Dupilumab for treating severe chronic rhinosinusitis with nasal polyps

Part 1 slides for Zoom – redacted

Technology appraisal committee B, 3 September 2025

Chair: Charles Crawley

External assessment group: BMJ Technology Assessment Group

Technical team: Emilene Coventry, Nigel Gumbleton, Emily Crowe

Company: Sanofi

Dupilumab for treating severe chronic rhinosinusitis with nasal polyps

- ✓ **Recap from first appraisal committee meeting**
- ❑ Consultation comments
- ❑ Company response and EAG critique
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Dupilumab (Dupixent, Sanofi)

Marketing authorisation	• Indicated 'as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control' • MHRA MA January 2021
Mechanism of action	• IgG4 monoclonal antibody that blocks IL-4 and IL-13 signalling • Decreases mediators in type 2 inflammation that drive the condition
Administration	• 300 mg every 2 weeks • Self-administered by subcutaneous injection using single-use prefilled syringe or pen
Price	• £1,264.89 per pack of 2 pre-filled pens or pre-filled syringes • £16,500 per patient per year • Simple discount PAS applies

CRSwNP, chronic rhinosinusitis with nasal polyps; EMA, European Medicines Agency; MHRA, Medicines and Healthcare products Regulatory Agency; MA, marketing authorisation; IL-4, interleukin 4; IL-13, interleukin 13; PAS, patient access scheme

Draft guidance recommendation

Dupilumab is not recommended for severe chronic rhinosinusitis with nasal polyps

Committee recognised:

- severe CRSwNP is a distressing condition with a serious impact on people's lives
- the need for an effective, targeted treatment
- potential uncaptured benefits related to EQ-5D's lack of sensitivity in severe CRSwNP
- dupilumab's potential to reduce need for oral corticosteroids

But high level of uncertainty, in the model specifically:

- data used to estimate treatment effectiveness beyond 1 year
- transition probabilities for people moving from the post-op controlled to the uncontrolled health state
- utility values

Analyses requested by committee at the first appraisal committee meeting

Model treatment effect: beyond 1 year based on AROMA data formally matched to the SINUS trials that accounts for differences in how responders are classified

Transition probabilities: clarity on the proportions of different types patients in the post-op uncontrolled health state to inform the annual rate of revision surgery and data and assumptions used for calculation

Utilities:

- values based on EQ-5D from SINUS trials capped at general population age and sex-matched utility values
- utility gain from revision surgery based on Remenschneider et al. 2015

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Consultation comments

Comments received from:

- SINUS UK
- SmellTaste (formerly Fifth Sense)
- Association of Respiratory Nurses
- Clinical expert Claire Hopkins
- 7 web comments
- Company (Sanofi)

Comments from patient groups

SINUS UK and SmellTaste (formerly Fifth Sense)

- Welcome committee conclusion that CRSwNP is a distressing condition with a serious impact on people's lives and lack of effective treatment options
- Disappointed with recommendation; leaves 10% for whom surgery does not work with no other option; dupilumab 'lifeline' for these people – can committee focus on these?
- Accepts uncertainties in economic model and that this needs to be re-evaluated
- 0.73 utility value for [uncontrolled] CRSwNP does not reflect significant impact on quality of life or committee conclusion; EQ-5D does not fully capture impact of CRSwNP - e.g. 'mobility' and 'self care' are not likely to be factors; smell loss not captured; SNOT-22 better
- Would like to see ICER better reflect true impact of CRSwNP with hope that this would allow dupilumab to be available on the NHS – huge benefit to many patients e.g. lessening financial burden to patients and NHS, significant quality of life impact (especially smell and taste)
- Comments from patients: frustration at lack of treatment options; reiterate how debilitating condition is, especially smell/taste loss

Comments from professional group

Association of Respiratory Nurses

- More evidence may be needed: some limited data in severe asthma patients with co-existing polyps and nasal issues who have benefited
- Would be more cost effective for people with severe, uncontrolled disease whose quality of life is affected and have a significant symptom burden

