2.66 (0.46) | 2.47 (0.53) | 2.42 (0.59) |

| | Updated population: Patients with ≥1 prior sinus surgery and SNOT-22 ≥50 | | Previous population: Patients with ≥1 prior sinus surgery | |
|---|---|---|---|---|
| | Placebo | Dupilumab pooled doses | Placebo | Dupilumab pooled doses |
| SNOT-22 total score* (scale 0-110), mean (SD) | 68.29 (13.86) | 67.83 (12.64) | 53.47 (19.92) | 50.35 (20.32) |
| Smell test (UPSIT) score** (scale 0-40), mean (SD) | 11.61 (6.08) | 11.43 (6.62) | 13.01 (7.46) | 12.65 (7.57) |
| LoS score* (scale 0-3), mean (SD) | 2.90 (0.29) | 2.87 (0.46) | 2.77 (0.48) | 2.80 (0.55) |
| LMK-CT total score* (scale 0-24), mean (SD) | 19.92 (3.65) | 19.60 (3.50) | 19.16 (4.10) | 19.01 (3.89) |
| Rhinosinusitis disease severity* (VAS 0-10cm), mean (SD) | 8.80 (1.29) | 8.72 (1.56) | 8.10 (2.00) | 7.92 (2.00) |
| Baseline NPIF** (L/min), mean (SD) | 75.53 (44.42) | 76.46 (51.84) | 87.68 (55.43) | 90.44 (58.74) |
| Baseline blood eosinophils (x$10^9$ cells/L), mean (SD) | 0.51 (0.32) | 0.54 (0.46) | 0.46 (0.32) | 0.47 (0.39) |
| Any comorbid type 2 medical history including asthma and NSAID-ERD, n (%) | 89 (88.1) | 118 (91.5) | 154 (82.4) | 232 (85.3) |
| Comorbid asthma, n (%) | 76 (75.2) | 97 (75.2) | 121 (64.7) | 183 (67.3) |
| Comorbid NSAID-ERD, n (%) | 41 (40.6) | 47 (36.4) | 65 (34.8) | 94 (34.6) |
| Any comorbid type 2 medical history excluding asthma and NSAID-ERD, n (%) | 66 (65.3) | 88 (68.2) | 117 (62.6) | 177 (65.1) |
| Age of asthma onset in patients with comorbid asthma (years), mean (SD) | 33.74 (13.90) | 35.98 (14.88) | 32.91 (14.88) | 34.68 (15.53) |
| Baseline ACQ-6 score* in patients with comorbid asthma, mean (SD) | 1.82 (1.10) | 1.86 (1.13) | 1.59 (1.06) | 1.48 (1.10) |
| Baseline GINA 4 or 5 in patients with comorbid asthma, n (%) | 37 (48.7) | 35 (36.1) | 57 (30.5) | 64 (23.5) |

ACQ-6 = 6-item Asthma Control Questionnaire; BMI = body mass index; ERD = exacerbated respiratory disease; GINA = Global Initiative for Asthma; ITT = intention-to-treat; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; NC = nasal congestion/obstruction; NPIF = peak nasal inspiratory flow; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = every 2 weeks; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale

* Higher scores indicate greater disease severity.

** Higher scores indicate lower disease severity.

Source: Sanofi. Data on File, Post-hoc analyses.[8]

## NPS and SNOT-22 score

NPS and SNOT-22 score endpoints were successfully met in patients with ≥1 prior sinus surgery and baseline SNOT-22 total score ≥50 in the pooled ITT population; results are summarised in Table 21.

*Table 21. Summary of primary and key secondary endpoint results in patients with ≥1 prior sinus surgery and baseline SNOT-22 total score ≥50 in SINUS-24 and SINUS-52 pooled ITT population*

| Endpoint | Placebo (N=101) | | Dupilumab (N=129) | | |
|---|---|---|---|---|---|
| | Mean (SD) | LS mean change from baseline (SE) | Mean (SD) | LS mean change from baseline (SE) | LS Mean difference vs. placebo (95% CI; p-value) |
| Bilateral NPS | 6.038 (1.143) | 0.359 (0.206) | 3.822 (2.108) | −2.062 (0.193) | −2.421 (−2.818, −2.024; p<0.0001) |
| SNOT-22 score | 53.234 (19.880) | −13.412 (2.695) | 26.648 (19.380) | −40.517 (2.540) | −27.105 (−32.307, −21.903; p<0.0001) |

CI = confidence interval; ITT = intention-to-treat; NPS = nasal polyp score; SD = standard deviation; SE = standard error; SNOT-22 = 22-item Sino-Nasal Outcome Test
Sources: Sanofi. Data on File, Post-hoc analyses.

## EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs)

*Table 22. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with ≥1 prior sinus surgery and baseline SNOT-22 total score ≥50 in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (total score <50 or ≥8.9-point improvement) and NPS (≥1-point improvement) vs. previous base-case population*

| | **Updated population: Patients with ≥1 prior sinus surgery and SNOT-22 ≥50** | | **Previous population: Patients with ≥1 sinus surgery; previous response criteria*** | |
|---|---|---|---|---|
| | **Placebo (N=101)** | **Dupilumab Q2W (N=129)** | **Placebo (N=187)** | **Dupilumab Q2W (N=272)** |
| **Baseline** | | | | |
| *All* | | | | |
| Number | 99 | 126 | 184 | 446 |
| Mean (SD) | 0.718 (0.182) | 0.683 (0.207) | 0.776 (0.176) | 0.782 (0.184) |
| *Responders at Week 24* | | | | |
| Number | 5 | 88 | 20 | 153 |
| Mean (SD) | 0.761 (0.126) | 0.697 (0.194) | 0.820 (0.113) | 0.775 (0.183) |
| *Non-responders at Week 24* | | | | |
| Number | 94 | 38 | 164 | 109 |
| Mean (SD) | 0.716 (0.185) | 0.650 (0.235) | 0.771 (0.182) | 0.801 (0.198) |
| **Week 24** | | | | |
| *All* | | | | |
| Number | 93 | 122 | 176 | 254 |
| Mean (SD) | 0.770 (0.176) | 0.827 (0.184) | 0.815 (0.168) | 0.872 (0.153) |
| Change from baseline | | | | |
| Number | 93 | 122 | 176 | 254 |
| Mean (SD) | 0.054 (0.157) | 0.147 (0.206) | 0.040 (0.147) | 0.088 (0.176) |
| LS mean (SE) | 0.082 (0.021) | 0.160 (0.020) | 0.045 (0.012) | 0.101 (0.011) |
| LS mean diff (95% CI) | NA | 0.077 (0.036, 0.119) | NA | 0.056 (0.031, 0.082) |
| p value vs. placebo | NA | 0.0003 | NA | <0.0001 |
| *Responders at Week 24* | | | | |
| Number | 5 | 88 | 20 | 153 |
| Mean (SD) | 0.811 (0.119) | 0.851 (0.155) | 0.912 (0.104) | 0.888 (0.134) |
| Change from baseline | | | | |
| Number | 5 | 88 | 20 | 153 |
| Mean (SD) | 0.050 (0.210) | 0.154 (0.208) | 0.092 (0.139) | 0.113 (0.179) |
| LS mean (SE) | 0.114 (0.011) | 0.202 (0.004) | 0.121 (0.005) | 0.120 (0.002) |
| LS mean diff (95% CI) | NA | 0.087 (0.067, 0.108) | NA | −0.001 (−0.010, 0.008) |
| p value vs. placebo | NA | <0.0001 | NA | 0.8479 |
| *Non-responders at Week 24* | | | | |

| | **Updated population: Patients with ≥1 prior sinus surgery and SNOT-22 ≥50** | | **Previous population: Patients with ≥1 sinus surgery; previous response criteria*** | |
|---|---|---|---|---|
| | **Placebo (N=101)** | **Dupilumab Q2W (N=129)** | **Placebo (N=187)** | **Dupilumab Q2W (N=272)** |
| Number | 88 | 34 | 156 | 101 |
| Mean (SD) | 0.767 (0.179) | 0.764 (0.236) | 0.803 (0.170) | 0.847 (0.176) |
| Change from baseline | | | | |
| Number | 88 | 34 | 156 | 101 |
| Mean (SD) | 0.054 (0.156) | 0.128 (0.203) | 0.034 (0.147) | 0.048 (0.165) |
| LS mean (SE) | 0.085 (0.025) | 0.129 (0.030) | 0.042 (0.014) | 0.074 (0.016) |
| LS mean diff (95% CI) | NA | 0.044 (−0.016, 0.103) | NA | 0.032 (−0.001, 0.064) |
| p value vs. placebo | NA | 0.1506 | NA | 0.0589 |
| **Week 52** | | | | |
| *Responders at Week 24 AND Week 52* | | | | |
| Number | 1 | 24 | 2 | 43 |
| Mean (SD) | 0.873 (NC) | 0.853 (0.187) | 0.882 (0.013) | 0.904 (0.153) |
| Change from baseline | | | | |
| Number | 1 | 24 | 2 | 43 |
| Mean (SD) | 0.072 (NC) | 0.184 (0.264) | 0.085 (0.019) | 0.132 (0.212) |
| LS mean (SE) | 0.151 (0.154) | 0.184 (0.040) | 0.091 (0.087) | 0.145 (0.022) |
| LS mean diff (95% CI) | NA | 0.033 (−0.277, 0.342) | NA | 0.054 (−0.121, 0.229) |
| p value vs. placebo | NA | 0.8370 | NA | 0.5432 |
| *Non-responders at Week 24 AND Week 52* | | | | |
| Number | 41 | 7 | 74 | 22 |
| Mean (SD) | 0.770 (0.212) | 0.634 (0.400) | 0.781 (0.226) | 0.797 (0.265) |
| Change from baseline | | | | |
| Number | 41 | 7 | 74 | 22 |
| Mean (SD) | 0.073 (0.171) | 0.032 (0.058) | 0.026 (0.190) | 0.014 (0.103) |
| LS mean (SE) | 0.081 (0.034) | 0.039 (0.067) | 0.017 (0.022) | 0.007 (0.037) |
| LS mean diff (95% CI) | NA | −0.042 (−0.170, 0.086) | NA | −0.009 (−0.086, 0.067) |
| p value vs. placebo | NA | 0.5199 | NA | 0.8091 |
| *Non-responders at Wek 24 OR Week 52* | | | | |
| Number | 44 | 14 | 80 | 38 |
| Mean (SD) | 0.774 (0.207) | 0.743 (0.318) | 0.791 (0.222) | 0.845 (0.224) |
| Change from baseline | | | | |
| Number | 44 | 14 | 80 | 38 |
| Mean (SD) | 0.075 (0.168) | 0.124 (0.217) | 0.033 (0.187) | 0.051 (0.163) |
| LS mean (SE) | 0.087 (0.032) | 0.115 (0.048) | 0.021 (0.022) | 0.051 (0.029) |
| LS mean diff (95% CI) | NA | 0.028 (−0.071, 0.128) | NA | 0.031 (−0.034, 0.096) |
| p value vs. placebo | NA | 0.5752 | NA | 0.3569 |

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
* SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement).
Source: Sanofi. Data on File, Post-hoc analyses.[8]

# Patients with comorbid asthma and SNOT-22 total score ≥50

## Baseline characteristics

Baseline demographics of the updated sensitivity analysis subgroup population (i.e., patients with comorbid asthma and baseline SNOT-22 total score ≥50) were consistent with those of the previous population (i.e., patients with ≥1 prior sinus surgery), with a majority of Caucasian and non-Latino individuals and a mean age ~50 years (Table 23). Baseline disease characteristics of the updated population were representative of a population with slightly more severe disease compared with those of the previous population, with a higher rate of SCS use in the past 2 years, generally worse disease measures and a higher proportion of comorbid NSAID-ERD.

*Table 23. Baseline characteristics of patients with comorbid asthma and baseline SNOT-22 total score ≥50 in SINUS-24 and SINUS-52 pooled ITT population vs. previous base-case population*

| | **Updated sensitivity analysis subgroup: Patients with comorbid asthma and SNOT-22 ≥50** | | **Previous population: Patients with ≥1 prior sinus surgery** | |
|---|---|---|---|---|
| | **Placebo** | **Dupilumab pooled doses** | **Placebo** | **Dupilumab pooled doses** |
| N | 103 | 143 | 187 | 272 |
| Male, n (%) | 43 (41.7) | 65 (45.5) | 103 (55.1) | 165 (60.7) |
| Age, mean (SD) | 49.00 (12.50) | 51.51 (11.79) | 50.97 (13.16) | 51.66 (12.23) |
| Race, n (%) | | | | |
| Caucasian/White | 92 (89.3) | 126 (88.1) | 170 (90.9) | 239 (87.9) |
| Black/African decent | 5 (4.9) | 3 (2.1) | 4 (2.1) | 3 (1.1) |
| Asian/Oriental | 5 (4.9) | 6 (4.2) | 12 (6.4) | 25 (9.2) |
| American Indian/Alaska Native | 1 (1.0) | 6 (4.2) | 1 (0.5) | 4 (1.5) |
| Native Hawaiian/Other Pacific Islander | 0 | 0 | 0 | 0 |
| Multiple | 0 | 1 (0.7) | 0 | 1 (0.4) |
| Unknown | 0 | 1 (0.7) | 0 | 0 |
| Ethnicity | | | | |
| Hispanic or Latino | 17 (16.7) | 36 (25.2) | 14 (7.6) | 33 (12.2) |
| Not Hispanic or Latino | 85 (83.3) | 107 (74.8) | 171 (92.4) | 238 (87.8) |
| Territory | | | | |
| North America | 20 (19.4) | 25 (17.5) | 27 (14.4) | 53 (19.5) |
| European Union | 37 (35.9) | 43 (30.1) | 82 (43.9) | 100 (36.8) |
| Rest of the World | 46 (44.7) | 75 (52.4) | 78 (41.7) | 119 (43.8) |
| BMI (kg/m$^2$), mean (SD) | 28.14 (6.16) | 27.99 (5.41) | 27.70 (5.46) | 27.54 (5.20) |
| Time since first diagnosis of nasal polyps (years), mean (SD) | 11.74 (8.91) | 11.21 (8.55) | 13.75 (9.16) | 14.51 (9.93) |
| ≥3 previous surgeries for nasal polyps, n (%) | 24 (23.3) | 27 (18.9) | 47 (25.1) | 64 (23.5) |
| Time since most recent surgery for nasal polyps (years), mean (SD) | 6.75 (5.78) | 6.50 (5.06) | 7.06 (6.33) | 7.22 (6.52) |
| SCS use in the past 2 years, n (%) | 82 (79.6) | 117 (81.8) | 118 (63.1) | 174 (64.0) |
| Bilateral endoscopic NPS* (scale 0-8), mean (SD) | 5.94 (1.31) | 6.26 (1.23) | 5.74 (1.27) | 5.94 (1.26) |
| NC score* (scale 0-3), mean (SD) | 2.63 (0.46) | 2.64 (0.47) | 2.47 (0.53) | 2.42 (0.59) |
| SNOT-22 total score* (scale 0-110), mean (SD) | 69.67 (14.70) | 66.50 (11.75) | 53.47 (19.92) | 50.35 (20.32) |
| Smell test (UPSIT) score** (scale 0-40), mean (SD) | 11.87 (6.51) | 11.89 (6.81) | 13.01 (7.46) | 12.65 (7.57) |

| | Updated sensitivity analysis subgroup: Patients with comorbid asthma and SNOT-22 ≥50 | | Previous population: Patients with ≥1 prior sinus surgery | |
|---|---|---|---|---|
| | Placebo | Dupilumab pooled doses | Placebo | Dupilumab pooled doses |
| LoS score* (scale 0-3), mean (SD) | 2.88 (0.30) | 2.84 (0.46) | 2.77 (0.48) | 2.80 (0.55) |
| LMK-CT total score* (scale 0-24), mean (SD) | 19.59 (3.50) | 19.52 (3.34) | 19.16 (4.10) | 19.01 (3.89) |
| Rhinosinusitis disease severity* (VAS 0-10cm), mean (SD) | 8.96 (1.20) | 8.52 (1.61) | 8.10 (2.00) | 7.92 (2.00) |
| Baseline NPIF** (L/min), mean (SD) | 73.09 (46.92) | 78.45 (53.74) | 87.68 (55.43) | 90.44 (58.74) |
| Baseline blood eosinophils (x$10^9$ cells/L), mean (SD) | 0.52 (0.320 | 0.56 (0.44) | 0.46 (0.32) | 0.47 (0.39) |
| Any comorbid type 2 medical history including asthma and NSAID-ERD, n (%) | 103 (100) | 143 (100) | 154 (82.4) | 232 (85.3) |
| Comorbid asthma, n (%) | 103 (100) | 143 (100) | 121 (64.7) | 183 (67.3) |
| Comorbid NSAID-ERD, n (%) | 47 (45.6) | 61 (42.7) | 65 (34.8) | 94 (34.6) |
| Any comorbid type 2 medical history excluding asthma and NSAID-ERD, n (%) | 74 (71.8) | 100 (69.9) | 117 (62.6) | 177 (65.1) |
| Age of asthma onset in patients with comorbid asthma (years), mean (SD) | 33.20 (15.31) | 36.64 (15.58) | 32.91 (14.88) | 34.68 (15.53) |
| Baseline ACQ-6 score* in patients with comorbid asthma, mean (SD) | 1.97 (1.12) | 1.90 (1.15) | 1.59 (1.06) | 1.48 (1.10) |
| Baseline GINA 4 or 5 in patients with comorbid asthma, n (%) | 48 (46.6) | 43 (30.1) | 57 (30.5) | 64 (23.5) |

ACQ-6 = 6-item Asthma Control Questionnaire; BMI = body mass index; ERD = exacerbated respiratory disease; GINA = Global Initiative for Asthma; ITT = intention-to-treat; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; NC = nasal congestion/obstruction; NPIF = peak nasal inspiratory flow; NPS = nasal polyp score; NSAID = non-steroidal anti-inflammatory drug; Q2W = every 2 weeks; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analogue scale

* Higher scores indicate greater disease severity.

** Higher scores indicate lower disease severity.

Source: Sanofi. Data on File, Post-hoc analyses.[8]

## NPS and SNOT-22 score

NPS and SNOT-22 score endpoints were successfully met in patients with comorbid asthma and baseline SNOT-22 total score ≥50 in the pooled ITT population; results are summarised in Table 24.

*Table 24. Summary of primary and key secondary endpoint results in patients with comorbid asthma and baseline SNOT-22 total score ≥50 in SINUS-24 and SINUS-52 pooled ITT population*

| Endpoint | Placebo (N=103) | | Dupilumab (N=143) | | |
|---|---|---|---|---|---|
| | Mean (SD) | LS mean change from baseline (SE) | Mean (SD) | LS mean change from baseline (SE) | LS Mean difference vs. placebo (95% CI; p-value) |
| Bilateral NPS | 6.089 (1.185) | 0.118 (0.196) | 4.058 (2.127) | −2.284 (0.188) | −2.402 (−2.785, −2.019; p<0.0001) |
| SNOT-22 score | 54.698 (23.021) | −14.085 (2.656) | 27.184 (20.022) | −40.069 (2.536) | −25.984 (−31.143, −20.825; p<0.0001) |

CI = confidence interval; ITT = intention-to-treat; LMK-CT = Lund-Mackay computed tomography; LoS = loss-of-smell; NC = nasal congestion/obstruction; NPS = nasal polyp score; SD = standard deviation; SE = standard error; SNOT-22 = 22-item Sino-Nasal Outcome Test; TSS = total symptom score; UPSIT = University of Pennsylvania Smell Identification Test

Sources: Sanofi. Data on File, Post-hoc analyses.

## EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs)

*Table 25. EQ-5D-5L utilities (Hernandez 2020 crosswalk method, UK tariffs) in patients with comorbid asthma and baseline SNOT-22 total score ≥50 in SINUS-24 and SINUS-52 ITT pooled population according to the response criteria of SNOT-22 total score (total score <50 or ≥8.9-point improvement) and NPS (≥1-point improvement) vs. previous base-case population*

| | **Updated sensitivity analysis subgroup: Patients with comorbid asthma and SNOT-22 ≥50** | | **Previous population: Patients with ≥1 sinus surgery; previous response criteria*** | |
|---|---|---|---|---|
| | **Placebo (N=103)** | **Dupilumab Q2W (N=143)** | **Placebo (N=187)** | **Dupilumab Q2W (N=272)** |
| **Baseline** | | | | |
| *All* | | | | |
| Number | 101 | 140 | 184 | 446 |
| Mean (SD) | 0.697 (0.205) | 0.697 (0.197) | 0.776 (0.176) | 0.782 (0.184) |
| *Responders at Week 24* | | | | |
| Number | 7 | 99 | 20 | 153 |
| Mean (SD) | 0.700 (0.168) | 0.731 (0.173) | 0.820 (0.113) | 0.775 (0.183) |
| *Non-responders at Week 24* | | | | |
| Number | 94 | 41 | 164 | 109 |
| Mean (SD) | 0.697 (0.208) | 0.615 (0.230) | 0.771 (0.182) | 0.801 (0.198) |
| **Week 24** | | | | |
| *All* | | | | |
| Number | 95 | 138 | 176 | 254 |
| Mean (SD) | 0.742 (0.213) | 0.816 (0.191) | 0.815 (0.168) | 0.872 (0.153) |
| Change from baseline | | | | |
| Number | 95 | 138 | 176 | 254 |
| Mean (SD) | 0.049 (0.143) | 0.118 (0.161) | 0.040 (0.147) | 0.088 (0.176) |
| LS mean (SE) | 0.059 (0.019) | 0.133 (0.018) | 0.045 (0.012) | 0.101 (0.011) |
| LS mean diff (95% CI) | NA | 0.074 (0.037, 0.111) | NA | 0.056 (0.031, 0.082) |
| p value vs. placebo | NA | <0.0001 | NA | <0.0001 |
| *Responders at Week 24* | | | | |
| Number | 7 | 98 | 20 | 153 |
| Mean (SD) | 0.794 (0.116) | 0.855 (0.142) | 0.912 (0.104) | 0.888 (0.134) |
| Change from baseline | | | | |
| Number | 7 | 98 | 20 | 153 |
| Mean (SD) | 0.094 (0.189) | 0.123 (0.162) | 0.092 (0.139) | 0.113 (0.179) |
| LS mean (SE) | 0.076 (0.048) | 0.159 (0.022) | 0.121 (0.005) | 0.120 (0.002) |
| LS mean diff (95% CI) | NA | 0.083 (-0.017, 0.184) | NA | −0.001 (−0.010, 0.008) |
| p value vs. placebo | NA | 0.1022 | NA | 0.8479 |
| *Non-responders at Week 24* | | | | |
| Number | 88 | 40 | 156 | 101 |
| Mean (SD) | 0.737 (0.219) | 0.718 (0.253) | 0.803 (0.170) | 0.847 (0.176) |
| Change from baseline | | | | |

| | **Updated sensitivity analysis subgroup: Patients with comorbid asthma and SNOT-22 ≥50** | | **Previous population: Patients with ≥1 sinus surgery; previous response criteria*** | |
|---|---|---|---|---|
| | **Placebo (N=103)** | **Dupilumab Q2W (N=143)** | **Placebo (N=187)** | **Dupilumab Q2W (N=272)** |
| Number | 88 | 40 | 156 | 101 |
| Mean (SD) | 0.045 (0.139) | 0.105 (0.161) | 0.034 (0.147) | 0.048 (0.165) |
| LS mean (SE) | 0.064 (0.024) | 0.113 (0.030) | 0.042 (0.014) | 0.074 (0.016) |
| LS mean diff (95% CI) | NA | 0.049 (-0.006, 0.103) | NA | 0.032 (−0.001, 0.064) |
| p value vs. placebo | NA | 0.0798 | NA | 0.0589 |
| **Week 52** | | | | |
| *Responders at Week 24 AND Week 52* | | | | |
| Number | 0 | 23 | 2 | 43 |
| Mean (SD) | NA | 0.858 (0.179) | 0.882 (0.013) | 0.904 (0.153) |
| Change from baseline | | | | |
| Number | 0 | 23 | 2 | 43 |
| Mean (SD) | NA | 0.152 (0.261) | 0.085 (0.019) | 0.132 (0.212) |
| LS mean (SE) | NE | 0.132 (0.040) | 0.091 (0.087) | 0.145 (0.022) |
| LS mean diff (95% CI) | NA | NE | NA | 0.054 (−0.121, 0.229) |
| p value vs. placebo | NA | NE | NA | 0.5432 |
| *Non-responders at Week 24 AND Week 52* | | | | |
| Number | 45 | 11 | 74 | 22 |
| Mean (SD) | 0.722 (0.245) | 0.617 (0.323) | 0.781 (0.226) | 0.797 (0.265) |
| Change from baseline | | | | |
| Number | 45 | 11 | 74 | 22 |
| Mean (SD) | 0.052 (0.171) | 0.065 (0.129) | 0.026 (0.190) | 0.014 (0.103) |
| LS mean (SE) | 0.056 (0.034) | 0.069 (0.058) | 0.017 (0.022) | 0.007 (0.037) |
| LS mean diff (95% CI) | NA | 0.013 (−0.102, 0.127) | NA | −0.009 (−0.086, 0.067) |
| p value vs. placebo | NA | 0.8301 | NA | 0.8091 |
| *Non-responders at Wek 24 OR Week 52* | | | | |
| Number | 51 | 19 | 80 | 38 |
| Mean (SD) | 0.738 (0.236) | 0.724 (0.293) | 0.791 (0.222) | 0.845 (0.224) |
| Change from baseline | | | | |
| Number | 51 | 19 | 80 | 38 |
| Mean (SD) | 0.064 (0.171) | 0.106 (0.140) | 0.033 (0.187) | 0.051 (0.163) |
| LS mean (SE) | 0.074 (0.030) | 0.112 (0.045) | 0.021 (0.022) | 0.051 (0.029) |
| LS mean diff (95% CI) | NA | 0.038 (-0.054, 0.131) | NA | 0.031 (−0.034, 0.096) |
| p value vs. placebo | NA | 0.4191 | NA | 0.3569 |

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ITT = intention-to-treat; LS = least squares; NA = not applicable; NE = not evaluable; NP = nasal polyp; NPS = nasal polyp score; Q2W = once every two weeks; SD = standard deviation; SE = standard error; SNOT-22: 22-item Sino Nasal Outcome Test
* SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement).
Source: Sanofi. Data on File, Post-hoc analyses.[8]

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**Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on **Wednesday 13 August**. Please submit via NICE Docs.

| | |
|---|---|
| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Sinus UK CIC |

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| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | None |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| 1 | We welcome the Committee's conclusion that "CRSwNP is a distressing condition with a serious impact on people's lives". |
| 2 | We accept there are "uncertainties in the economic model" and that this needs to be reevaluated. We would challenge some of the assumptions that the EAG has made to populate the ICER in their submission. |

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|---|---|
| | We feel a health utility value for CRSwNP of approximately 0.73, as proposed by the EAG, does not accurately represent the significant impact on quality of life that we know CRSwNP has, nor does it reflect the Committee's conclusion that this is a "distressing condition with a serious impact on people's lives".<br><br>We would like to see the ICER better reflect the true impact of CRSwNP with the hope that this would give a cost per QALY that would allow Dupilumab to be available on the NHS. A treatment we feel could be of huge benefit to many patients. |

Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

**Note:** We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Fifth Sense (operating as SmellTaste) |

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| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | None |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | It is positive that the NICE appraisal committee has understood and recognised that severe Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) has a serious impact on people's lives, that there is lack of effective treatment options for CRSwNP and a need for an effective, targeted treatment. The Committee also concluded that Dupilumab is an effective treatment. However, the |

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| | Committee's recommendation not to approve Dupilumab leaves the group of patients with a clear unmet need – the 10% of patients for whom endoscopic sinus surgery does not provide lasting relief from symptoms, due to the continued regrowth of polyps – without any solution to the ongoing problems they face. Dupilumab offers a lifeline to this group of patients, and if it is not approved then the status quo for them will continue, with ongoing poor quality of life, continued reliance on oral corticosteroids and the associated side-effects of these, and long waiting times for follow-up surgeries and continued use of/reliance on primary care. |
| 2 | In our view, the severe and ongoing impact on this 10% of patients is not being fully captured in the quality of life calculations that are informing the Committee's decision not to approve the drug.<br><br>A big part of the reason for this is because NICE's preferred tool for capturing health-related quality of life, the Eq5d, does not adequately capture the impact of CRSwNP. For many people with CRSwNP, the 'mobility' and 'self-care' domains of the tool aren't likely to be factors. Also, as some of the patients we engaged with pointed out, people's responses in the 'usual activities' domain may also not represent the true impact because they have been living with the condition for a long time (in many cases, years) and have become used to it – or, more accurately, resigned to it. In addition, some of the wide-ranging quality-of-life impacts of the disease, particularly smell loss and the myriad ways this impacts on people's lives, are not readily captured by the Eq5d's five domains.<br><br>This was supported by both the Clinical and Patient Experts at the Committee meeting, who agreed that the SNOT-22 is a much better measure of quality of life for this disease. Most of the CRSwNP patients we surveyed as part of our evidence submission also felt that the Eq5d did not adequately capture the impact of their disease.<br>The Committee acknowledges the lack of sensitivity of the Eq5d and the points made by the Clinical and Patient Experts in the draft guidance, but is still basing its recommendations on the data from this tool. Whilst we understand why NICE chooses to use the Eq5d to give a comparator for quality of life between different diseases, surely there needs to be some flexibility for diseases like this when the Eq5d is much less effective. In this appraisal, the data from Eq5d appears to one of the main reasons for the Committee's recommendation not to approve the drug, and it is patients who are being disadvantaged as a result.<br>• Can the Committee follow up on its acknowledgement of the lack of sensitivity of the Eq5d in this appraisal and consider using data generated from SNOT-22 so that patients are not disadvantaged due to the limitations of the Eq5d?<br>• Can the Committee also consider data that is focused only on the 10% of patients most 'at need' and use this to inform the calculations used in the economic model? |
| 3 | Further to the above, we would also like to ensure that the following benefits of Dupilumab are being taken into account in terms of how it can help address the following issues that affect both patients and also the UK health system:<br><br>1. The ongoing financial burden experienced by this 10% of patients, sometimes over the course of years, in trying to manage the symptoms of the disease that they are unable to access effective long-term treatment for, including repeat prescriptions, over the counter medicines, travel costs associated with medical appointments and, sometimes, the costs of private treatment that some patients tell us they seek out of desperation to get a resolution or to avoid long waiting times.<br>2. The costs to the NHS of this ongoing cycle of these patients through the health system.<br>3. The lack of recognition of the significant quality of life impact of CRSwNP (including the impact of smell loss) by GPs (something frequently reported to us by patients; see patient |

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| | comments below) which make it hard for some people to get a referral to an ENT specialist or indeed any sort of treatment at all.<br>4. Waiting times of up to two years for sinus surgery which means many patients are reliant on primary care and self-care for lengthy periods (see point 1). On this point, the National Elective Care Programme Team at NHS England are looking at Ear Nose & Throat services, on behalf of the Cabinet Office, as part of ambitions laid out in the NHS 10-year plan to address waiting lists for hospital and community care, within which ENT waiting lists rank among the highest. SmellTaste is involved in this initiative via our relationship with ENT UK. Approving Dupilumab for the 10% most 'at need' CRSwNP patients therefore has the potential to reduce waiting times and hence support a key government policy objective. |
| 4 | One of the Clinical Experts suggested in the Committee meeting, as recorded in the draft guidance, that a clear approval criteria and process be put in place that will ensure that only patients who meet these criteria (i.e. those most 'at need' as outlined above) can be prescribed the drug at a limited number of specialist rhinology clinics. We would support such an approach, if it enabled those most at-need patients to get access to the drug. |
| 5 | In our evidence submission we highlighted an equality issue: *We believe there is a health inequality in relation to Dupilumab, where patients with severe CRSwNP who also have severe asthma with type 2 inflammation are able to be prescribed the drug on the basis of their asthma, but patients with severe CRSwNP alone, or less severe asthma, are currently unable to be prescribed it.*<br><br>It appears that this has been referenced in the draft guidance as follows:<br>*Some stakeholders suggested that recommending dupilumab was likely to reduce inequalities by providing access to a targeted biological treatment for people with severe CRSwNP, which has already been recommended by NICE for other chronic type 2 inflammatory conditions such as severe asthma and atopic dermatitis. Because its recommendations do not restrict access to treatment for some people over others, the committee agreed that these were not potential equality issues.*<br><br>We would like to clarify our point for the committee so they can give it due consideration. CRSwNP is a co-morbidity of severe asthma with type 2 inflammation. Therefore, NHS England patients with *both* diseases who meet the qualifying criteria for Dupilumab to treat their asthma, and are prescribed this by a respiratory consultant, will benefit twice as the drug will also treat their CRSwNP. However, as things stand, those patients 'unfortunate' enough to *only* have severe CRSwNP – no matter how severe this is – are unable to be prescribed Dupilumab, and therefore get not benefit at all. This doesn't seem equal, or fair. It also highlights wider issues around patient access to medicines with multiple indications due to the way the NHS prices medicines. |
| 6 | These are comments from some of our beneficiaries in direct response to the draft guidance:<br><br>**Comment 1**<br>"From a personal viewpoint surgery is an expensive waste of time and resources. None of my 5 surgeries has worked and each time the consultant has said he cannot remove all polyps for fear of damaging the olfactory nerve.<br>Quality of life is key to me. I have been without smell or taste for 45 years and I once read that this condition is like permanently living in a vacuum. Having a key sense taken away means isolation from many pleasures of life with family and friends, and a nagging doubt that dangerous chemicals, gases etc. will not be detected.<br>What really frustrates me about the NICE decision is that I am left with no alternative. The one treatment that restores my smell and taste is steroid injections, admittedly for up to 3 months only, but it is better than nothing. However, my GPs over the last 40 years will not prescribe these due to "side effects".<br>A drug such as Dupilumab is, therefore, much more important and it is so frustrating that the NHS is refusing me one treatment and NICE is refusing me an alternative." |

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| | |
|---|---|
| | **Comment 2**<br>"I have had Polyps removed and full corrective surgery for Chronic rhinosinusitis back at the beginning of last year. I take 24 drops of Fluticasone everyday to prevent further recurring polypoidal build up together with twice daily asthma steroid inhalers to keep at bay the progression of type 2 inflammatory disease which is the root cause of CRSwNP. The most effective treatment known would be Dupilumab! I have this information from two highly regarded professors in this field who work within our NHS. They have both told me this drug would prevent further deterioration and more frequent cycles of oral steroids which have such negative side effects in bone health to name one of them.<br>I have suffered with loss of smell and believe that to underestimate the effect that the loss of this has on a persons quality of life is almost discriminatory! how can the loss of one of our senses be considered ok? I have had two instances at home when I did not notice a fire starting within the home. Firstly, the shock and how you are effected by the realisation that your house could have burned down and secondly the constant reminder whilst in this smell free bubble of the life you are missing.<br>Furthermore, if this is combined with loss of taste things become very miserable indeed I am sure. What more would anyone want in life than to smell the seaside, cut grass and taste some fresh fruit."<br><br>**Comment 3**<br>"I am pretty devastated to learn that unless I can have access to Dupilumab there is little that can be done for my CRSwNP and my lack of smell & taste.<br>The only option available to me now would be a repeated course of corticosteroids, and then a maintenance dose ongoing.<br>Having looked at the document and the committee discussion, I can only say that I am happy that all the points seem to have been raised, so I just wish to reiterate how debilitating this condition can make you feel. To have no smell is extremely distressing as it is an isolating and debilitating condition which excludes you from certain social situations and interactions, and, as was discussed, is dangerous. I have experienced situations where I have consumed foodstuffs that I had not realised did not smell right as I had no way of detecting this, and it was only pointed out to me after I had eaten (sour milk - which was in date - on my cereals is just one example). Also a pan had boiled dry and I did not realise as I could not smell it.<br>The sense of disappointment that I feel cannot be overstated. My sleep is affected, and I feel tired and fatigued. I suffer from asthma and COPD, along with other things, and to know that there is a drug available that could control this condition without the use of steroids, and is being used in 30 countries already, is extremely frustrating. It just does not feel fair. How ill do you have to be before these drugs are available to us? When I see all the newsfeed on the drugs now available on the NHS for people that are overweight, I feel even more aggrieved. Why not us??<br>As discussed, the option of using corticosteroids as a long term treatment is a really difficult choice to make. For me, I feel it is a trade off, given the nasty side effects of these drugs. What is more important - perhaps getting some smell back (not by any means a definitive result) weighed up against the possibility of bone and skin thinning - fractures, spine collapse, lack of mobility, maybe even winding up in a wheelchair? Added to this, the possibility of diabetes, obesity and blood pressure issues - none of which I have at the moment. The prognosis if I decide to not continue with the corticosteroids is that my polyps will grow back and eventually I will not be able to breathe through my nose. What sort of decision is this to have to make?"<br><br>**Comment 4**<br>"Knowing how losing my sense of smell has completely affected many facets of my life over the last fifteen years, the benefits of Dupilumab would be life changing. However, it is always difficult to quantify what this actually means. So, to give one example, I read an article in the Metro about an astronaut on the ISS drinking coffee. Apparently, in taking food and drink on the ISS because of the environment they would use a straw, so they didn't smell the food or drink. Anyway, the |

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| | |
|---|---|
| | article stated that they had found a way of drinking coffee without a straw so the astronaut could smell the coffee before they tasted it. When asked about the new experience the astronaut said by smelling the coffee beforehand improved the experience by 70%! For obvious reasons, I found this article hit a nerve with me, and if this was the impact for simply drinking coffee, then just imagine what the impact would be if we could smell everything again, it would be like winning the lottery!<br>I was at the women's golf last weekend at Royal Porthcawl, and whilst it was it was good, I wished I could smell the sea, sand dunes etc. so essentially one dimension of the experience was missing!"<br><br>**Comment 5**<br>"I have CRSwNP and no sense of smell. I understand it's hard to quantify quality of life but I would give anything to get my sense of smell back and not go through packs of tissues each week!<br>I wondered if NICE has considered the expensive ineffective medication that people like me use (budesonide for nasal rinse) that Dupilumab would replace, therefore making it more cost effective especially when you consider the long waiting lists for ENT appts and many failed operations that are also costly.<br>I'm not sure if my comments help but wanted to help in any way I can to be able to use something that could vastly improve my quality of life!"<br><br>**Comment 6 (from patient who is currently taking Dupilumab for CRSwNP)**<br><br>"I did just want to say regarding Dupilumab, in the beginning I was having an injection every 2 weeks but now it's every 6-8 weeks as I don't feel the need to have it so often anymore which is brilliant and if other patients having the medication got to the same place as me then that's a huge saving.<br>For most things there's a tablet or other medication or even pathways that people take and can have to relieve symptoms but with Chronic Sinus problems there are a lot of people that conventional medicines aren't enough and don't work, having had Chronic sinus problems and 2 operations which didn't work my life was miserable as I'm sure it is for other sufferers and it's all about quality of life and mental health which both are severely affected with this disease. I suffer with psoriasis and am under the hospital for it, oral medication, injections and light therapy are all available for this disease as is the same for a lot of diseases, Chronic Sinus problems are debilitating on a person and would improve someone's life tenfold and I think that's what needs to be looked at by the board that would approve this, I know cost comes into it and it is expensive but you can't put a cost on someone's well being." |

Insert extra rows as needed

**Checklist for submitting comments**

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Association of Respiratory Nurses |

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| **Name of commentator person completing form:** | [redacted] / ARNS |

| Comment number | Comments<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | I think more evidence may be needed, there is some limited data in severe asthma patients who have co-existing polyps and nasal issues who have seen benefit from this treatment. |
| 2 | In relation to clinical and cost effectiveness patients at the severe end of disease who are uncontrolled, and it is affecting their quality of life and have a significant symptom burden it would be more effective for than the general population. It would be extremely expensive to give to the general population. I think the summaries do acknowledge this. |
| 3 | There does not appear to be any concerns with the recommendations with regards to unlawful discrimination against any group of people however in practice there can be difference of opinions depending on geographic area and can depend on the speciality patients are under with regards to access due to funding for treatment. |

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

**Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]**

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** 5pm on **Wednesday 13 August**. Please submit via NICE Docs.