Comments from clinical expert

Claire Hopkins, Professor of Rhinology, Guy's and St Thomas' Hospitals NHS Trust

- Disappointed; background information did not capture severe effect on quality of life or challenges in diagnosis and care; postcode lottery to access available resources
- Surgery gives short-term relief but in 30% to 50% symptoms recur – need for repeated surgeries and courses of oral corticosteroids (with associated side effects) until they give up; about 10% have no benefit at all from surgery
- Committee did not consider patients who have no effective treatment, e.g. aspirin-exacerbated respiratory disease, multiple surgeries; unjust to consider only relative cost effectiveness when no other effective treatment
- Committee overlooked importance of sense of smell from both a safety and mental health point of view; not captured by the EQ-5D data used to inform the ICER
- Dupilumab has dramatic impact on quality of life: "life changing"
- Committee should make exceptions to allow treatment for small, well-defined group of patients within specialist centres; chance to optimise whole treatment pathway, reduce revision surgeries (and therefore waiting lists) and improve outcomes
- UK one of only 2 European countries where biologics not available for selected patients

ICER, incremental cost effectiveness ratio

Web comments

7 contributions

- Disappointed; urge NICE to reconsider, support targeted access for the most severe patients, and ensure fair, modern treatment options
- Patient impact: CRSwNP severely affects quality of life – sleep, smell, breathing, mood, daily function – despite medication and repeated surgeries
- Evidence base: strong clinical trial and real-world data show dupilumab has significant benefits in terms of symptom control, reduced surgery, improved smell, and less corticosteroid use
- Equity concern: current draft recommendation leaves UK patients disadvantaged compared with most of Europe, where biologics are reimbursed
- System burden: without access, patients face repeated surgeries, steroid-related harms, and wider NHS/societal costs.
- Economic model: current ICER assumptions undervalue CRSwNP's true burden; a re-evaluation could demonstrate cost-effectiveness

Equality considerations

SmellTaste (formerly Fifth Sense)

- People with severe CRSwNP face unequal access to dupilumab
- People with both severe asthma and CRSwNP can receive the drug on the NHS through their asthma diagnosis while those with CRSwNP alone, regardless of severity, cannot

Association of Respiratory Nurses

- Recommendations do not appear to unlawfully discriminate against any group of people
- In practice funding can vary depending on geographic area and the speciality care provided

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Company ACM2 updated base case assumptions vs ACM1 (1/4)

Assumption	Company ACM2 updated base case	Company ACM1 base case
Population	People with uncontrolled CRSwNP who have had at least 1 surgery **and a SNOT-22 score of at least 50**	People with uncontrolled CRSwNP who have had at least 1 surgery
Response criteria	SNOT-22 **total score under 50 or** an at least 8.9 point improvement And an improvement of at least 1 in NPS	SNOT-22 least 8.9 point improvement and an improvement of at least 1 in NPS
Long-term effectiveness from year 2	Based on analysis of AROMA with matching against SINUS trials. **Year 2:** [redacted] **year 3:** [redacted] **year 4+:** [redacted]	Based on analysis of AROMA. **Year 2**: [redacted] **year 3**: [redacted] **year 4+**: [redacted]

NICE ACM, appraisal committee meeting; CRSwNP, chronic rhinosinusitis with nasal polyps; ECM, established clinical management; NPS, nasal polyp score; SNOT-22, 22-item sinonasal outcomes test

Company ACM2 updated base case assumptions vs ACM1 (2/4)

Assumption	Company ACM2 updated base case	Company ACM1 base case
Source of utility values	**EQ-5D data** from pooled SINUS trials based on updated population (SNOT-22 ≥50). **Inadequately controlled disease utility value average between baseline and week 52 (SINUS pooled data)**	SNOT-22 data from pooled SINUS trials mapped to EQ-5D. Inadequately controlled disease utility value based on non-responders at week 52
Utility gain following revision surgery	From Tashman 2024: **0.0644**	From Soler 2011: 0.051 (sensitivity analysis using Remenschneider 2015: 0.080)

Company ACM2 updated base case assumptions vs ACM1 (3/4)

Assumption	Company ACM2 updated base case	Company ACM1 base case
ECM probability of moving from controlled to inadequately controlled state from year 2	Aligned with transition probability for post-op controlled to uncontrolled state calculated from Benson et al. 2023) **42.8%**	Extrapolation of the rate of ECM SINUS trials week 52 responders among week 24 responders, annualised: [redacted]
Transition probability from uncontrolled or inadequately controlled to post-op controlled	Updated extrapolation of the mean rate of surgery from Benson et al. 2023: **7.1%**	Extrapolation of the mean rate of surgery from Benson et al. 2023: 14.8%