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Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

**Note:** We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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As  both an expert adviser to the HTA assessment, and as a specialist involved on a daily basis in the treatment of patients with recalcitrant, severe, chronic rhinosinusitis with nasal polyps, I am very disappointed by the outcome.

The background information presented to the Advisory Board failed to capture the severity that the disease has on the quality of life of many patients with nasal polyps. In addition, the background information underestimated the challenges that patients often face in receiving a timely diagnosis and appropriate care. Many patients are currently lost within primary care or within ENT units unequipped to offer comprehensive surgery. This creates a significant post code lottery for patients to even access the resource is currently available to them.

Whilst surgery provides significant short-term relief to many patients, in 30 to 50% the response is short-lived and symptoms recur as soon as six months after surgery. This means that a number of patients embark on a relentless merry go round of repeated surgeries and courses of oral corticosteroids until they get to a point when they simply give up, refusing to put themselves through another surgery that fails to provide any meaningful benefit. Approximately 10% of patients do not derive any significant improvement from surgery at all and risk osteoporosis, diabetes and other side effects from repeated short courses or long-term use of oral corticosteroids.

The importance of sense of smell from both a safety and mental health point of view has been completely overlooked by the advisory board, and is not captured by the EQ5D used to the calculate the ICER.

Having been involved in effectiveness trials for dupilumab and now using it for patients within private practise I have seen the dramatic impact on quality of life that use of this drug can achieve. It really is life changing for these patients

Whilst I understand the need for sensible use of health of limited healthcare resources, and the need for health economic analysis of cost effectiveness when considering new treatments, I feel that the Advisory Board failed to consider that there are a number of patients with nasal polyps for whom currently we simply have no effective treatment. In particular,  for patients with aspirin exacerbated respiratory disease, previously known as samter's triad, or those that have previously had multiple surgeries it seems unjust to consider only relative cost effectiveness when there simply is no other effective treatment. I believe that the Advisory Board should make exceptions to allow treatment for a small well-defined group of patients within specialist centres. This is an opportunity to optimise the whole treatment pathway for patients with nasal polyps, both reducing the need for revision surgeries (and therefore waiting lists) and improving outcomes.

We are one of only 2 European countries where there is no reimbursement for the use of biologics for selected patients with nasal polyps. While the currently available treatment option of comprehensive surgery should remain the preferred choice for patients uncontrolled with topical medications, when this has been shown to be ineffective, biologics offer the prospect of restoring quality of life. Sadly, UK patients are now uniquely being denied this opportunity.

# Single Technology Appraisal

## Dupilumab for treating severe chronic rhinosinusitis with nasal polyps [ID6480]
## Comments on the draft guidance received through the NICE website

| | |
|---|---|
| **Name** | [redacted] |
| **Organisation** | British Rhinological society |
| **Comments on the DG:** | |

On behalf of the British Rhinological Society, as its President, I write to express our disappointment and concern regarding the current draft recommendation from NICE not to approve Dupilumab for use in patients with chronic rhinosinusitis with nasal polyps (CRSwNP).

This recommendation is particularly disheartening for the multidisciplinary teams who manage these patients, and above all, for the patients themselves—many of whom live with severe, persistent symptoms despite maximal medical therapy and multiple surgeries. CRSwNP can significantly impair quality of life, affecting sleep, smell, mental health, and daily functioning. For a subset of patients with refractory disease, biologics like Dupilumab offer a much-needed alternative—one that is evidence-based, non-surgical, and aligned with modern precision medicine.

There is now a substantial and growing body of evidence—both from clinical trials and real-world outcomes—demonstrating that Dupilumab significantly improves symptom control, reduces polyp burden, enhances sense of smell, and decreases the need for repeated surgery and systemic steroids. These improvements are not marginal—they are often transformative for appropriately selected patients.

By declining to recommend Dupilumab for routine NHS use, there is a real risk of:

- Denying patients a proven and safe treatment option after exhausting conventional therapies
- Widening health inequality, as access becomes determined by postcode or private funding
- Increasing long-term costs due to repeated surgeries, steroid-associated comorbidities, and indirect societal burdens

We recognise the financial pressures on the NHS, but urge NICE to consider the long-term benefits of avoiding repeated interventions and improving quality of life in this high-burden condition. The UK is now an outlier in being one of the only countries in Europe where there is no reimbursement for use of biologics in treating the most severe patients with

CRSwNP who remain symptomatic despite previous surgery and maximal medical treatment.

The BRS stands ready to support any further dialogue, to provide expert clinical input, and to help refine criteria that ensure appropriate and cost-effective use of Dupilumab in carefully selected patients. We believe strongly that this treatment has a vital role in the multidisciplinary management of severe CRSwNP and that its rejection would represent a backward step in patient care.
We have previously created guidance to assist with identifying those patients who we believe would benefit most from access to biological therapies while considering the financial constraints facing the NHS and we would encourage NICE to consider access for at least a small, and easily defined group of patients, as set out in the guidance (https://onlinelibrary.wiley.com/doi/10.1111/coa.13779)

Kind regards

[redacted]
British Rhinological society

| **Name** | [redacted] |
|---|---|
| **Comments on the DG:** | |

As a GP and CRSwNP patient I endorse the below comments from SinusUK. I have recently been started on Tezepilumab for chronic asthma and this has helped my CRSwNP significantly and improved my QOL 100%. I am now able to exercise and work much more efficiently as my symptoms have improved so much. I have much more energy and my sleep and mood are better as a result. CRSwNP has a much greater impact on QOL than is generally understood.

We welcome the Committee's conclusion that "CRSwNP is a distressing condition with a serious impact on people's lives".

We accept there are "uncertainties in the economic model" and that this needs to be re-evaluated. We would challenge some of the assumptions that the EAG has made to populate the ICER in their submission.

We feel a health utility value for CRSwNP of approximately0.73, as proposed by the EAG, does not accurately represent the significant impact on quality of life that we know CRSwNP has, nor does it reflect the Committee's conclusion that this is a "distressing condition with a serious impact on people's lives".

We would like to see the ICER better reflect the true impact of CRSwNP with the hope that this would give a cost per QALY that would allow Dupilumab to be available on the NHS. A treatment we feel could be of huge benefit to many patients.

| Name | [redacted] |
|---|---|
| **Comments on the DG:** | |
| It is reassuring to read the Committee's conclusion that "CRSwNP is a distressing condition with a serious impact on people's lives".<br><br>I would challenge some of the assumptions that the EAG has made to populate the ICER in their submission.<br><br>I feel a health utility value for CRSwNP of approximately 0.73 does not accurately represent the significant impact on quality of life that we know CRSwNP has, nor does it reflect the Committee's conclusion that this is a "distressing condition with a serious impact on people's lives".<br><br>We would like to see the ICER better reflect the true impact of CRSwNP with the hope that this would give a cost per QALY that would allow Dupilumab to be available on the NHS. A treatment we feel could be of huge benefit to many patients.<br><br>Having lived with this condition for nearly 20 years (diagnosed 7 years ago) I am concerned that as I grow old I will still not be able to breathe through my nose and will still suffer from disrupted breathing patterns (asleep and awake) along with other health problems that may come with old age. My polyps returned after 6 months post surgery (6 years ago). It is not realistic to have surgery every time they grow back. Taking strong steroids impacts my mood and body so I avoid them even though I can't breathe through my nose at all. | |

| Name | [redacted] |
|---|---|
| **Comments on the DG:** | |
| I feel a health utility value for CRSwNP of approximately 0.73 proposed by the EAG, does not accurately represent the significant impact on quality of life that CRSwNP has.<br>It does not correlate with the Committee's conclusion that this is a "distressing condition with a serious impact on people's lives".<br><br>I request that the ICER better reflects the significant impact of CRSwNP. This would hopefully give a cost per QALY that would allow Dupilumab to be available on the NHS.<br>This treatment would be of huge benefit to many patients. The impact upon individuals from this condition must not be underestimated. | |

| Name | [redacted] |
|---|---|
| **Comments on the DG:** | |
| Has all of the relevant evidence been taken into account? | |

I believe a lot of sufferers suffer in silence due to the lack of GP knowledge. I really struggled to get referred to a specialist so it affects a lot more people than on record.

Are the recommendations sound and a suitable basis for guidance to the NHS?
This drug is available for this condition in most countries across the world

We feel a health utility value for CRSwNP of approximately0.73, as proposed by the EAG, does not accurately represent the significant impact on quality of life that we know CRSwNP has, nor does it reflect the Committee's conclusion that this is a "distressing condition with a serious impact on people's lives".
I for one have been suffering for 15 years am waiting for 3rd operation and just had 3rd course of steroids in 9 months. This impacts my daily life and mental health severely.

We would like to see the ICER better reflect the true impact of CRSwNP with the hope that this would give a cost per QALY that would allow Dupilumab to be available on the NHS. A treatment we feel could be of huge benefit to many patients including myself.

| **Name** | [redacted] |
|---|---|
| **Comments on the DG:** | |

I have been living with this condition for around 12 years now.
I was doagnosed and treated in UK.
I also suffer from asthma but because isnt severe i dont qualify for biologics.
Below is a list of how the condition is affecting me.

- 2 surgeries under general anesthesia for removing nasal polyps with long recoveries.
- sleepless nights due to difficulty in breathing from nose.
- Waking up with a dry throat as if someone filled my throat with sand
- feeling exhausted daily.
- permanent loss of smell and taste. - Not being able to enjoy food or smell when my kids need a nappy change.
- having to blow my nose constantly in order to get rid of mucus. Always geeting the looks especially in public places.
- picking my nose trying to get rid of crusty mucus.
- getting ill from common colds and not being able to recover unless taking antibiotics and oral steroids.
- time spent using medication, booking doctor appointments, getting prescription and trying to get rid of symtoms every day just so i can improve my quality of life.
-burden on family.

We welcome the Committee's conclusion that "CRSwNP is a distressing condition with a serious impact on people's lives".

We accept there are “uncertainties in the economic model” and that this needs to be re-evaluated. We would challenge some of the assumptions that the EAG has made to populate the ICER in their submission.

We feel a health utility value for CRSwNP of approximately 0.73, as proposed by the EAG, does not accurately represent the significant impact on quality of life that we know CRSwNP has, nor does it reflect the Committee’s conclusion that this is a “distressing condition with a serious impact on people’s lives”.

We would like to see the ICER better reflect the true impact of CRSwNP with the hope that this would give a cost per QALY that would allow Dupilumab to be available on the NHS. A treatment we feel could be of huge benefit to many patients.

Thank you

| **Name** | [redacted] |
|---|---|
| **Comments on the DG:** | |

1. I am pleased there is a clear acknowledgement that “CRSwNP is a distressing condition with a serious impact on people’s lives”.

2. I understand the process of the economic model but find it worrying that there are clear “uncertainties in the economic model” and that this needs to be re-evaluated. From my understanding and personal experience of CRSwNP the health utility value for CRSwNP of 0.73 proposed is not a true reflection of the disease and the impact on quality of life. It is a seemingly invisible and pervasive disease that is life long.

3. I would like to see the ICER better reflect the true impact of CRSwNP with the hope that this would give a cost per QALY that would allow Dupilumab to be available on the NHS.

4. Dupilumab would mean that this population would have access to an actual treatment for CRSwNP. Patients are currently having to fight for a range of medications, endure multiple surgeries over a life time which are only temporary symptom relievers. Many patients have co-ocuring conditions such as asthma which are impacted when CRSwNP is not adequately controlled, increasing the risk to life and further need for use of oral corticosteroids.

5. As stated I think it is positive that Dupilumab 'has already been recommended by NICE for other chronic type 2 inflammatory conditions such as severe asthma and atopic dermatitis' and I hope that considerations, further evidence and developments in the economic model will mean CRSwNP will be the next.

| Name | [redacted] |
|---|---|
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# Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

EAG response to draft guidance

August 2025

**Source of funding**

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 174243.

# 1 Introduction

Following the first appraisal committee meeting (ACM1) for dupilumab, the committee highlighted key areas of uncertainty in the economic model including the long-term effects of dupilumab, the number of people who will need subsequent surgery, the length of time waiting for subsequent surgery, and the estimation of quality of life.

In order to determine the most plausible ICER, the committee requested further evidence on the following:

- treatment effectiveness in the first year based on NPS and SNOT-22;
- evidence of treatment effectiveness beyond one year from the AROMA trial, formally matched to the SINUS trials.

The committee also noted their preferred assumptions for the following model inputs:

- utility values based on EQ-5D data from the SINUS trials;
- utility gain values from revision surgery based on Remenschneider *et al.* 2015;
- general population mortality based on the ONS life tables from 2017 to 2019;
- increased mortality and costs for people with asthma;
- the same post-revision surgery utility regardless of previous treatment;
- everyone able to self-administer dupilumab; and
- all surgery follow-up costs from Clarke *et al.* 2022 included.

Section 2 of this report provides the Evidence Assessment Group's (EAG's) response to the evidence supplied by the company in response to each of the committee's requests highlighted in the draft guidance. In addition, the EAG provides cost-effectiveness results of additional scenario analysis conducted by the EAG and updated EAG base case in Section 3.

# 2 EAG response

## 2.1 Updated population definition

The company's response highlights a change to their population from that originally reported in the CS. The population outlined by NICE in the scope was, 'People with previously treated severe chronic rhinosinusitis with nasal polyps (CRSwNP)', which the company defined based on the 2020 EPOS criteria, which is commonly used in clinical practice. The 2020 EPOS guidance defines uncontrolled disease as, *'symptoms of nasal blockage, discharge, facial pain/pressure, reduced sense of smell and sleep disturbance of >5 in addition to nasal endoscopy findings and the need for rescue medication'.*

The company and the EAG's clinical experts confirmed the above definition to be appropriate, and the population was not raised as an area of uncertainty by the committee. However, the company noted that clinicians at the committee meeting stated that severe disease can also be defined based on SNOT-22 score. The company supported this statement with evidence from Toma and Hopkins (2016),[1] which stratified disease severity based on SNOT-22, with scores of 8-20 reflecting mild disease, >20-50 reflecting moderate disease and >50 classed as severe disease. They also reported that severe disease is classified based on SNOT-22 scores ≥50 in Europe, providing the DUPIREAL study as an example where this threshold was used as part of the inclusion criteria.[2] Based on the above considerations, the company chose to update their population for the draft guidance response to, *'CRSwNP patients with severe, uncontrolled disease who have had at least 1 surgery and have a SNOT-22 score ≥50'*.

The EAG's clinical experts agreed that SNOT-22 scores greater than 50 can be used to indicate severe CRSwNP, although they also highlighted the importance of considering this alongside the EPOS criteria, rather than as a standalone threshold. This mirrors the inclusion criteria of some of the studies cited in the company response, where a combination of SNOT-22 scores and NPS were used to indicate severe disease.[2-4] The company's updated definition, therefore, appears to reflect one of the definitions used in clinical practice. However, the EAG notes that the updated definition excludes nearly half of the original population in the CS, with 230 of the original 459 patients (50.1%) included in the updated analysis. As such, the updated results are only applicable to those patients in clinical practice who are considered to have severe disease based on the company's updated definition, using a combination of the EPOS criteria and a SNOT-22 score of >50.

While the EAG considers the updated definition of the population not to be unreasonable, it has concerns about the updated results. Assignment to treatment groups in the SINUS-24 and SINUS-52 trials was not stratified by SNOT-22 score and, as such, the update to the definition of the population has resulted in the breaking of randomisation. In an attempt to mitigate the methodological concerns arising from breaking randomisation, the company reported the comparative baseline characteristics of the original and updated populations (Table 1). Differences in disease characteristics demonstrate a greater severity of disease in the updated population, including a higher percentage of patients with SCS use in the previous 2 years, higher SNOT-22 scores and a higher percentage of patients with comorbid asthma than in the original population. Population demographics were more similar between the two populations. The greatest differences between the two populations were seen for ethnicity (a higher percentage of Hispanic or Latino patients in the updated population) and sex (a higher percentage of males in the updated dupilumab arm than in the original population), but neither of these characteristics were considered to be treatment-effect modifiers by the EAG's clinical experts.

However, the EAG is concerned that breaking randomisation will have wider consequences that cannot be dismissed by apparently similar baseline characteristics in the treatment groups, such as unmeasured confounding. That is, unobserved confounding factors that are likely to be present and have an unknown influence on the comparative effectiveness.

Table 1. Comparisons of baseline characteristics between the original population in the CS and the updated population in the company's response (Reproduced from Table 21 of the company's response)

| | Updated population: Patients with ≥1 prior sinus surgery and SNOT-22 ≥50 | | Previous population: Patients with ≥1 prior sinus surgery | |
|---|---|---|---|---|
| | Placebo | Dupilumab pooled doses | Placebo | Dupilumab pooled doses |
| N | 101 | 129 | 187 | 272 |
| Male, n (%) | 53 (52.5) | 68 (52.7) | 103 (55.1) | 165 (60.7) |
| Age, mean (SD) | 49.98 (12.40) | 51.98 (11.29) | 50.97 (13.16) | 51.66 (12.23) |
| Race, n (%)<br>Caucasian/White<br>Black/African decent | <br>94 (93.1)<br>2 (2.0) | <br>115 (89.1)<br>2 (1.6) | <br>170 (90.9)<br>4 (2.1) | <br>239 (87.9)<br>3 (1.1) |

| | | | | |
|---|---|---|---|---|
| Asian/Oriental<br>American Indian/Alaska Native<br>Native Hawaiian/Other Pacific Islander<br>Multiple<br> | 4 (4.0)<br>1 (1.0)<br>0<br>0<br>0 | 8 (6.2)<br>3 (2.3)<br>0<br>1 (0.8)<br>0 | 12 (6.4)<br>1 (0.5)<br>0<br>0<br>0 | 25 (9.2)<br>4 (1.5)<br>0<br>1 (0.4)<br>0 |
| Ethnicity<br>Hispanic or Latino<br>Not Hispanic or Latino | <br>13 (13.0)<br>87 (87.0) | <br>21 (16.4)<br>107 (83.6) | <br>14 (7.6)<br>171 (92.4) | <br>33 (12.2)<br>238 (87.8) |
| Territory<br>North America<br>European Union<br>Rest of the World | <br>15 (14.9)<br>43 (42.6)<br>43 (42.6) | <br>23 (17.8)<br>45 (34.9)<br>61 (47.3) | <br>27 (14.4)<br>82 (43.9)<br>78 (41.7) | <br>53 (19.5)<br>100 (36.8)<br>119 (43.8) |
| BMI (kg/m$^2$), mean (SD) | 27.83 (5.49) | 27.90 (5.58) | 27.70 (5.46) | 27.54 (5.20) |
| Time since first diagnosis of nasal polyps (years), mean (SD) | 12.94 (8.85) | 13.20 (9.07) | 13.75 (9.16) | 14.51 (9.93) |
| ≥3 previous surgeries for nasal polyps, n (%) | 27 (26.7) | 33 (25.6) | 47 (25.1) | 64 (23.5) |
| Time since most recent surgery for nasal polyps (years), mean (SD) | 6.82 (5.93) | 6.80 (5.67) | 7.06 (6.33) | 7.22 (6.52) |
| SCS use in the past 2 years, n (%) | 73 (72.3) | 91 (70.5) | 118 (63.1) | 174 (64.0) |
| Bilateral endoscopic NPS* (scale 0-8), mean (SD) | 5.89 (1.25) | 6.12 (1.26) | 5.74 (1.27) | 5.94 (1.26) |
| NC score* (scale 0-3), mean (SD) | 2.66 (0.45) | 2.66 (0.46) | 2.47 (0.53) | 2.42 (0.59) |
| SNOT-22 total score* (scale 0-110), mean (SD) | 68.29 (13.86) | 67.83 (12.64) | 53.47 (19.92) | 50.35 (20.32) |
| Smell test (UPSIT) score** (scale 0-40), mean (SD) | 11.61 (6.08) | 11.43 (6.62) | 13.01 (7.46) | 12.65 (7.57) |
| LoS score* (scale 0-3), mean (SD) | 2.90 (0.29) | 2.87 (0.46) | 2.77 (0.48) | 2.80 (0.55) |
| LMK-CT total score* (scale 0-24), mean (SD) | 19.92 (3.65) | 19.60 (3.50) | 19.16 (4.10) | 19.01 (3.89) |
| Rhinosinusitis disease severity* (VAS 0-10cm), mean (SD) | 8.80 (1.29) | 8.72 (1.56) | 8.10 (2.00) | 7.92 (2.00) |
| Baseline NPIF** (L/min), mean (SD) | 75.53 (44.42) | 76.46 (51.84) | 87.68 (55.43) | 90.44 (58.74) |
| Baseline blood eosinophils (x10$^9$ cells/L), mean (SD) | 0.51 (0.32) | 0.54 (0.46) | 0.46 (0.32) | 0.47 (0.39) |
| Any comorbid type 2 medical history including asthma and NSAID-ERD, n (%) | 89 (88.1) | 118 (91.5) | 154 (82.4) | 232 (85.3) |
| Comorbid asthma, n (%) | 76 (75.2) | 97 (75.2) | 121 (64.7) | 183 (67.3) |
| Comorbid NSAID-ERD, n (%) | 41 (40.6) | 47 (36.4) | 65 (34.8) | 94 (34.6) |
| Any comorbid type 2 medical history excluding asthma and NSAID-ERD, n (%) | 66 (65.3) | 88 (68.2) | 117 (62.6) | 177 (65.1) |
| Age of asthma onset in patients with comorbid asthma (years), mean (SD) | 33.74 (13.90) | 35.98 (14.88) | 32.91 (14.88) | 34.68 (15.53) |

| | | | | |
|---|---|---|---|---|
| Baseline ACQ-6 score* in patients with comorbid asthma, mean (SD) | 1.82 (1.10) | 1.86 (1.13) | 1.59 (1.06) | 1.48 (1.10) |
| Baseline GINA 4 or 5 in patients with comorbid asthma, n (%) | 37 (48.7) | 35 (36.1) | 57 (30.5) | 64 (23.5) |

Abbreviations: ACQ-6, 6-item Asthma Control Questionnaire; BMI, body mass index; ERD, exacerbated respiratory disease; GINA, Global Initiative for Asthma; ITT, intention-to-treat; LMK-CT, Lund-Mackay computed tomography; LoS, loss-of-smell; NC, nasal congestion/obstruction; NPIF, peak nasal inspiratory flow; NPS, nasal polyp score; NSAID, non-steroidal anti-inflammatory drug; Q2W, every 2 weeks; SD, standard deviation; SNOT-22, 22-item Sino-Nasal Outcome Test; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analogue scale

* Higher scores indicate greater disease severity.

** Higher scores indicate lower disease severity.

The company provided comparisons of the change from baseline in SNOT-22 score and NPS between the original and updated populations (Table 2). The change in population did not affect the interpretation of the results, with statistically significantly greater improvements with dupilumab than placebo for both outcomes. The only notable difference between the two populations was seen for NPS, where the reduction in NPS score in the placebo arm was clinically meaningful in the original population, but did not exceed the threshold for a minimal clinically important difference (MCID) in the updated population. However, this may reflect the greater disease severity of the updated population.

Table 2. Comparisons of change from baseline NPS and SNOT-22 between the original population in the CS and the updated population in the company's response (Reproduced from Table 3 of the company's response)

| | Original population | | New population | |
|---|---|---|---|---|
| | Placebo (n=187) | Dupilumab (n=272) | Placebo (n=101) | Dupilumab (n=129) |
| **Change from baseline (responders at Week 24)** | | | | |
| NPS | | | | |
| Mean (SD) | −1.825 (1.173) | −2.961 (1.349) | 0.188 (0.964) | −2.285 (1.793) |
| LS Mean Diff vs. placebo (95% CI) | −1.141 (−1.242 to −1.041) | | −2.421 (−2.818 to −2.024) | |
| P-value vs. placebo | <0.0001 | | <0.0001 | |
| SNOT-22 | | | | |
| Mean (SD) | −24.550 (9.859) | −36.649 (19.608) | -14.755 (19.561) | -41.320 (22.687) |
| LS Mean Diff vs. placebo (95% CI) | −7.826 (−8.843 to −6.809) | | -27.105 (-32.307 to -21.903) | |
| P-value vs placebo | <0.0001 | | <.0001 | |

Abbreviations: CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; ECM, established clinical management; LS, least square; NPS, nasal polyp score; Q2W, once every two weeks; SD, standard deviation; SE, standard error; SNOT-22, 22-item Sino-Nasal Outcome Test

While the EAG does not have major concerns about the updated population used by the company, it notes the inconsistencies between the population and results in the original CS and those in the company's response. Results have not been reported for other outcomes in the CS, which may not be a major issue, given that NPS and SNOT-22 score were considered the most important outcomes by the EAG's clinical experts. However, the discrepancy between the two sets of results should be noted. A greater concern is the lack of results provided for some of the subgroups, such as patients with NSAID-ERD. The EAG's clinical experts discussed how these patients tend to have more severe disease and may therefore meet the company's updated criteria for severe CRSwNP.

The EAG notes that following draft guidance, a new economic model was submitted, which included updates to various parameters and only included the updated population. Therefore, the EAG did not have access to a model that included the new parameters and also an option to change between the original and updated population. All subsequent analyses have therefore been undertaken using the company's updated population. Therefore, the EAG consider that any recommendation based on the updated cost-effectiveness results would only be applicable to the updated subgroup of patients who meet the updated definition: "*CRSwNP patients with severe, uncontrolled disease who have had at least 1 surgery and have a SNOT-22 score ≥50".*

## 2.2 Updated response criteria

To align with the updates to the population, the company also updated its criteria used to assess a patient's response to treatment:

- Original definition: an improvement in SNOT-22 score of ≥8.9 points and improvement in NPS ≥1.
- Updated definition: SNOT-22 score <50 **or** an improvement in SNOT-22 score of ≥8.9 points and improvement in NPS ≥1.

The EAG's clinical experts did not consider the updated definition to align with how treatment response is assessed in clinical practice, instead preferring the original definition presented in the CS. They highlighted that there are other reasons, unrelated to the impact of treatment, which could cause someone's SNOT-22 score to fall below 50. They also noted how the reduction of 8.9 points is a more important indication of response to treatment, aligning with the clinically validated MCID presented in the CS.

The EAG considers that the change to the response criteria is likely to impact the results but does not appear to be justified or reflect clinical practice in the NHS. This is particularly important, given that the responder analysis forms part of the company's base case. A key concern is that the updated criteria may result in patients being classed as treatment responders despite experiencing only a small reduction in SNOT-22 score. For instance, a patient with a baseline SNOT-22 score of 51 would only require a reduction of 2 points to be considered as having responded to treatment. The same patient would not have been classed as a responder using the original criteria, as they did not report the required 8.9 point reduction in SNOT-22 score.

The company provided a comparison of results using the original and update response criteria (Table 3). A greater treatment effect was reported when using the updated response criteria, with a higher percentage of responders identified using the updated criteria. However, comparisons were only provided between the original criteria based on the original population (who had less severe disease) and the updated criteria based on the updated population (who had more severe disease). The EAG considers that a comparison of responders in the updated population, using the original and the updated response criteria, would have been more appropriate. Without this information, it is not possible to determine how many additional responders were identified as a result of the updated criteria. As such, the impact of using the updated response criteria in the economic model is unclear.

The results in Table 3 indicate that the change in both population and response criteria do not change the statistical significance of the results at weeks 24 and 52. However, the magnitude of the treatment effect is considerably greater with the use of the updated population and updated response criteria. In addition to the differences in treatment effect, the wide 95% CIs reported for the updated criteria mean that the magnitude of any benefits with dupilumab are uncertain.

Table 3. Comparisons of the response analysis between the original response criteria applied to the original population in the CS and the updated response criteria applied to the updated population in the company's response (Reproduced from Table 6 of the company's response)

| | Original base case: people with inadequately controlled CRSwNP AND ≥1 sinus surgery | | Updated base case: people with inadequately controlled CRSwNP AND ≥1 sinus surgery AND SNOT-22 ≥50 | |
|---|---|---|---|---|
| | **ECM** | **Dupilumab 300 mg Q2W** | **ECM** | **Dupilumab 300 mg Q2W** |
| Overall population response at Week 24 | | | | |
| | N=187 | N=272 | N=101 | N=129 |

| | | | | |
|---|---|---|---|---|
| Responders | [redacted] | [redacted] | [redacted] | [redacted] |
| Non-responders | [redacted] | [redacted] | [redacted] | [redacted] |
| OR vs placebo (95% CI) | [redacted] | | [redacted] | |
| P value vs placebo | <0.0001 | | <0.0001 | |
| Overall population: Response at Week 52 | | | | |
| | N=88 | N=88 | N=49 | N=40 |
| Responders | [redacted] | [redacted] | [redacted] | [redacted] |
| Non-responders | [redacted] | [redacted] | [redacted] | [redacted] |
| OR vs placebo (95% CI) | [redacted] | | [redacted] | |
| P value vs placebo | <0.0001 | | <0.0001 | |
| Subpopulation: Responders at Week 24 - Response at Week 52 | | | | |
| | N=5 | N=46 | N=1 | N=26 |
| Responders | [redacted] | [redacted] | [redacted] | [redacted] |
| Non-responders | [redacted] | [redacted] | [redacted] | [redacted] |
| OR, 95% CI vs placebo | NE (NE, NE) | | NE (NE, NE) | |
| P-value vs placebo | <0.0001 | | <0.0001 | |

Abbreviations: CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; ECM, established clinical management; ITT, intent-to-treat; NE, not evaluable; OR, odds ratio; Q2W, every 2 weeks; SNOT-22, 22-item Sino-Nasal Outcome Test

The company's updated population has resulted in even smaller numbers of patients available to inform response used in the first year decision tree of the economic model, as shown in Table 6 of the company's response. The EAG notes that this will have increased uncertainty in results. As an exploratory analysis, the EAG has applied the same responder rates as used in the company's original base case to explore the magnitude of the impact on the ICER (see Section 3).

Overall, while the EAG has some concerns about the breaking of randomisation required for the updated population, the new definition of patients with severe disease appears to reflect one of the definitions used in clinical practice. While both the original and updated definitions of the population and treatment response demonstrate statistically significant benefits of dupilumab over ECM, the magnitude of the treatment effect is considerably greater with the updated definitions. However, it is important to note that these results only apply to patients with the most severe disease based on the company's updated definition of the population (including the criteria for a SNOT-22 score >50). The EAG has greater concerns about the updated definition of treatment response, which does not appear to reflect clinical practice in the NHS. However, given that the company's response only presents results based on the updated criteria, the EAG's critique of these results are presented in the following sections, alongside its key concerns associated with the company's updated analysis.

## 2.3 Evidence to support the long-term effectiveness of dupilumab treatment used in the company's model

#### *2.3.1.1 Matching analysis*

In the absence of data beyond 52 weeks from the SINUS trials, data from the AROMA trial was used to provide evidence of longer-term effectiveness of dupilumab for patients with CRSwNP. While AROMA provided evidence for a relevant population, the committee were concerned about the lack of a comparator arm in the trial to allow comparisons with ECM. The lack of a comparator arm in AROMA meant that the ECM of the model was informed by the SINUS trials, resulting in a comparison between two different populations. The committee also noted that, while the company's model used a combination of NPS and SNOT-22 scores to define response, only SNOT-22 data was available from AROMA. To reduce concerns about the differences in population and methods of responder analysis, the committee requested that the treatment effect beyond the 52 weeks was based on AROMA data, but this should be formally matched to the SINUS trials.

In response to the committee's concerns, the company performed an exploratory matching exercise between the AROMA and SINUS populations. This appears to be based on applying propensity score weights to the AROMA population to better match those in the pooled SINUS-24 and SINUS-52 population. The company response states that the AROMA trial was weighted on the following characteristics:

- rate of prior SCS use;
- rate of comorbid NSAID-ERD;
- mean NC score; and
- mean SNOT-22 total scores.

The original analysis for AROMA included 691 patients, of which 639 remined in the study for over 24 months. Following adjustment of the AROMA population, the effective sample size was 512, which the EAG considers sufficiently large to provide robust estimates. The baseline characteristics of the adjusted AROMA population were largely similar to those of the SINUS trials. While there were some differences between the two groups, such as the percentage of white patients (89.1% in the SINUS trials compared to 72.2% in AROMA), none of the characteristics were identified by the EAG's clinical experts as potential treatment effect modifiers or prognostic factors.

While baseline characteristics appear to be similar between the two trials, the EAG has some concerns about the methodology used for the exploratory matching exercise. The AROMA trial did not report on NPS, which was identified by the EAG's clinical experts and in the CS as an important measure of disease severity and treatment response. It is therefore possible that there are underlying differences in disease severity between the two populations that could not be accounted for within the company's analysis. While patients were matched on NC score, the EAG's clinical experts noted that this is as a more variable measure of disease severity than NPS and is less commonly used in clinical practice. Nonetheless, the EAG consider that the baseline characteristics of the weighted population appear reasonable, but the lack of information for some measures of disease severity, and the possibility of unmeasured confounders that cannot be adjusted for, means that, despite the adjustments performed by the company, there could be some underlying differences between the two populations.

An additional source of uncertainty for the EAG is the choice of population from the SINUS trials against which the AROMA population was matched. As discussed in Section 2.1, the company chose to update the population to only include the patients who have more severe levels of disease, which only consists of around 50% of the previously defined severe population. However, the company chose to match the AROMA population to the original ITT population of the SINUS trials. The EAG considers that it would have been more appropriate to match AROMA to the updated population, as this is the population included in the company's updated base case. This is particularly important given that the company has demonstrated that the baseline disease characteristics differ between the original and updated populations. As such, there may be differences between the updated SINUS population and the re-weighted AROMA population that have not been accounted for by the company's matching exercise.

The EAG notes that the CS reported SNOT-22 scores for the AROMA trial, but similar results were not reported for the adjusted AROMA population. This would have provided a useful indication of the impact of re-weighting the AROMA population. Additionally, a comparison between the SNOT-22 scores from the SINUS trials and the first 12 months of the AROMA trial would have provided a further indication of how well the two populations were matched.

Although the company matched the AROMA population to the ITT population of the SINUS trials, the company reported the number of responders for the re-weighted AROMA population at each follow-up visit using both the original and the updated definitions of the population (Table 4). The EAG

notes that, while there are a relatively high number of patients during the first 12 months of the trial, where data is available from the SINUS trials, the number of patients is considerably lower beyond this point, particularly for the updated population at month 24. With the exception of month 6, the percentage of responders is similar between each analysis method, suggesting that the matching exercise had limited impact on the responder analysis in the company's base case. However, given the concerns about the lack of reporting of NPS for the AROMA trial, the matching of the AROMA population to the original population, and a lack of comparison between SNOT-22 scores for the SINUS and AROMA trials, it is difficult to assess how well this is likely to reflect the response rates of the updated population.

Table 4. Comparisons of the responder analysis between the unadjusted and adjusted AROMA populations

| | Responders, n (%) | | |
|---|---|---|---|
| Visit | Unadjusted AROMA population (n=443)* n (%) | Adjusted AROMA population (original population) n=512* | Adjusted AROMA population (updated population) n=185)* |
| Visit 4 (Month 6) | 285 (89.80) | 284 (89.4) | 106 (96.3) |
| Visit 6 (Month 12) | 155 (95.50) | 150 (94.7) | 64 (96.8) |
| Visit 8 (Month 18) | 61 (100.00) | 53 (99.2) | 23 (100) |
| Visit 10 (Month 24) | 16 (100.00) | 15 (98.0) | 6 (100) |

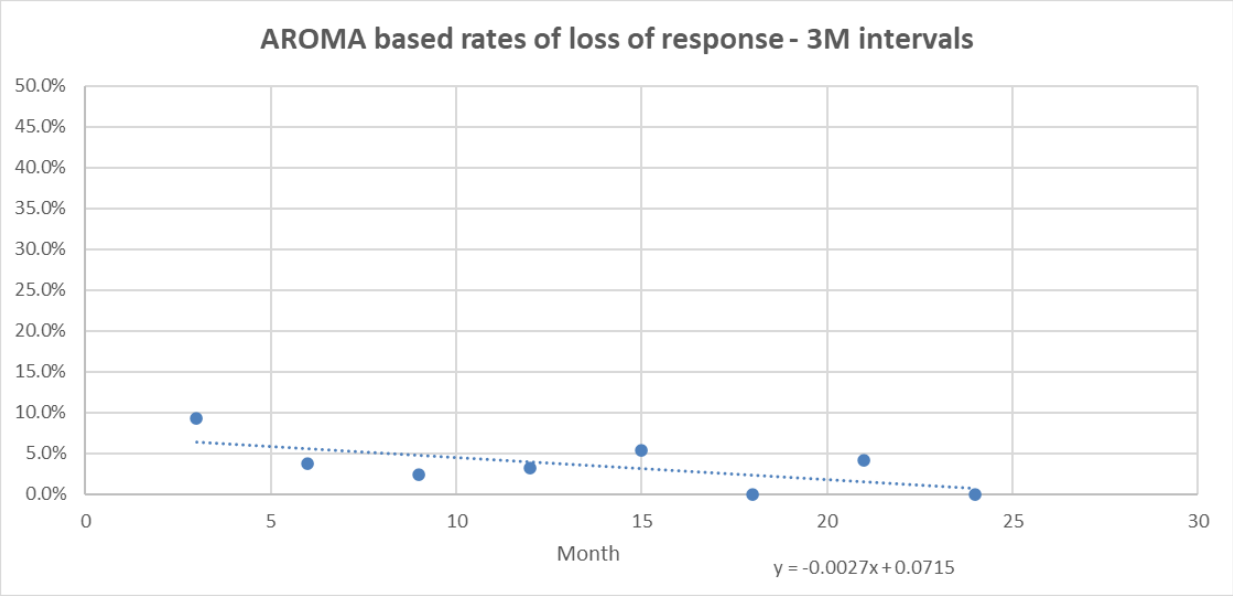
* number of patients with baseline and post-baseline SNOT-22 values excluding non-responders from any prior visit

#### *2.3.1.2 Application of AROMA data in the economic model*

In the dupilumab arm of the model, the company used the matched AROMA dataset to classify non-responders at each three month time point between baseline and 36 months based on SNOT-22 only (as NPS is unavailable from AROMA) using the updated response analysis (SNOT-22 <50 or change from baseline in SNOT-22 ≥8.9-point improvement). Patients who were classed as a non-responder at the previous timepoint, based on either not meeting the SNOT-22 responder criteria or due to having surgery or SCS are excluded. By month 24, data were only available for six patients, all of whom were still classed as responders.