ACM, appraisal committee meeting; ECM, established clinical management

Company ACM2 updated base case assumptions vs ACM1 (4/4)

Assumption	Company ACM2 updated base case	Company ACM1 base case
Percentage of scheduled doses given to patients (adherence)	Extrapolated from real-world data (Sanofi UK homecare): [redacted]	Extrapolated adherence reported in pooled analysis of SINUS-24/52: 99.26%

ACM, appraisal committee meeting; ECM, established clinical management; SNOT-22, 22-item sinonasal outcomes test

Company response: updated population definition (1/3)

Definition of severe CRSwNP now includes SNOT-22 score of 50 or more

Background

Original modelled population definition of severe CRSwNP: uncontrolled disease and at least 1 surgery based on 2020 European Position Paper on Rhinosinusitis and Nasal Polyps criteria

Company draft guidance response

- Toma and Hopkins 2016 classified severe CRSwNP as SNOT-22 score over 50; this definition used in Europe and as inclusion criteria in phase 4 study DUPIREAL in severe disease
- Original population: mean SNOT-22 score 51.63 (SD: 20.19), median of 50; score range of 8 to 110 suggests some patients would not meet the specific SNOT-22 ≥50 severity threshold
- Likely to have affected utilities calculated from EQ-5D data
- Updated population: **CRSwNP patients with severe, uncontrolled disease, at least 1 previous surgery, and SNOT-22 score of 50 or over**

EAG critique

- New definition appears to reflect one of the definitions used in clinical practice
- Excludes nearly half original company submission population: 230 of original 459 patients (50.1%) included in the updated analysis

ACM, appraisal committee meeting; CRSwNP, chronic rhinosinusitis with nasal polyps; NPS, nasal polyp score; SD, standard deviation; SNOT-22, 22-item sinonasal outcomes test

Company and EAG base case aligned assumptions

Company response: updated population definition (2/3)

EAG: concerns around breaking randomisation

EAG critique

- Updated results only apply to people in clinical practice with severe disease based on the company's updated definition, using EPOS criteria and a SNOT-22 score of at least 50
- Updated population results in breaking randomisation (original populations not stratified by SNOT-22 score) – company has tried to mitigate by reporting comparative baseline characteristics
- But concerns remain: unobserved confounding factors with unknown influence on comparative effectiveness
- Change in population did not affect interpretation of results, with statistically significantly greater improvements with dupilumab than placebo for NPS and SNOT-22 (see updated SINUS results)

ACM, appraisal committee meeting; EAG, external assessment group; EPOS, European Position Paper on Rhinosinusitis and Nasal Polyps; MCID, minimal clinically important difference; NPS, nasal polyp score; SD, standard deviation; SNOT-22, 22-item sinonasal outcomes test

Company response: updated population definition (3/3)

EAG: concerns around some missing results – for example NSAID-ERD

EAG critique (cont'd)

- No major concerns about updated population – but inconsistencies between population and results in original submission and company response to draft guidance, for example, results only reported for NPS and SNOT-22 in company response
- Greater concern: no results for some subgroups, for example people with NSAID-ERD, who have more severe disease so may meet company's updated criteria for severe CRSwNP
- EAG unable to manipulate model between original and updated population so any recommendation based on updated results would only apply to updated population

Clinical experts: is the updated population definition workable in NHS practice?

Does committee agree with the updated population definition?

ACM, appraisal committee meeting; CRSwNP, chronic rhinosinusitis with nasal polyps; EAG, external assessment group; NPS, nasal polyp score; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated respiratory disease; SD, standard deviation; SNOT-22, 22-item sinonasal outcomes test

Company response: updated model response criteria (1/5)

Updated response criteria to align with updated definition of severe CRSwNP

Background

- Original company response criteria: change from baseline of at least 1 in nasal polyp score and at least 8.9 in SNOT-22

Company draft guidance response

- Updated response criteria:
  - SNOT-22 under 50 **or** improvement in SNOT-22 of at least 8.9 **and**
  - nasal polyp score improvement of at least 1

CRSwNP, chronic rhinosinusitis with nasal polyps; MCID, minimal clinically important difference; SNOT-22, 22-item sinonasal outcomes test

Company and EAG base case aligned assumptions

Company response: updated model response criteria (2/5)