The company fit a linear trendline to the proportion of patients who lost response to dupilumab at each time point, as shown in Figure 1.

Figure 1. Company analysis of loss of response based on SNOT-22 responder criteria applied to the AROMA matched population




Using the linear trendline, the company estimated a loss of response between month 12 and 24. Between months 24 to 36 the company assume the same loss of response as estimated using the linear trendline at month 24. In addition to the estimated loss of response, the company also applied the discontinuation rate observed in AROMA, calculated as [redacted]% and applied each year. The EAG notes that minimal data were available to cross-check the values used for this and provide any further critique. The total probability of discontinuation estimated by the company for years 2 to 5, applied in the economic model to represent long-term loss of response in each annual cycle (transition from controlled to inadequately controlled), is shown in Table 5 below.

Table 5. Probability of loss of control on dupilumab, i.e. moving to inadequately controlled health state, estimated by the company using the AROMA observational study

| Model cycle | Loss of response, based on matched AROMA analysis | Discontinuation, based on reported AROMA discontinuations | Probability of moving to the inadequately controlled health state |
|---|---|---|---|
| Year 2 | [redacted] | [redacted] | [redacted] |
| Year 3 | [redacted] | [redacted] | [redacted] |
| Year 4 | [redacted] | [redacted] | [redacted] |
| Year 5+ | [redacted] | [redacted] | [redacted] |

In addition to the issues and uncertainties discussed above regarding the matching analysis undertaken, the EAG also has the following concerns with the resulting long-term probabilities applied in the model:

- Response in the matched AROMA dataset is classified using the company's updated criteria, which includes SNOT-22<50. As previously discussed in Section 2.2, the EAG does not agree with this updated criteria. As the EAG does not have the equivalent analysis using the original response criteria, it is unclear what impact this would have.
- As previously mentioned in the EAG report, NPS was not available in AROMA and therefore the responder criteria uses only SNOT-22 data, which differs to the criteria for response used in the first year of the economic model.
- As discussed in the draft guidance, the committee stated that it would be inappropriate to use data from the first 12 months of AROMA. Although the company do not directly include the data from the first 12 months, the linear trend line used to inform the probability from year 2 includes baseline to 12 month data, which may have influenced the calculated rates. The EAG has recalculated the trend line to include only data from month 12 onwards and applied the resulting in a scenario analysis. This results in a minimal increase in the ICER.
- The EAG notes that it is unclear if the values applied for the loss of response and discontinuation from AROMA have been correctly converted from a rate to a probability, creating uncertainty in the values applied in the economic model.

In the original EAG base case presented at ACM1, the transition probability to inadequately controlled from year 2 onwards was based on the extrapolation of the rate of responders at week 52 amongst week 24 responders in the SINUS trials, annualised. It was noted that these were highly uncertain due to the small patient numbers available, particularly in the ECM arm. Due to the company's updated population, there is now only one patient available to inform the ECM arm, resulting in 100% of patients remaining a responder. The EAG therefore considers this data inappropriate and highly uncertain to inform the model. However, the EAG also considers there to be a large uncertainty in the alternative option available using the AROMA analysis. The EAG has used the same analysis as the company in the updated base case analysis to inform long-term transition probabilities but notes the uncertainty in these values. As the EAG was not provided with an updated matched analysis of AROMA using the original population and response criteria, a scenario could not be applied to explore the impact of this. However, a scenario presented by the company using the updated trial-derived probability for dupilumab ([redacted]% lose control each year) to inform long-term effectiveness increased the ICER by £[redacted] to £[redacted].

To inform the long-term transition probabilities for the ECM arm, the company now apply the same transition probability as that applied for uncontrolled to post-op controlled (42.3%) as the company states this uses real-world evidence, as is used in the dupilumab arm. This is lower than was used in the company's original base-case and may be considered conservative.

## 2.4 Updated utility values

### *2.4.1 Health state utility values*

Based on the updated population now used in the company's model, updated utility values were derived using the trial observed EQ-5D-5L (cross-walked to EQ-5D-3L) including only patients who had baseline SNOT-22 ≥50. As noted in Section 2.1, if any recommendation for dupilumab is similarly restricted to the company's updated population, with SNOT-22 score ≥50, then notwithstanding the aforementioned uncertainties associated with the updated population, the EAG agrees with the use of the trial based EQ-5D values in the economic model. However, the EAG considers that some issues still remain, discussed below.

As noted in the EAG's original report and critique, the EAG's preferred analysis would usually be EQ-5D from the trial with utility values derived from a regression analysis. However, the EAG considered

the company's regression analysis to be methodologically flawed due to potential multicollinearity and endogeneity. Therefore, based on the available values, the EAG's preference was for the observed change from baseline in observed EQ-5D-5L data cross-walked to EQ-5D-3L in the base-case analysis. The company has not performed an updated regression analysis to obtain the updated utility values and still uses the observed change from baseline approach. The EAG is unable to explore the extent that a difference in approach would have made to the cost-effectiveness results.

As noted in the company response, the EAG and committee's preference for utility values being higher than general population was to cap values at the age-matched general population norm and apply a multiplier to subsequent health states in order to retain the proportional differences between states. In the company's updated analysis for the new population, the utility value for the controlled disease health state was higher than the matched general population, however, due to not being substantially different, the company did not apply the cap. The utility values with a cap applied was provided in a scenario analysis only. The EAG notes that despite lowering the utility values in each health state, the inclusion of the cap resulted in a slight increase in the company's base case ICER (£[redacted] to £[redacted]) due to more patients in the dupilumab arm remaining in the controlled health state for longer compared to ECM.

The EAG's updated analysis based on the updated population (see Section 3) includes the cap and corresponding multiplier to health state utility values.

### *2.4.2 Surgery utility gain*

The company provided an updated value for the utility gain of endoscopic sinonasal surgery (ESS) based on Tashman *et al*. 2024[5] (0.0644), stating that this uses EQ-5D(-5L) and is more recent data than the previous committee and EAG preferred value from Remenschneider *et al*. 2015 (0.08).[6]

The EAG notes that Tashman *et al*. used a USA value set to derive the utility values from the collected EQ-5D data, which is a deviation from the NICE reference case. However, on further inspection, the EAG notes that Remenschneider *et al*. 2015[6] also used the USA value set as opposed to the required UK value set. The EAG was unable to identify any UK specific EQ-5D values associated with ESS utility gain for chronic rhinosinusitis patients and therefore considers the most appropriate utility value to be used in the model to be an unresolvable uncertainty.

Based on the values available, the EAG agrees that the value derived from Tashman *et al*. is the most appropriate. In light of the uncertainties, the EAG also provide a scenario analysis applying the

previous value from Remenschneider *et al*. to show the impact on the ICER of using an alternative value.

## 2.5 Economic model transition probabilities

During ACM1 and reflected in the published draft guidance, the committee and EAG noted uncertainties in the values derived for both the post-op controlled to uncontrolled and uncontrolled to post-op controlled (i.e. probability of surgery). In response to draft guidance, the company supplied further details discussed further below.

The company provided further data and calculations used to calculate the probability of transitioning from post-op controlled to uncontrolled and reiterated that this is distinct from the probability of revision surgery.

The EAG notes that several assumptions are required to hold in order for the company's estimate to be considered robust. Benson *et al.* 2023[7] reported a mean time between second and third surgery during follow-up as 875 days (2.4 years). Based on a surgery wait time of at least two years (730 days) obtained from clinical experts, the company therefore assume that everyone who loses control following surgery does so within the first 145 days (0.4 years) and at a constant rate. The EAG notes that the mean time between surgeries reported in Benson *et al.* represents the observed period of the study only. If the assumption that everyone who loses control does so in the first 145 days (0.4 years) does not hold, then the resulting transition probability will differ.

Based on an estimate that 17% of patients lost control following revision surgery within 0.4 years, the company calculated an annual transition probability to uncontrolled of 42.8% (17%/0.4years). The EAG notes that the company do not appear to have correctly converted a probability of 0.17 in 0.4 years to an annual probability, as this would first require conversion to a constant rate:

*Rate= -LN(1-probability)/time*

Followed by conversion of the rate to an annual probability:

*Probability = 1-exp(-rate*time)*

Therefore, based on the same assumptions used by the company regarding surgery wait times, the EAG calculates the annual probability 0.3724. Updating the company ICER to include this resulted in a small increase in the ICER of <£[redacted].

For the annual probability of surgery for a patient classed as uncontrolled (uncontrolled to post-op controlled) the company updated their estimate based on further analysis of the Benson *et al.* study[7] of uncontrolled patients moving between different surgeries (i.e. second to third, third to fourth). The EAG notes that the data provided in the response were insufficient for the EAG to cross-check the calculations and data used. Therefore, the EAG requested further details on the calculations used to create Table 12 in the company response and the corresponding updated probability of surgery of 7.1%. While the company provided a detailed spreadsheet, the EAG was unable to cross-reference the data in Table 12 to that provided and a revised version was not provided by the company in time for the EAG critique. The EAG notes that values used to calculate the probability of surgery appear to incorporate the 42.8% loss of response probability, which the EAG considers to be incorrect. Without further detail, the EAG was unable to update the resulting probability of surgery.

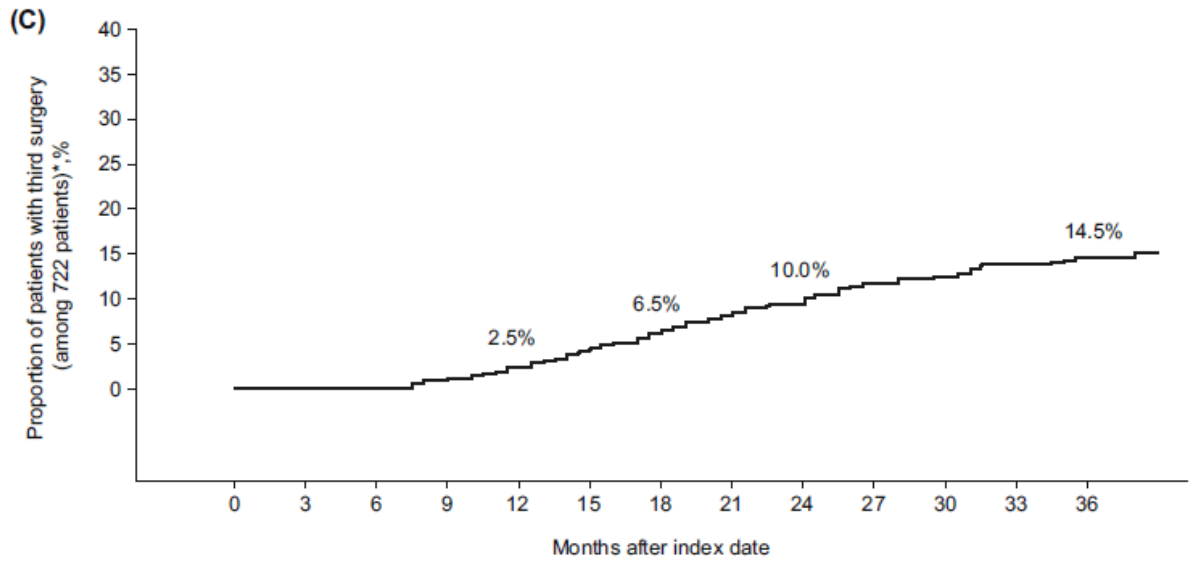
Despite being unable to cross-check the detailed calculations, the EAG notes that the company has applied a lower rate of surgery in the model, as it was previously noted by the EAG that the value used may be higher than expected. Based on the data provided by the company, the EAG still considers this parameter to be uncertain in the model.

During ACM1 the committee stated how the Benson *et al.* data and two-year assumed waiting time could be used to estimate the rate of loss of control and the corresponding rate of revision surgery for patients once in the uncontrolled health state. The committee also commented that based on a two-year wait time, the low probability of surgery used in the model could be considered too low. In response to the committee comments, the EAG has performed an alternative analysis of data from Benson *et al.* and by applying the same assumption of a two-year wait list for surgery, recalculated both transition probabilities.

Figure 2 below reproduced from Benson *et al*. 2023[7] shows the incidence of nasal polyp surgery estimated by Kaplan–Meier analysis of time from second surgery to third. As shown, three years after the second surgery, 14.5% of patients had undergone a third surgery. Given that 14.5% of patients had a third surgery 3 years after second surgery and assuming a two year waiting list, it is possible to estimate the probability of transitioning to the uncontrolled health state to be on a

waitlist for surgery by back-calculating to ensure that 14.5% of patients would be in the uncontrolled health state after three years. This was estimated as a 0.15 annual probability. The probability of surgery is then simply estimated as a conversion of a two-year waiting time to an annual probability (0.3935).

Figure 2. Analysis of time from second surgery to third surgery, reproduced from Figure 1c of Benson *et al.* 2023[7]




While the EAG recognises that these probabilities differ to those previously used in the EAG base case, these have been incorporated into the EAG preferred analysis to represent committee preferences from ACM1. However, due to the uncertainty remaining around these parameters, the company's values are applied in a scenario around the EAG base case for committee consideration. The EAG notes that both the EAG preferred and company analyses include the assumption of a two-year waiting list for surgery.

## 2.6 Long-term compliance

Previously, the company model used the compliance rate observed in the pooled SINUS studies (99.26%). The company's updated model applies a compliance rate based on UK Sanofi homecare data for dupilumab for the entire model time horizon.

The company provided a range of evidence to show that using a lower dose of dupilumab, via dose de-escalation to Q4W beyond week 24, did not impact the effectiveness of dupilumab. This is used to support applying a lower compliance rate throughout the model after week 24, which is not using

the same source as the effectiveness data used in the model. The EAG notes that although the company states that the compliance rate from the SINUS studies is applied post week 24 in the economic model, this is applied incorrectly, resulting in the compliance rate from the Sanofi homecare data being used to calculate treatment costs from the start of the model. The EAG has amended this error.

Despite the company noting that, "*…it is not unreasonable that the likely compliance rate for dupilumab in the real world for CRSwNP would be like the observed rates for the current asthma indication*", the company applied average compliance rate of both asthma and atopic dermatitis patients receiving dupilumab ([redacted]%).

The EAG considers the compliance rate of asthma patients ([redacted]%) to be more applicable than atopic dermatitis and considers this most appropriate to model long-term compliance in the economic model. However, the EAG deems it more appropriate to model this only from year 2 onwards as the SINUS trials are informing efficacy for the first year of the model.

## 2.7 Summary of remaining key uncertainties

The EAG notes a number of key uncertainties relating to the company's response, which have been highlighted throughout its critique. The remaining uncertainties in the evidence provided by the company are:

- The modification to the definition of the population to a more severe group of patients, which:
    - Appears to reflect one definition used in clinical practice, but differs from the definition previously agreed by the committee as relevant to NHS clinical practice;
    - Resulted in the exclusion of half the patients in the original CS; and
    - Required the breaking of randomisation.
- The updated definition of treatment response which:
    - Does not appear to reflect clinical practice in the NHS; and
    - Has resulted in a considerably greater treatment effect when applied to the updated population (although the EAG notes that no evidence was provided for treatment response when the previous definition was applied to the updated population);

    - Is applied in the economic model despite the uncertainties of its application in clinical practice.
- The methods used to match the population in the AROMA trials to the pooled SINUS trials and application in the economic model, which:
    - Could not adjust for important measures of disease severity (NPS) or any other unmeasured confounders;
    - Was based on the original, ITT, population rather than the updated, more severe, population;
    - Has resulted in low patient numbers beyond 12 months of treatment;
    - Applies a different response criteria in the model from year 2 onwards to that used in the first year decision tree;
    - Includes uncertainty if the rates have been inappropriately transformed to probabilities.
- The transition probabilities used in the model:
    - Obtained from unclear calculations used by the company to inform the updated probability of surgery;
    - Rely on strong assumptions regarding waiting lists and patients becoming uncontrolled within a specific timeframe.

# 3 Updated cost-effectiveness results and additional scenarios

The company provided an updated model and base-case following numerous updates made post draft guidance. As a result, the EAG's base-case has also updated. The EAG has included any committee preferences stated in the draft guidance in its updated base-case, as applied in the company's updated base-case. The committee requested a range of additional evidence and analyses as a result of ACM1. As discussed above, the EAG considers there to be a number of uncertainties remaining. The EAG has presented an updated base-case analysis and a range of scenarios around this below.

### *3.1.1 EAG model corrections*

As previously noted, the EAG identified two errors in the company model/calculations, which have been updated:

1. Apply the trial-based compliance rate in the estimation of dupilumab treatment costs for the first 24 weeks of the model.
2. Correction to the company's estimated transition probability for post-op controlled to uncontrolled to ensure correct conversion from a rate to a probability.

The EAG corrected company base case results are presented in Table 6.

Table 6. EAG corrected company updated base-case results, post draft guidance

| Interventions | Total Costs (£) | Total LY* | Total QALYs | Incremental costs (£) | Incremental LYs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| **Deterministic results** | | | | | | | |
| ECM only | [redacted] | [redacted] | [redacted] | - | - | - | - |
| Dupilumab + ECM | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £[redacted] |
| **Probabilistic results** | | | | | | | |
| ECM only | [redacted] | [redacted] | [redacted] | - | - | - | - |
| Dupilumab + ECM | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £[redacted] |

Abbreviations:; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year
*Undiscounted

### *3.1.2 EAG's exploratory analyses using the company's base case*

As discussed in Section 2, the EAG considers there to be a number of uncertainties remaining, and has therefore undertaken some additional analyses on the company base-case (EAG corrected). The scenarios performed by the EAG around the corrected company base case are detailed in Table 7, with the corresponding results shown in Table 8 (deterministic only).

Table 7. Summary of EAG's exploratory analyses using company's base case

| Exploratory analysis number | Company's base case assumption | EAG scenario | Justification for EAG assumption | Section in EAG response |
|---|---|---|---|---|
| 1 | EQ-5D trial-derived utilities based on updated population (SNOT-22>50) | EQ-5D trial-derived utilities based on updated population (SNOT-22>50) with cap applied for general population norms | Trial utility values were slightly higher in the controlled health state than general population. In line with the EAG's original approach and committee preference at ACM1, the EAG applies a cap to ensure values are not higher than the general population | 2.4 |
| 2 | Compliance informed by SINUS pooled trial data in the first 24 weeks of the model, followed by homecare compliance data from Sanofi based on asthma and atopic dermatitis | Compliance informed by SINUS pooled trial data in the first 52 weeks of the model, followed by homecare compliance data from Sanofi based on asthma only | Effectiveness data from SINUS informs the first year of the model and therefore appropriate to use associated compliance rate. Asthma considered to be more applicable to CRSWNP than atopic dermatitis | 2.7 |
| 3 | Dupilumab loss of response beyond 52 weeks informed by AROMA analysis for dupilumab | Dupilumab loss of response beyond 52 weeks informed by extrapolation of the updated trial-derived probability for dupilumab ([redacted]% lose control each year) | The EAG had concerns with the company's matching analysis resulting in uncertainty in the application in the economic model | 2.3 |
| 4 | Dupilumab loss of response probability calculated from AROMA uses trendline fit to all available data from AROMA, including 0 to 12 months | Dupilumab loss of response probability calculated from AROMA uses trendline fit to all available data from AROMA, excluding 0 to 12 months | The linear trend line used to inform the probability of dupilumab loss of response rom year 2 includes baseline to 12 month data, when patient will have had greatest response to dupilumab and which therefore may have influenced the calculated rates | 2.3.1.2 |
| 5 | Transition probability for post-op controlled to uncontrolled = 42.8%<br>Transition probability from uncontrolled to post-op controlled | Transition probability for post-op controlled to uncontrolled = 15.0%<br>Transition probability from uncontrolled to post-op controlled = | The EAG notes that there are a number of assumptions applied in the calculation of the company's transition probabilities and the EAG was not provided with adequate data to cross-check | 2.5 |

| | | | | |
|---|---|---|---|---|
| | = 7.1% (also applied to inadequately controlled to post-op controlled) | 39.35% (also applied to inadequately controlled to post-op controlled) | the calculations used for the revision surgery probability prior to submission of this report.<br>The EAG has provided an alternative approach using the same study as the company, which results in alternative transition probabilities. | |
| 6 | Responder rates based on updated population and response criteria | Responder rates based on the original population and response criteria | The EAG notes that this is an exploratory scenario only. Based on the uncertainties associated with the updated response criteria applied by the company, the EAG wanted to observe the impact on the ICER using the original response criteria. However, as this is not available for the company's updated population, the EAG applied the response rates originally used in the company's previous base case. | 2.2 |

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; EAG, External Assessment Group; EQ-5D, EuroQol five dimension

Table 8. Results of EAG's deterministic exploratory analyses using company's base case

| | Results per patient | Dupilumab + background therapy | Background therapy only | Incremental value |
|---|---|---|---|---|
| 0 | Company updated base case | | | |
| | Total costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | ICER (£/QALY) | | | [redacted] |
| 0 | EAG corrected company updated base case | | | |
| | Total costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | ICER (£/QALY) | | | [redacted] |
| 1 | EQ-5D trial-based utilities with cap applied for general population norms | | | |
| | Total costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | ICER (£/QALY) | | | [redacted] |
| 2 | Compliance based on SINUS for first year then asthma homecare data | | | |
| | Total costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | ICER (£/QALY) | | | [redacted] |
| 3 | Dupilumab loss of response beyond 52 weeks informed by extrapolation trial-derived probability | | | |
| | Total costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | ICER (£/QALY) | | | [redacted] |
| 4 | Exclude first 12 months of AROMA data from linear trendline | | | |
| | Total costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | ICER (£/QALY) | | | [redacted] |
| 5 | Alternative model transition probabilities based on Benson *et al.*[7] | | | |
| | Total costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | ICER (£/QALY) | | | [redacted] |
| 6 | Responder rates based on original population and response criteria | | | |
| | Total costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | ICER (£/QALY) | | | [redacted] |

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

### 3.1.3 EAG preferred assumptions

Following the update to the company model and population, the EAG has updated its base-case analysis. As previously discussed, the EAG has concerns with some of the updated data used in the model; however, in place of alternative options, the EAG has provided an updated preferred base case but notes the uncertainty surrounding many of the inputs. Below are the details of the remaining differences between the company and EAG preferred analysis, with the cumulative results of each analysis shown in Table 9. Results are presented deterministically only but the EAG notes that the probabilistic and deterministic results were previously shown to be similar.

| Parameter | Company base case | EAG preference | Justification |
|---|---|---|---|
| Health state utility values | EQ-5D trial derived utilities based on updated population (SNOT-22>50) | EQ-5D trial derived utilities based on updated population (SNOT-22>50) with cap applied for general population norms | Trial utility values were slightly higher in the controlled health state than general population. In line with the EAG's original approach and committee preference at ACM1, the EAG applies a cap to ensure values are not higher than the general population |
| Compliance | SINUS pooled trial data in the first 24 weeks of the model, followed by homecare compliance data from Sanofi based on asthma and atopic dermatitis | SINUS pooled trial data in the first 52 weeks of the model, followed by homecare compliance data from Sanofi based on asthma only | Effectiveness data from SINUS informs the first year of the model and, therefore, appropriate to use the associated compliance rate. Asthma is considered to be more applicable to CRSwNP than atopic dermatitis |
| Long-term effectiveness from year 2 | Based on analysis of AROMA | Same as company but using adjusted trendline to exclude data from first 12 months | Including first 12 months in linear trendline estimate may have influenced the applicable rates |
| Transition probability from post-op controlled to uncontrolled and uncontrolled to post-op controlled | Transition probability for post-op controlled to uncontrolled = 42.8%<br>Transition probability from uncontrolled to post-op controlled = 7.1% (also applied to inadequately controlled to post-op controlled) | Transition probability for post-op controlled to uncontrolled = 15.0%<br>Transition probability from uncontrolled to post-op controlled = 39.35% (also applied to inadequately controlled to post-op controlled) | The EAG notes that there are a number of assumptions applied in the calculation of the company's transition probabilities and the EAG was not provided with adequate data to cross-check the calculations used for the revision surgery probability during the draft guidance.<br>The EAG has provided an alternative approach using |

| | | | |
|---|---|---|---|
| | | | the same study as the company, which results in alternative transition probabilities |

Abbreviations: ACM, appraisal committee meeting; CRSwNP, chronic rhinosinusitis with nasal polyps; EAG, External Assessment Group; EQ-5D, EuroQol five dimension

Table 9. EAG's preferred model assumptions, cumulative ICER (deterministic)

| Preferred assumption | Section in EAG response | Cumulative incremental costs | Cumulative incremental QALYs | Cumulative ICER (£/QALY) |
|---|---|---|---|---|
| Corrected company base case | Section 3.1 | [redacted] | [redacted] | [redacted] |
| SINUS trial derived EQ-5D utility values with a general population cap | Section 2.4 | [redacted] | [redacted] | [redacted] |
| Compliance beyond first year based on asthma Sanofi homecare data | Section 2.6 | [redacted] | [redacted] | [redacted] |
| Re-estimation of linear trendline fit to AROMA data to exclude first 12 months | Section 2.3.1.2 | [redacted] | [redacted] | [redacted] |
| Transition probabilities based on alternative data from Benson *et al.* and two year waiting list | Section 2.5 | [redacted] | [redacted] | [redacted] |
| **EAG preferred base case** | - | [redacted] | [redacted] | [redacted] |

Abbreviations: EAG, External Assessment Group; EQ-5D, EuroQol five dimension; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

### *3.1.4 EAG's exploratory analyses using the EAG base case*

As previously detailed in Section 2.7, the EAG considers a number of uncertainties to remain, some of which cannot be explored in the economic model due to data only being available for the updated population and response criteria. However, the EAG has run a number of scenarios to highlight the potential impact on the ICER for committee, shown in Table 10.

Table 10. Results of EAG's deterministic exploratory analyses using EAG's base case

| | Results per patient | Dupilumab + background therapy | Background therapy only | Incremental value |
|---|---|---|---|---|
| 0 | EAG updated base case | | | |
| | Total costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | ICER (£/QALY) | — | — | [redacted] |
| 1 | Transition probabilities derived from Benson *et al.* as used in the company base case model | | | |
| | Total costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | ICER (£/QALY) | — | — | [redacted] |
| 2 | Utility gain from surgery based on Remenschneider *et al.* 2015[6] | | | |
| | Total costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | ICER (£/QALY) | — | — | [redacted] |
| 3 | Responder rates based on original population and response criteria | | | |
| | Total costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | ICER (£/QALY) | — | — | [redacted] |

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

# 4 References


1. Toma S, Hopkins C. Stratification of SNOT-22 scores into mild, moderate or severe and relationship with other subjective instruments. Rhinology. 2016;54(2):129-33.
2. De Corso E, Pasquini E, Trimarchi M, La Mantia I, Pagella F, Ottaviano G, et al. Dupilumab in the treatment of severe uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP): A multicentric observational Phase IV real-life study (DUPIREAL). Allergy. 2023;78(10):2669-83.
3. Cantone E, Cassiano B, Pezzella P, Russo MB, Detoraki A. The Effects of Mepolizumab on CRSwNP: Real-Life Evidence. J Pers Med. 2024;14(1112).
4. Lombardo N, Piazzetta G, Lobello N, Cicala G, Patafi M, Benincasa AT, et al. Real-Life Effects of Omalizumab on Chronic Rhinosinusitis with Nasal Polyposis. Journal of Personalized Medicine. 2023;14(3).
5. Tashman K, Adams D, Vickery TW, Holbrook EH, Gray ST, Bleier BS, et al. Five-year EuroQol 5-Dimension Outcomes After Endoscopic Sinus Surgery. Laryngoscope. 2024;134(6):2592-601.
6. Remenschneider AK, Scangas G, Meier JC, Gray ST, Holbrook EH, Gliklich RE, et al. EQ-5D-derived health utility values in patients undergoing surgery for chronic rhinosinusitis. Laryngoscope. 2015;125(5):1056-61.
7. Benson VS, Fu Q, Yang S, Sousa AR, Chan RH, Howarth P, et al. Real-world characterisation of patients with chronic rhinosinusitis with nasal polyps with and without surgery in England. Clin Otolaryngol. 2023;48(4):680-8.

Thank you for the opportunity to provide further clarity about the implementation of the probabilistic sensitivity analysis (PSA). Following our discussion last week after receiving the second committee meeting outcome (ACM2), we would like to provide a concise update to address the PSA and deterministic sensitivity analysis (DSA) discrepancy. We have broken down our response into the following sections.

1. **Brief description of the issue with the PSA**
2. **Correction to the PSA**
3. **Updated results with no change to the committee preferred assumptions and model inputs**
4. **Appendix**

## 1. Brief description of the issue with the PSA

When reviewing the results of the EAG model including ACM2 preferred assumptions, we observed that the probabilistic ICER was consistently around £1,500 higher than the deterministic ICER once the utility cap was introduced. This discrepancy was not observed under other scenarios without the cap. To explore this consistent discrepancy, we checked the *Utility* worksheet formulas, and how these were varied through the *Sensitivity Analyses* worksheet. We realised that the complexity of the formulas used in the PSA (several added layers) was the root cause of the discrepancy and have made some amendments to the formulas to remove this complexity but preserve the correct functioning of the model (in respect to the committee preferred assumptions and inputs). Specifically:

- The baseline utility anchor was standardised to a single source to ensure that each state started from the same consistent baseline in both the DSA and the PSA. (Note that this baseline utility is still varied in the PSA).
- The formulas were overly complex and introduced the possibility for variation in the utility parameters to occur more than once for each iteration. See Section 2 and Table 1 below (please also see a screenshot of the issue in the Appendix section below - Figure 4).

It is important to note two things. Firstly, we have used the EAG model supplied to us on Friday 12 September 2025 (with ACM2 committee preferred assumptions and inputs) to make these changes and secondly that we did not alter or remove the utility cap, or the multiplier which still varies in each run according to the variation in the baseline and in the change from baseline (deterministic multiplier remains 0.9830). None of the other agreed inputs in the EAG model have been modified. The PSA results using the updated model are within a few hundred pounds of the DSA values. This is consistent with the observed behaviour in other scenarios.

## 2. Correction to the PSA

The original approach to implementing the utility values capping and probabilistic variation relied on complex nested formulas with multiple lookups (this became even more complex as we responded to questions through the process). Although technically functional, this structure had limitations, particularly around how the capping multiplier was applied during PSA. Ultimately this made following the formulas cumbersome and prone to error with some parameters likely being varied more than once, or the utility capping multiplier not being applied to all health states at each iteration of the PSA (please find a screenshot of the issue in the Appendix section - Figure 4). This ICER discrepancy between PSA and DSA was not present when the model was on deterministic mode or even on when the model was on probabilistic mode but the utility capping was not applied (which was the company base case).

To address these issues, we have implemented the following efficiencies whilst retaining all the committee preferred assumptions:

*Unified baseline anchor:* All health-state utilities now reference a single baseline value ('Baseline Characteristics Data'!$J$11 – varied in the *Baseline Characteristics Data* worksheet when the probabilistic mode is activated). This ensures that the same baseline is applied consistently across the decision tree and the Markov component of the model, for each PSA iteration.

*Incremental CFB from one source*: Utility CFBs (EQ-5D) are now drawn exclusively from the relevant column "O" of the *Utility Data* worksheet (varied the *Utility Data* worksheet if probabilistic mode is activated). These increments are added to the baseline, yielding a straightforward "baseline + delta" calculation for each state.

*Consistent application of utility capping multipliers*: The multiplier is now applied once only, at the final step of each formula (health state utility calculation). This removes the possibility of applying it more than once during each iteration and ensures that the capping of utilities is implemented correctly. These simplification of the formulas removes unnecessary complexity to make the model more transparent but retains correct functioning. (See bullets below which describe exactly how the utility is calculated and the corresponding formulas in Table 1 below).

- *Controlled disease*: utilities are now expressed as baseline + 'Utility Data'!O41 (all responders CFB at W52).
- *Inadequately controlled disease*: utilities are now calculated as the average of the uncontrolled and baseline + 'Utility Data'!O46 (CFB of ECM non-responders at W52).
- *Uncontrolled disease*: simplified to baseline * multiplier.
- The incremental benefit from surgery has been standardised at 0.0644 (hard-coded), in line with the preferred evidence source. Please not this was already hard-coded in the previous versions of the model.
- Post-operative utilities are now expressed as the sum of the relevant pre-surgical health-state utility value (e.g. inadequately controlled or uncontrolled) plus the fixed surgical increment * multiplier.

The key changes to the formulas are presented in Table 1 below along with a side-by-side comparison of the point estimates for the utility values before and after their application. These are all identical with 2 exceptions. Whilst it makes no substantive difference to the outcomes of the model, we feel it is important to bring a small error in the application of the cap that causes these differences to the attention of the committee.

In reviewing the inadequately controlled health state formula we noticed that it was previously picking up the uncontrolled utility value (or baseline utility value) without the multiplier. This was unimportant to the Sanofi base case without the cap but as the committee prefers to use the cap in their base case, we have corrected this. The updated inadequately controlled state now attracts a slightly lower utility by about 0.005. This small utility adjustment also affects the three post-operative controlled states that are derived from the inadequately controlled state, reducing their utility by the same small margin. However, this minimal change has minimal impact on the utility values for patients cycling through the Markov model over the lifetime horizon (as the post-operative HS is mainly composed of "POST-OP from uncontrolled" which utility point value remains unchanged) and moves the ICER down by only £74.

Finally, as baseline utility, utility CFBs and utility capping multiplier values are already varied in, respectively, *Baseline Characteristics Data worksheet* and *Utility Data* worksheet, the formulas in

*Sensitivity Analyses* worksheet for lines 73 to 91 have been updated to avoid duplicating the variations. All calculations apply to the relevant cell of the *Utility* worksheet and are simply "carried" through the Sensitivity Analyses worksheet to feed the Markov model calculations.

*Table 1 Simplified formulas – EAG cost-effectiveness model – ACM2 committee preferred assumptions*

| Parameter | Cell | Deterministic value without PSA fix | Deterministic value with PSA fix | Simplified formula |
|---|---|---|---|---|
| **Decision tree** | | | | |
| DUP + ECM W0-12 | 'Utility'!J20 | 0.698 | Same | ='Baseline Characteristics Data'!$J$11*multiplier |
| DUP + ECM W13-24 | 'Utility'!J21 | 0.843 | Same | =('Baseline Characteristics Data'!$J$11+'Utility Data'!O31)*multiplier |
| DUP + ECM W25-52 RESP | 'Utility'!J22 | 0.876 | Same | =AVERAGE(('Baseline Characteristics Data'!$J$11+'Utility Data'!O11),('Baseline Characteristics Data'!$J$11+'Utility Data'!O12))*multiplier |
| DUP + ECM W25-52 NORESP | 'Utility'!J23 | 0.806 | Same | =AVERAGE(('Baseline Characteristics Data'!$J$11+'Utility Data'!O16),('Baseline Characteristics Data'!$J$11+'Utility Data'!O17))*multiplier |
| ECM W0-12 | 'Utility'!K20 | 0.698 | Same | ='Baseline Characteristics Data'!$J$11*multiplier |
| ECM W13-24 | 'Utility'!K21 | 0.767 | Same | =('Baseline Characteristics Data'!$J$11+'Utility Data'!O35)*multiplier |
| ECM W25-52 RESP | 'Utility'!K22 | 0.816 | Same | =AVERAGE(('Baseline Characteristics Data'!$J$11+'Utility Data'!O21),('Baseline Characteristics Data'!$J$11+'Utility Data'!O22))*multiplier |
| ECM W25-52 NORESP | 'Utility'!K23 | 0.768 | Same | =AVERAGE(('Baseline Characteristics Data'!$J$11+'Utility Data'!O26),('Baseline Characteristics Data'!$J$11+'Utility Data'!O27))*multiplier |
| **Markov Model** | | | | |
| CONTROLLED | 'Utility'!J26 | 0.866 | Same | =('Baseline Characteristics Data'!$J$11+'Utility Data'!$O41)*multiplier |
| INADEQUATELY CONTROLLED | 'Utility'!J27 | 0.732 | 0.727 | =AVERAGE('Baseline Characteristics Data'!$J$11*multiplier,(('Baseline Characteristics Data'!$J$11+'Utility Data'!O46)*multiplier)) |
| UNCONTROLLED | 'Utility'!J28 | 0.686 | Same | ='Baseline Characteristics Data'!$J$11*multiplier |
| Utility gain from surgery | 'Utility'!J29 | 0.0644 | Same | =0.0644 |
| POST-OP CONTROLLED - patients from DUP+ECM NORESP, ECM NORESP or INADEQUATELY CONTROLLED | 'Utility'!J30 'Utility'!J31 'Utility'!J32 | 0.783 | 0.778 | =(Utility_InadequatelyControlled+Utility_Surgery)*multiplier |
| POST-OP CONTROLLED - patients from UNCONTROLLED | 'Utility'!J33 | 0.738 | Same | =(Utility_PostOp_Uncontrolled+Utility_Surgery)*multiplier |
| **Utility capping multiplier** | | | | |
| UTILITY CAPPING MULTIPLIER calculation (vs. relevant population norm utility value for mean age) | 'Utility Data'!P12 | 0.983 | Same | =IF('Model Mechanics'!$E$80=1,IF(MIN('Baseline Characteristics Data'!$J$11+O12,1)>XLOOKUP(Age,'Utility Calcs'!$B$216:$B$317,'Utility Calcs'!$C$216:$C$317,MIN('Baseline Characteristics Data'!$J$11+O12,1),-1,1),XLOOKUP(Age,'Utility Calcs'!$B$216:$B$317,'Utility Calcs'!$C$216:$C$317,MIN('Baseline Characteristics Data'!$J$11+O12,1),-1,1),'Baseline Characteristics Data'!$J$11+O12)/('Baseline Characteristics Data'!$J$11+O12),1) |

# 3. Updated results with no change to the committee preferred assumptions and model inputs

## Updated probabilistic sensitivity analysis (PSA)

The PSA results (corrected PSA variation and utility capping multiplier) are presented in Table 2. The results align with the deterministic results (deterministic ICER = [redacted]/QALY). Please note that these results have been produced using the EAG model including the committee preferred assumptions following ACM2. No change has been applied apart from the PSA formula correction described above.