Overall population results for response – pooled SINUS trials

Base case	Original		Updated	
Timepoint and outcome	Plac + ECM	Dup + ECM	Plac + ECM	Dup + ECM
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	
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	

CI, confidence interval; ECM, established clinical management; OR, odds ratio; plac, placebo

Company response: updated model response criteria (3/5)

Subpopulation of responders at week 24 who also have response at week 52 – pooled SINUS trials

Base case	Original		Updated	
Outcome	Plac + ECM (n=5)	Dup + ECM (n=46)	Plac + ECM (n=1)	Dup + ECM (n=26)
Responders	[redacted]	[redacted]	[redacted]	[redacted]
Non-responders	[redacted]	[redacted]	[redacted]	[redacted]
OR, 95% CI vs placebo	Not evaluable		Not evaluable	
P-value vs placebo	<0.0001		<0.0001	

Company draft guidance response

- Notes small number of responders at week 24 with response at week 52 [to inform first year of model]
- These data do not inform transition probabilities in longer term Markov part of model because committee preferred AROMA data for this

CI, confidence interval; ECM, established clinical management; OR, odds ratio; plac, placebo

Company response: updated model response criteria (4/5)

Response data inputs used in the economic model

Timepoint	Original base case (inadequately controlled CRSwNP and at least 1 sinus surgery)		Updated base case (inadequately controlled CRSwNP and at least 1 sinus surgery and SNOT-22 at least 50)	
	Placebo + ECM	Dup + ECM	Placebo + ECM	Dup + ECM
% response at week 24	[redacted]	[redacted]	[redacted]	[redacted]
% response at week 52	[redacted]	[redacted]	[redacted]	[redacted]

EAG: company compares

- original population (less severe disease) plus original response criteria with
- updated population (more severe disease) using updated response criteria

More appropriate to compare original and updated response criteria in updated population – cannot determine how many more responders identified, impact in economic model not clear

Dup, dupilumab; EAG, external assessment group; ECM, established clinical management; SNOT-22, 22-item sinonasal outcomes test

Company response: updated model response criteria (5/5)

EAG: change does not appear to be justified or reflect clinical practice

EAG critique

- EAG's clinical experts did not agree with new definition of response – preferred definition in original company submission
- Reasons not related to treatment could cause SNOT-22 score to fall below 50; reduction of 8.9 points more important and aligns with MCID in original company submission
- Updated response criteria mean someone with only a small change in SNOT-22 score could be classed as a treatment responder, for example, with a baseline score of 51, a 2-point reduction classed as response – would not be the case using original criteria (≥8.9 change)
- Important issue because responder analysis forms part of the company's base case
- Statistical significance unchanged but considerably greater treatment effect and wider CIs
- EAG unable to use company original response criteria in the ACM2 model, so explored impact on ICER of using responder rates from original company base

Is the company original response criteria or updated response criteria most appropriate?

ACM, appraisal committee meeting; CI, confidence interval; EAG, external assessment group; ICER, incremental cost effectiveness ratio; MCID, minimal clinically important difference; SNOT-22, 22-item sinonasal outcomes test

Company response: model treatment effect beyond 1 year (1/3) Updated base case uses AROMA data matched to SINUS trials

Background: ACM1 conclusion: treatment effect beyond 1 year based on AROMA data formally matched to SINUS trials that accounts for differences in how responders are classified

Company draft guidance response

- Applied weights to patients in the AROMA registry to match the characteristics of patients in the SINUS trial (rate of prior systemic corticosteroid use, rate of comorbid NSAID-ERD, mean nasal congestion score and mean SNOT-22 total scores)
- Adjusted AROMA population used to calculate weighted long term discontinuation rates for real-world dupilumab use; used updated population and updated response criteria, censored patients needing rescue therapy

Probability of moving to inadequately controlled state from controlled years 2 onwards dupilumab + ECM	Year 2	Year 3	Year 4	Year 5+
Updated company base case ACM2	[redacted]	[redacted]	[redacted]	[redacted]
Original (based on AROMA with no matching to SINUS, rescue therapy not censored)	[redacted]	[redacted]	[redacted]	[redacted]

ACM, appraisal committee meeting; ECM, established clinical management; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated respiratory disease; SNOT-22, 22-item sinonasal outcomes test

Company and EAG base case different assumptions

Company response: model treatment effect beyond 1 year (2/3) EAG: concerns about methodology used for the exploratory matching exercise