*Table 2. Corrected probabilistic results for patients with ≥1 prior sinus surgery and baseline SNOT-22 total score ≥50, according to the response criteria of SNOT-22 total score (≥8.9-point improvement) and NPS (≥1-point improvement)*

| Treatments | TOTAL costs | TOTAL LYs | TOTAL QALYs | Incr. costs | Incr. LYs | Incr. QALYs | ICER |
|---|---|---|---|---|---|---|---|
| Dupilumab + ECM | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ECM | [redacted] | [redacted] | [redacted] | | | | |

ECM = established clinical management; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

The scatter plot for incremental cost-effectiveness results, cost-effectiveness acceptability curve (CEAC) and convergence plot/curve for this updated base case with fixed PSA formulas are presented in Figure 1, Figure 2 and Figure 3, respectively.

*Figure 1. Scatter plot for incremental cost-effectiveness results (1,000 iterations) – updated base case – fixed PSA*

DUP = dupilumab; ECM = established clinical management; QALY = quality-adjusted life-year; WTP = willingness-to-pay

*Figure 2. Cost-effectiveness acceptability curve (1,000 iterations) – updated base case – fixed PSA*

DUP = dupilumab; ECM = established clinical management

*Figure 3. Convergence ICER plot/curve (1,000 iterations) – updated base case – fixed PSA*

ICER = incremental cost-effectiveness ratio

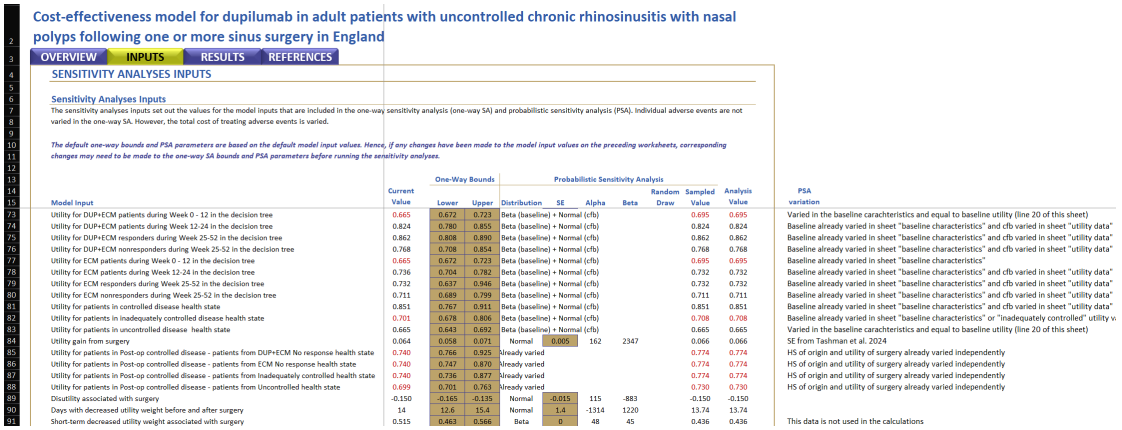
Thank you for the opportunity to provide this document to support the PSA correction.

# 4. Appendix

## Probabilistic sensitivity analysis variation discrepancy

As seen in Figure 4 below (screenshot of the *Sensitivity Analyses* worksheet – EAG version – ACM2 preferred assumptions), there are some value discrepancies between column "current value" (which informs the *Utility* worksheet values) and columns "sampled value" and "analysis value" which inform the Markov model worksheets. The latter 2 columns inform utility for each health state in the Markov calculations and are varied within the *Sensitivity Analyses* worksheet, but "current values" are already varied elsewhere in the model and some of them (here coloured in red) are therefore using different values (baseline with or without utility capping multiplier and/or possible duplicate variations). This is now addressed in the proposed amendments to the model.

*Figure 4. Screenshot of the "Sensitivity Analyses" tab of the EAG model – ACM2 preferred assumptions (probabilistic mode activated)*



Cost-effectiveness model for dupilumab in adult patients with uncontrolled chronic rhinosinusitis with nasal polyps following one or more sinus surgery in England

OVERVIEW | INPUTS | RESULTS | REFERENCES

SENSITIVITY ANALYSES INPUTS

Sensitivity Analyses Inputs

The sensitivity analyses inputs set out the values for the model inputs that are included in the one-way sensitivity analysis (one-way SA) and probabilistic sensitivity analysis (PSA). Individual adverse events are not varied in the one-way SA. However, the total cost of treating adverse events is varied.

*The default one-way bounds and PSA parameters are based on the default model input values. Hence, if any changes have been made to the model input values on the preceding worksheets, corresponding changes may need to be made to the one-way SA bounds and PSA parameters before running the sensitivity analyses.*

| | | One-Way Bounds | | Probabilistic Sensitivity Analysis | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Model Input | Current Value | Lower | Upper | Distribution | SE | Alpha | Beta | Random Draw | Sampled Value | Analysis Value | PSA variation |
| Utility for DUP+ECM patients during Week 0 - 12 in the decision tree | 0.665 | 0.672 | 0.723 | Beta (baseline) + Normal (cfb) | | | | | 0.695 | 0.695 | Varied in the baseline carachteristics and equal to baseline utility (line 20 of this sheet) |
| Utility for DUP+ECM patients during Week 12-24 in the decision tree | 0.824 | 0.780 | 0.855 | Beta (baseline) + Normal (cfb) | | | | | 0.824 | 0.824 | Baseline already varied in sheet "baseline characteristics" and cfb varied in sheet "utility data" |
| Utility for DUP+ECM responders during Week 25-52 in the decision tree | 0.862 | 0.808 | 0.890 | Beta (baseline) + Normal (cfb) | | | | | 0.862 | 0.862 | Baseline already varied in sheet "baseline characteristics" and cfb varied in sheet "utility data" |
| Utility for DUP+ECM nonresponders during Week 25-52 in the decision tree | 0.768 | 0.708 | 0.854 | Beta (baseline) + Normal (cfb) | | | | | 0.768 | 0.768 | Baseline already varied in sheet "baseline characteristics" and cfb varied in sheet "utility data" |
| Utility for ECM patients during Week 0 - 12 in the decision tree | 0.665 | 0.672 | 0.723 | Beta (baseline) + Normal (cfb) | | | | | 0.695 | 0.695 | Baseline already varied in sheet "baseline characteristics" |
| Utility for ECM patients during Week 12-24 in the decision tree | 0.736 | 0.704 | 0.782 | Beta (baseline) + Normal (cfb) | | | | | 0.732 | 0.732 | Baseline already varied in sheet "baseline characteristics" and cfb varied in sheet "utility data" |
| Utility for ECM responders during Week 25-52 in the decision tree | 0.732 | 0.637 | 0.946 | Beta (baseline) + Normal (cfb) | | | | | 0.732 | 0.732 | Baseline already varied in sheet "baseline characteristics" and cfb varied in sheet "utility data" |
| Utility for ECM nonresponders during Week 25-52 in the decision tree | 0.711 | 0.689 | 0.799 | Beta (baseline) + Normal (cfb) | | | | | 0.711 | 0.711 | Baseline already varied in sheet "baseline characteristics" and cfb varied in sheet "utility data" |
| Utility for patients in controlled disease health state | 0.851 | 0.767 | 0.911 | Beta (baseline) + Normal (cfb) | | | | | 0.851 | 0.851 | Baseline already varied in sheet "baseline characteristics" and cfb varied in sheet "utility data" |
| Utility for patients in inadequately controlled disease health state | 0.701 | 0.678 | 0.806 | Beta (baseline) + Normal (cfb) | | | | | 0.708 | 0.708 | Baseline already varied in sheet "baseline characteristics" or "inadequately controlled" utility va |
| Utility for patients in uncontrolled disease health state | 0.665 | 0.643 | 0.692 | Beta (baseline) + Normal (cfb) | | | | | 0.665 | 0.665 | Varied in the baseline carachteristics and equal to baseline utility (line 20 of this sheet) |
| Utility gain from surgery | 0.064 | 0.058 | 0.071 | Normal | 0.005 | 162 | 2347 | | 0.066 | 0.066 | SE from Tashman et al. 2024 |
| Utility for patients in Post-op controlled disease - patients from DUP+ECM No response health state | 0.740 | 0.766 | 0.925 | Already varied | | | | | 0.774 | 0.774 | HS of origin and utility of surgery already varied independently |
| Utility for patients in Post-op controlled disease - patients from ECM No response health state | 0.740 | 0.747 | 0.870 | Already varied | | | | | 0.774 | 0.774 | HS of origin and utility of surgery already varied independently |
| Utility for patients in Post-op controlled disease - patients from Inadequately controlled health state | 0.740 | 0.736 | 0.877 | Already varied | | | | | 0.774 | 0.774 | HS of origin and utility of surgery already varied independently |
| Utility for patients in Post-op controlled disease - patients from Uncontrolled health state | 0.699 | 0.701 | 0.763 | Already varied | | | | | 0.730 | 0.730 | HS of origin and utility of surgery already varied independently |
| Disutility associated with surgery | -0.150 | -0.165 | -0.135 | Normal | -0.015 | 115 | -883 | | -0.150 | -0.150 | |
| Days with decreased utility weight before and after surgery | 14 | 12.6 | 15.4 | Normal | 1.4 | -1314 | 1220 | | 13.74 | 13.74 | |
| Short-term decreased utility weight associated with surgery | 0.515 | 0.463 | 0.566 | Beta | 0 | 48 | 45 | | 0.436 | 0.436 | This data is not used in the calculations |

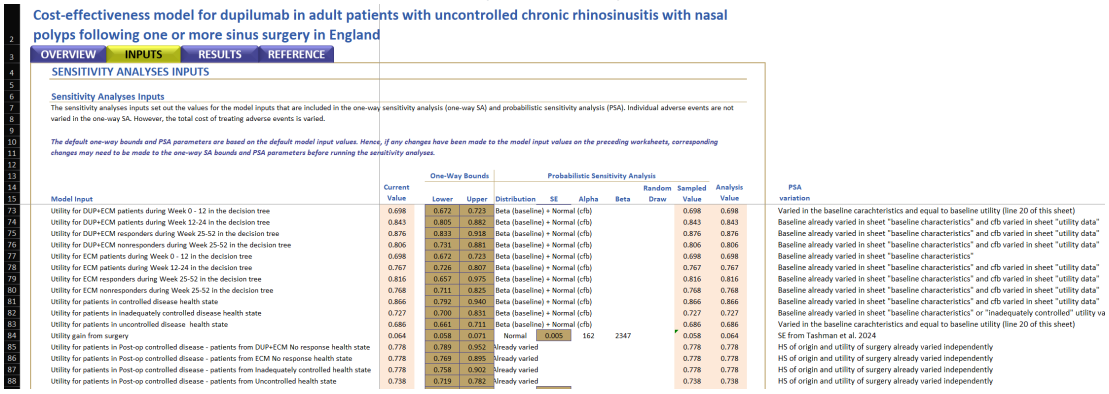
## Visual scale for changes to the cost-effectiveness model

As seen in Figure 5 below, all cells with formula changes (but *no deterministic value change*) are coloured in light orange, whereas all cells with formula change (and *deterministic value change* [only the inadequately controlled utility value by -0.005 and subsequent post-op utility values]) are coloured in dark orange to help show where there have been updates with the EAG cost-effectiveness model.

*Figure 5. Screenshot of the model changes – Utility worksheet – EAG model – ACM2 preferred assumptions (deterministic)*

| Health state | Utility DUP+ECM | Utility ECM | Source | | |
|---|---|---|---|---|---|
| Decision tree | | | Note: the utility values presented below are capped | 0.686 | 0.686 |
| Week 0 - 12 | 0.698 | 0.698 | Patients' baseline utility weight from the SINUS-24 and SINUS-52 trials | 0.843 | 0.767 |
| Week 13-24 | 0.843 | 0.767 | Patients' utility weight at week 24 by treatment arm | 0.876 | 0.816 |
| Week 25-52 responders | 0.876 | 0.816 | Average of responders utility weight at week 24 and week 52 by treatment arm | 0.806 | 0.768 |
| Week 25-52 nonresponders | 0.806 | 0.768 | Average of non-responders utility weight at week 24 and week 52 by treatment arm | | |
| | | | | | |
| Markov model | Utility | | | | |
| Controlled disease | 0.866 | | All responders' utility weight at week 52 | | |
| Inadequately controlled disease | 0.727 | | Average of the utility weight at week 52 from ECM patients who did not respond at week 24 or week 52 and the utilit | | |
| Uncontrolled disease | 0.686 | | Assumed to be the baseline utility (or utility of Inadequately controlled HS if lower) | | |
| Utility gain from surgery | 0.064 | | Tashman et al. 2024 | | |
| Post-op controlled disease - patients from DUP+ECM No response HS | 0.778 | | Assumed to be 0.0644 (utility gain from surgery) higher than the utility of inadequately controlled | | |
| Post-op controlled disease - patients from ECM No response HS | 0.778 | | Assumed to be 0.0644 (utility gain from surgery) higher than the utility of inadequately controlled | | |
| Post-op controlled disease - patients from Inadequately controlled HS | 0.778 | | Assumed to be 0.0644 (utility gain from surgery) higher than the utility of inadequately controlled | | |
| Post-op controlled disease - patients from Uncontrolled HS | 0.738 | | Assumed to be 0.0644 (utility gain from surgery) higher than the utility of Uncontrolled | | |

*Figure 6. Screenshot of the model changes – Sensitivity Analyses worksheet – EAG model – ACM2 preferred assumptions (deterministic)*



Cost-effectiveness model for dupilumab in adult patients with uncontrolled chronic rhinosinusitis with nasal polyps following one or more sinus surgery in England

OVERVIEW | INPUTS | RESULTS | REFERENCE

SENSITIVITY ANALYSES INPUTS

Sensitivity Analyses Inputs

The sensitivity analyses inputs set out the values for the model inputs that are included in the one-way sensitivity analysis (one-way SA) and probabilistic sensitivity analysis (PSA). Individual adverse events are not varied in the one-way SA. However, the total cost of treating adverse events is varied.

*The default one-way bounds and PSA parameters are based on the default model input values. Hence, if any changes have been made to the model input values on the preceding worksheets, corresponding changes may need to be made to the one-way SA bounds and PSA parameters before running the sensitivity analyses.*

| | | One-Way Bounds | | Probabilistic Sensitivity Analysis | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Model Input | Current Value | Lower | Upper | Distribution | SE | Alpha | Beta | Random Draw | Sampled Value | Analysis Value | PSA variation |
| Utility for DUP+ECM patients during Week 0 - 12 in the decision tree | 0.698 | 0.672 | 0.723 | Beta (baseline) + Normal (cfb) | | | | | 0.698 | 0.698 | Varied in the baseline carachteristics and equal to baseline utility (line 20 of this sheet) |
| Utility for DUP+ECM patients during Week 12-24 in the decision tree | 0.843 | 0.805 | 0.882 | Beta (baseline) + Normal (cfb) | | | | | 0.843 | 0.843 | Baseline already varied in sheet "baseline characteristics" and cfb varied in sheet "utility data" |
| Utility for DUP+ECM responders during Week 25-52 in the decision tree | 0.876 | 0.833 | 0.918 | Beta (baseline) + Normal (cfb) | | | | | 0.876 | 0.876 | Baseline already varied in sheet "baseline characteristics" and cfb varied in sheet "utility data" |
| Utility for DUP+ECM nonresponders during Week 25-52 in the decision tree | 0.806 | 0.731 | 0.881 | Beta (baseline) + Normal (cfb) | | | | | 0.806 | 0.806 | Baseline already varied in sheet "baseline characteristics" and cfb varied in sheet "utility data" |
| Utility for ECM patients during Week 0 - 12 in the decision tree | 0.698 | 0.672 | 0.723 | Beta (baseline) + Normal (cfb) | | | | | 0.698 | 0.698 | Baseline already varied in sheet "baseline characteristics" |
| Utility for ECM patients during Week 12-24 in the decision tree | 0.767 | 0.726 | 0.807 | Beta (baseline) + Normal (cfb) | | | | | 0.767 | 0.767 | Baseline already varied in sheet "baseline characteristics" and cfb varied in sheet "utility data" |
| Utility for ECM responders during Week 25-52 in the decision tree | 0.816 | 0.657 | 0.975 | Beta (baseline) + Normal (cfb) | | | | | 0.816 | 0.816 | Baseline already varied in sheet "baseline characteristics" and cfb varied in sheet "utility data" |
| Utility for ECM nonresponders during Week 25-52 in the decision tree | 0.768 | 0.711 | 0.825 | Beta (baseline) + Normal (cfb) | | | | | 0.768 | 0.768 | Baseline already varied in sheet "baseline characteristics" and cfb varied in sheet "utility data" |
| Utility for patients in controlled disease health state | 0.866 | 0.792 | 0.940 | Beta (baseline) + Normal (cfb) | | | | | 0.866 | 0.866 | Baseline already varied in sheet "baseline characteristics" and cfb varied in sheet "utility data" |
| Utility for patients in inadequately controlled disease health state | 0.727 | 0.700 | 0.831 | Beta (baseline) + Normal (cfb) | | | | | 0.727 | 0.727 | Baseline already varied in sheet "baseline characteristics" or "inadequately controlled" utility va |
| Utility for patients in uncontrolled disease health state | 0.686 | 0.661 | 0.711 | Beta (baseline) + Normal (cfb) | | | | | 0.686 | 0.686 | Varied in the baseline carachteristics and equal to baseline utility (line 20 of this sheet) |
| Utility gain from surgery | 0.064 | 0.058 | 0.071 | Normal | 0.005 | 162 | 2347 | | 0.058 | 0.064 | SE from Tashman et al. 2024 |
| Utility for patients in Post-op controlled disease - patients from DUP+ECM No response health state | 0.778 | 0.789 | 0.952 | Already varied | | | | | 0.778 | 0.778 | HS of origin and utility of surgery already varied independently |
| Utility for patients in Post-op controlled disease - patients from ECM No response health state | 0.778 | 0.769 | 0.895 | Already varied | | | | | 0.778 | 0.778 | HS of origin and utility of surgery already varied independently |
| Utility for patients in Post-op controlled disease - patients from Inadequately controlled health state | 0.778 | 0.758 | 0.902 | Already varied | | | | | 0.778 | 0.778 | HS of origin and utility of surgery already varied independently |
| Utility for patients in Post-op controlled disease - patients from Uncontrolled health state | 0.738 | 0.719 | 0.782 | Already varied | | | | | 0.738 | 0.738 | HS of origin and utility of surgery already varied independently |

Thank you for the opportunity to provide this document to support the PSA correction.

Thank you for the opportunity to provide further clarity on the calculations used to describe the transitions between the post operative controlled and uncontrolled health states. We have broken down our response into the following sections.

1. **Brief description of the distinction between the two health states and transition probabilities**
2. **'Post operative controlled' to 'Uncontrolled' health state.**
   2.1. Derivation of the Sanofi estimate of 42.8% per year
   2.2. Context from published real world studies and clinical opinion
   2.3. Discussion about the EAG derivation of 15% per year
3. **'Uncontrolled' to 'Post operative controlled' health state.**
   3.1. Derivation of the Sanofi estimate of 7% per year
   3.2. Context from clinical opinion
   3.3. Discussion about the EAG derivation of 39% per year
4. **Conclusion**

# 1. Brief description of the distinction between the two health states and transition probabilities

Two key transitions are required to represent the clinical pathway following revision endoscopic sinus surgery (ESS) for CRSwNP patients in our model (severe uncontrolled with at least 1 prior surgery):

- **Transition A: Post-operative controlled → uncontrolled (relapse after revision surgery).**
- **Transition B: Uncontrolled → post-operative controlled (revision surgery).**

It is important to note that these transitions apply to different patient populations.

*Transition A* represents the probability that a patient who has just undergone a revision surgery (2$^{nd}$ or more) relapses within one year.

*Transition B* represents the annual probability that an uncontrolled patient undergoes revision surgery (2$^{nd}$ or more). This therefore concerns ANY uncontrolled patients, not patients who just underwent Transition A in the previous cycle (that is, loss control following a revision surgery).

There is an important distinction to be made between these two transitions because in 'usual clinical practice' many uncontrolled patients DO NOT go on to receive further surgery or take many years before accessing subsequent surgeries. This is because patients become 'stuck' at various points along the pathway for example circling round in primary care or are diverted to other medical therapy but, crucially, others some simply give up, having had multiple polyp recurrence following surgery and feel that there is no point in continuing even when their symptoms return.

This was reinforced at committee by the clinical expert as fully reflective of clinical practice in England. This was further highlighted by Professor Owen towards the end of the second committee meeting when she directed the attention of the committee to the model diagram and explained the independence of these two transition probabilities.

From a practical standpoint, this means the denominators are different and these transitions are not algebraically related in the real world. They should not be derived from each other to simply complete the 'loop', for example to ensure that the '*Post-operative controlled'* to *'uncontrolled'*

*(relapse after revision surgery)* back to *'post-operative controlled'* loop sums to 14.5% (taken from the Benson paper).

The following points takes each of these transition probabilities in turn.

# 2. 'Post operative controlled' to 'Uncontrolled' health state.

## 2.1 Derivation of the Sanofi estimate of 42.8% probability per year

There are several sources from which to estimate the transition probability from the *'Post-operative controlled' to 'uncontrolled' (relapse after revision surgery)* heath states. These are discussed in section 2.2 below. We chose the Benson 2023 publication because it provided the most up to date UK evidence however the derivation of the transition probabilities from it required some assumptions to be made.

The patient group of interest for the calculation of the post-op controlled to uncontrolled transition probability was the interval between second and third surgeries. This most closely aligns with the patient group of interest in the appraisal. The important data in Benson are:

- Number of patients with 2 surgeries = 722
- Number of patients with 3rd surgery = 122
- Mean interval between 2nd and 3rd surgery = 2.40 years

The clinicians at the first committee meeting verified our finding (taken from clinical opinion at an advisory board) that that the current waiting list for Endoscopic Sinus Surgery (ESS) in England is amongst the longest of any therapy area with an average wait of around 2.00 years, but the total duration of the pathway can be much longer.

- NHS average waiting time for ESS (UK advisory board, validated by clinical experts): 730 days = **2.00 years**

The time to relapse and referral is not available in Benson. Therefore, we have calculated this according to the data above. We have made the assumption that the 122 patients out of the total population (n=722 with two surgeries) who received a third surgery during the full observation period in Benson 2023 would had to have lost control after their second surgery and been referred within an average of 0.40 years (as on average, their third surgery took place 2.40 years after their second surgery). This accounts for the current NHS constraints to access surgery and allows us to calculate the annualised relapse probability.

- Time for patients to be referred to third surgery: 2.40 – 2.00 = **0.40 years** (5 months)
- Proportion of patients having a 3rd surgery: P = 122/722 **= 0.17 (17%).**
- Annualised relapse probability = P / time to relapse = 0.17 / 0.40 (rounded) = 0.43 = 0.428 (**42.8%)**

## 2.2. Context from published real world studies and clinical opinion

In the Draft Guidance for Dupilumab for treating severe chronic rhinosinusitis with nasal polyps (ID6480), NICE reported that "the clinical experts said it would be almost impossible to wait only 1 year for revision surgery after referral, and at least 2 years was more likely. They also said that a probability of 42.8% per year for CRSwNP to become uncontrolled again after surgery was reasonable, noting that 10% of people still have severe symptoms despite surgery. This probability was confirmed by the clinical expert at the second committee meeting.

SINUS UK provided evidence to the committee from a survey of 51 people that showed that half had their symptoms return with 6 months of surgery. The clinical experts also noted that the polyps regrow within 6 months in about a third of people.

Published data confirms that the estimate used in the Sanofi model of 42.8% is reasonable. (Table 1)

*Table 1. Evidence for loss of control (relapse) following sinus surgery.*

| Transition | Data source &method | Annual probability | Notes / assumptions |
|---|---|---|---|
| B. Relapse – Expert validation | NICE draft guidance: "42.8% relapse per year reasonable" | 42.8% | Consensus of UK clinical experts; aligns with Benson sensitivity upper bound |
| B. Relapse – DeConde 2017 (cohort, US) | 12-month recurrence 38% baseline; prior ESS OR=2.6 (95% CI: 1.5–4.6) | 61.0% | Illustrative scenario: applying OR to 1-year baseline recurrence. Reflects higher relapse risk in revision populations |
| B. Relapse – Lourijsen 2022 (PolypESS RCT, NL) | ESS + medical therapy arm: substantial uncontrolled disease at 12 months; non-responders ~46% | 46.0% | High-quality RCT; confirms ~40–50% relapse at 1 y even under trial conditions |

Clinical experts advised that the most relevant sources for informing relapse after ESS are DeConde et al. (2017) and Lourijsen et al. (2022), owing to their strong methodological quality and direct reporting of annual probabilities.

DeConde et al. (2017) was a large, prospective multicentre cohort study that reported an annual probability of 38% recurrence at 12 months after ESS. Using multivariable logistic regression, the study identified prior ESS as an independent predictor of further recurrence, with a statistically significant odds ratio of 2.6 (95% CI: 1.5–4.6). This indicates that revision populations face relapse probabilities substantially higher than 38%, plausibly in the 50–60% range.

Lourijsen et al. (2022; PolypESS) was a randomised controlled trial comparing ESS plus medical therapy against medical therapy alone. At 12 months, despite surgery, 46% of patients remained uncontrolled, demonstrating with high internal validity that nearly half of patients relapse within one year.

Both studies report annual probabilities, not rates, making them directly comparable with model inputs. Their robust methodologies (prospective multicentre cohort design and randomisation) provide strong external validity, while the fact that they were highlighted by UK clinical experts during advisory boards, consultancy, and both NICE committee meetings underscores their clinical relevance. Importantly, these publications were also provided to NICE as confirmatory and alternative sources of evidence in our clarification questions response and draft guidance response.

Taken together, the peer-reviewed evidence and consistent expert endorsement support an annual relapse probability of around 40–60% following revision surgery, fully justifying the transition probability applied in our model.

## 2.3 Discussion about the EAG derivation of 15% per year

The EAG have calculated 15% for the loss of control transition probability. This is derived from a simplistic view of the data and includes insupportable assumptions with no cross checking to real world evidence.

In Benson 14.5% of patient had received a third surgery within 3 years of their second surgery. This is taken from the published Kaplan Meier curve. Given a 2 year wait list, if 14.5% of patients have surgery at 3 years then the EAG argue that 14.5% must have lost control at 1 year to be on the wait list and receive surgery at the 3-year time point. The EAG estimate relies on the very strong assumptions that all patients losing control receive subsequent surgery within 2 years and all patients who lose control are referred immediately for surgery.

This calculation is fundamentally flawed for several reasons.

- Not ALL patients go on to receive surgery after losing control. Many will simply not be put on the wait list as described above.
- Not ALL patients actually receive surgery by the 2-year time point. The 2 year estimate is the average time for patients to receive surgery after being referred. (By definition around half of those on the wait list will wait longer than 2 years).
- 15% is significantly lower than the alternatives published (DeConde 2017 and Laurijsen 2022) and if true would indicate that FESS in the UK is considerably more effective in the population of interest than the testimony of the clinical experts or patient groups suggests.
- If the probability was 15% then under clinical practice there would be a very short waiting list in the UK, a point made by the patient groups in committee. (Especially when considering the high surgery probability calculated by the EAG at 39.4% (See Section 3 below).

# 3. ‘Uncontrolled’ to ‘Post operative controlled’ health state.

## 3.1. Derivation of the Sanofi estimate of 7% per year

We have noted above in Section 2.1 that out of the 722 patients with two surgeries in Benson, 122 patients had a third surgery within 2.4 years. This leads to the simple calculation that 17% received a subsequent surgery and that the observed annualised probability is 7.1%:

- Denominator ($n_2$): 722 patients with ≥2 during observation.
- Numerator ($n_3$): 122 had a third surgery during observation.
- Mean interval between 2nd and 3rd surgery (875 days): S = 875 / 365.25 = **2.40 years** (2 years and 5 months)
- Proportion: P = 122 / 722 = 0.17 = **17%**
- Annual observed surgery probability: 0.17 / 2.40 = 0.071 = **7.1%**

Therefore, in an average year, **7.1%** of patients who have had a second operation go on to receive a third operation within current clinical practice.

It is critical to recognise that this DOES NOT represent the full ‘loop’. In Benson et al. (2023), patients with more than two surgeries had a mean total follow-up of 7.9 years. Accounting for the time required to undergo their first and second surgeries, these patients still had on average 5.2 years of follow-up remaining. This period is more than sufficient for relapse to occur, given that the published literature consistently reports annual relapse probabilities of 40–60% after surgery (DeConde 2017; Lourijsen 2022).

In other words, most of these patients would have relapsed during the available follow-up. Nevertheless, only 122 of 722 patients (17%) went on to have a further (third) surgery, at a mean interval of 2.40 years after their second procedure. This translates to an annualised surgery probability of ~7%. The discrepancy between the high likelihood of relapse and the small fraction receiving surgery demonstrates that the 7% figure does not reflect the natural history of disease but rather the systemic constraints of the NHS, including referral practices, waiting times, and surgical capacity.

## 3.2. Context from clinical opinion

This low probability of surgery observed in Benson highlights the significant capacity constraints with the NHS and for this reason the company was challenged at the first committee meeting that the original estimate of 14.8% probability for revision surgery was too high. We revised our calculations and derived the new estimate of 7.1% discussed above. This was supported by the clinical and patient experts. Therefore, we were surprised to see that the EAG had produced a much higher estimate in their response to the first committee meeting.

## 3.3. Discussion about the EAG derivation of 39.4% per year

The EAG have followed up their calculation of the loss of control transition probability (See section 2.3 above) by simply converting the expected 2 year wait for surgery to an annualised probability of 39.4% per year. This is contrary to their original position at ACM which criticised the original Sanofi estimate of 14.8% as too high.

A probability of 39.4% is not credible for the following reasons:

- It is not correct to complete the loop by adjusting the loss of control and revision surgery transitions to fit the data without regard for the published evidence.
- It is important to recognise that the probability of revision surgery is not solely connected to the probability of loss of control because fewer patients will go on to receive subsequent surgeries (See the reasons discussed above in Section 1).
- At committee the EAG confirmed that their methodology did make the strong assumption that all patients with loss of control would go on to have subsequent surgery AND that all patients becoming uncontrolled were immediately referred for their next surgery, which is not realistic, and opposed to the clinical experts' description of the current patient pathway.
- This is contrary to the testimony provided by the clinical and patient experts and the published literature.

# 4. Conclusions

We are grateful to the Committee B lead team for the opportunity to provide further clarification and supporting arguments to reinforce the Sanofi modelling assumptions.

In our response we have shown how the derivation of the Sanofi transition probabilities was carried out and how these fit with the published evidence.

At the first committee meeting the EAG agreed that the evidence for UK based transition probabilities to describe loss of control and revision surgery probabilities in the population of interest was scarce and after consideration of our methodology they adopted the company estimates in their original base case.

We have provided a commentary on the alternative approach put forward by the EAG for ACM2 and shown that whilst this may match the data in the Benson publication mathematically it applies assumptions that are too strong. For example, the ascertain that all patients with loss of control go on to have subsequent surgery within 2 years with no regard to the weight of the evidence or clinical testimony. Indeed, this was recognised as a weakness by the EAG at committee.

Finally, we would like to remind the lead team that in response to robust challenge around the veracity of the Sanofi calculations from one committee member, an opposing view was put forward after consideration of the Sanofi approach, by the academic statistician committee member in support of the Sanofi position.

# Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis [ID6480]

Post ACM2 EAG addendum

September 2025

**Source of funding**

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 174243.

# 1 EAG response following ACM2

### *1.1.1 Derivation of transition probabilities based on available data*

Firstly, the EAG highlights that while they previously used the company's values for transition probabilities prior to ACM1, it was noted that there was uncertainty in how these had been derived, which was discussed at ACM1. As a response to committee concerns at ACM1 the EAG updated their approach to address some of these uncertainties and also noted the limitations of the updated approach, as discussed in committee.

The EAG notes that a key issue is that the model structure has been designed in a way that follows clinical practice but does not lend itself to using the available data in the way that it has been reported. As such, to derive transition probabilities, assumptions needed to be made. The pivotal assumption applied in both the EAG and company approaches was the 2-year waiting list time. The difference in how this has been applied is what leads to the key differences in transition probabilities. In addition, while both the company and EAG approach used data on 2nd to 3rd revision surgery from Benson *et al.*,[1] the key data used differed between the EAG and the company, as the EAG had issues with the methods used to derive probabilities in the company's approach. The EAG notes that the values used from Benson *et al.* in the company approach do not represent the correct method to calculate a rate (or probability). The rate should be calculated as the number of events observed divided by the total exposure time, rather than by the mean time in only those patients who experienced the event (surgery). This can then be converted to an annual probability using the standard formula for rate to probability conversion, which was also not done by the company.

While the company transition probabilities may result in estimates that were in line with the views of the clinical expert, they did not have mathematical validity in how they were derived. Based on the feedback received at ACM2 from the clinical expert that suggests around 40% of patients would lose control with the first year following revision surgery, and the RCT evidence highlighted by the company that found 46% of patients were classed as uncontrolled in the 12 months following surgery (Lourijsen *et al.* 2022),[2] the EAG considers using a combination of the RCT data to represent the probability of loss of response and the Benson KM data to be an alternative approach to derive the transition probability for uncontrolled to post-op controlled. The EAG still considers the Benson KM data on 14.5% of patients having third surgery by 3 years to be the best data available to

represent the full loop of going from second surgery to third. However, using the estimate of 0.46 for the probability of post-op controlled to uncontrolled means that it is no longer essential to assume a waiting list of 2 years for surgery, as used previously in both the company's and EAG approach, in order to solve for the 'missing' probability to produce 14.5% having surgery at three years. Instead, it is possible to solve for the probability of surgery (uncontrolled to post-op controlled) given the 0.46 probability of losing control and 0.145 having surgery by three years, based on the following and solving the resulting quadratic formula for 'x' (uncontrolled to post-op controlled [i.e. surgery]):

*0.46 * x [people losing control in yr1 and getting surgery in yr2]*

*+ 0.46 * (1-'x') * x [people losing control in yr1, not getting surgery in yr2, but getting surgery in yr3]*

*+ (1-0.46) * 0.46 * x [people not losing control in yr1, losing control in yr2, getting surgery in yr3]*

*= 0.145*

**This results in a transition probability of uncontrolled to post-op controlled of 0.13**

The EAG notes that the resulting transition probabilities are in line with the testimony heard from the clinical and patient experts at ACM2, but also result in mathematically valid estimates. The EAG has presented the cost-effectiveness results including the committee's preferred assumptions and the alternative transition probabilities in Section 2.

### *1.1.2 Additional points*

During ACM2 it was noted that the EAG's approach to deriving the transition of uncontrolled to post-op controlled, based solely on a two-year waiting list for surgery, results in all patients who become uncontrolled being put immediately on to a waiting list for subsequent surgery. The EAG notes that the company model includes a proportion of patients who are ineligible for surgery (10%) and therefore not all patients in the uncontrolled health state would transition to the post-op controlled health state as these patients remain in the uncontrolled state.

During ACM2, the company noted that using their transition probabilities results in around 15% of patients receiving surgery by three years in the model, in line with the Benson data of 14.5%. The

company has not provided any further evidence of how they obtained this value, and the EAG was unable to verify this from the company's model.

The model structure includes an initial decision tree, in which some patients could have surgery, and additional health states to the previously mentioned 'uncontrolled' and 'post-op controlled', as patients can also be in the controlled state and temporary health state of inadequately controlled, which prevents patients from moving straight to uncontrolled from controlled. Therefore, it is not appropriate to directly compare values from the model trace for those who had surgery at 3 years with the 14.5% from Benson *et al*. However, the EAG notes that at 3 years in the Markov model (i.e. year 4 including the decision tree), 3.3% of patients in the company's model remain in the post-op controlled health state (from the uncontrolled health state). This is 16.9% in the EAG base-case presented at ACM2 and 5.3% in the scenario using the updated transition probabilities presented in Section 1.1.1. As discussed, this is not directly comparable to the 14.5% from Benson *et al.*

The EAG's view is that the EAG base case presented at ACM2 reflected the 14.5% from Benson *et al.* but was incoherent with clinician and patient experts' views on the proportion of patients likely to remain in the controlled health state. The updated ICER (committee preferred ICER), addresses this by imposing the annual probability of losing control from Lourijsen *et al.* 2022. However, a consequence of the model structure means that the proportion having surgery at 3 years is likely to be less than 14.5%. The EAG considers that the true ICER may lie somewhere between these two estimated ICERs.

# 2 Committee preferred ICER

Table 1 below presents the cost-effectiveness results using the committee preferences and the following updated transition probabilities:

- Uncontrolled to post-controlled = 0.1308 (also applied for inadequately controlled to post-op controlled);
- Post-op controlled to uncontrolled = 0.46.

Committee additional preferences:

- Updated population;
- Responder rates based on original response criteria and population (responder rates using the original response criteria with the updated population were not provided);

- EQ-5D utilities with a general population cap applied;
- EAGs approach for long-term effectiveness year 2+; excluding first 12 months AROMA in trendline;
- Adherence based on EAG approach; SINUS trial data for the first year followed by asthma Sanofi homecare data.

Table 1. Cost-effectiveness results using committee preferred assumptions and updated transition probabilities

| Interventions | Total Costs (£) | Total LY* | Total QALYs | Incremental costs (£) | Incremental LYs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| **Deterministic results** | | | | | | | |
| ECM only | [redacted] | [redacted] | [redacted] | - | - | - | - |
| Dupilumab + ECM | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Probabilistic results** | | | | | | | |
| ECM only | [redacted] | [redacted] | [redacted] | - | - | - | - |
| Dupilumab + ECM | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations:; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; NR, not reported
*Undiscounted

# 3 References

1. Benson VS, Fu Q, Yang S, Sousa AR, Chan RH, Howarth P, et al. Real-world characterisation of patients with chronic rhinosinusitis with nasal polyps with and without surgery in England. *Clin Otolaryngol* 2023; **48**: 680-8.
2. Lourijsen ES, Reitsma S, Vleming M, Hannink G, Adriaensen GFJPM, Cornet ME, et al. Endoscopic sinus surgery with medical therapy versus medical therapy for chronic rhinosinusitis with nasal polyps: a multicentre, randomised, controlled trial. *The Lancet Respiratory Medicine* 2022; **10**: 337-46.