Company draft guidance response (cont'd)

- For ECM, transition from controlled to uncontrolled from year 2 onwards now uses the post-surgery loss-of-response rate from Benson et al. (2023), estimated at 42.8%
- Conservative real-world figure compared to ACM1 [redacted]% annualised rate from SINUS-24/52

EAG critique

- Concerns over matching: AROMA did not report NPS so some differences in disease severity between populations may not have been accounted for
- AROMA matched to original SINUS ITT population* – more appropriate to match to updated population (especially because company showed that baseline disease characteristics differ between original and updated populations)
- No SNOT-22 scores reported for adjusted AROMA population
- Low number of patients beyond 12 months (6 in the updated AROMA population at month 24)

*Clinical experts: is it plausible to assume transition rates will be the same in the new population as in the original population?

ACM, appraisal committee meeting; EAG, external assessment group; ECM, established clinical management; ITT, intention to treat; NPS, nasal polyp score

Company response: model treatment effect beyond 1 year (3/3) EAG: concerns about long-term probabilities applied in model

EAG critique (cont'd)

- Disagrees with updated response criteria; impact of using original criteria unknown
- Inappropriate data inclusion: linear trend line used to inform probability from year 2 includes baseline to 12 month data, despite draft guidance stating using first 12 months inappropriate; EAG scenario month 12+ data; minimal ICER increase
- Conversion uncertainty: possible errors in converting AROMA rates to probabilities for loss of response and discontinuation
- Highly uncertain ECM data: original EAG base case used SINUS responder data – updated population means now only 1 ECM patient, with 100% response rate; inappropriate/unreliable
- Limited scenario testing: no updated matched AROMA analysis using original criteria; scenario impact unexplored
- ICER impact: company scenario using updated trial-derived probability for dupilumab increased ICER by £[redacted]

Is committee satisfied with the company's updated analysis? Should only month 12+ data from AROMA be used?

ACM, appraisal committee meeting; EAG, external assessment group; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; NPS, nasal polyp score

Company response: utilities (1/3)

Recalculated EQ-5D data used in company model for utilities

Background

- Company used SNOT-22 data from SINUS trials, mapped to EQ-5D, to calculate utilities
- Committee ACM1 conclusion: more appropriate to use SINUS trial EQ-5D data to calculate utilities, capped at population norms because trial EQ-5D controlled disease health state exceed population norms

Company draft guidance response

- Recognises issues around Crump et al. mapping algorithm for SNOT-22 to EQ-5D and NICE preference for EQ-5D data if available
- EQ-5D-5L utilities recalculated for updated population (mapped to EQ-5D-3L) – more realistic quality of life scores in more severe group
- No utility cap in base case but presented in sensitivity analysis
- Inadequately controlled disease utility value updated – average of baseline and non-responder at week 52 utility weights (SINUS pooled data; previously utility weight of non-responders at week 52); better reflects change in quality of life over timeframe

ACM, appraisal committee meeting; SD, standard deviation; SNOT-22, 22-item sinonasal outcomes test

Company response: utilities (2/3)

Capped EQ-5D-5L data (scenario)

Pooled SINUS trials EQ-5D-5L data (mapped to 3L) using updated population compared with original population (uncapped – base case)

Population	Original		Updated	
Health state	Dup + ECM	Plac + ECM	Dup + ECM	Plac + ECM
Decision tree				
W0 to W12	0.782		0.698	
W13 to W24[a]	0.883	0.827	0.858	0.780
W25 to W52 responders[b]	0.915	0.888	0.891	0.831
W25 to W52 non-responders[c]	0.845	0.814	0.820	0.781
Markov model				
Controlled disease (all responders utility at week 52)[d]	0.925		0.881	
Inadequately controlled disease[e]	0.793		0.739	
Uncontrolled disease	0.782		0.698	

[a]Utility at week 24; [b]average of utility for responders at W24 and W52; [c]average of utility for non-responders at W24 and W52; [d]population norm is 0.866; [e]average of the utility for non-responder patients at week 52 and baseline utility; utility values are adjusted to more appropriately reflect the expected midpoint of the time ranges represented by the health states

Abbreviations: dup, dupilumab; ECM, established clinical management; plac, placebo; SNOT-22, 22-item sinonasal outcomes test; W, week

Company response: utilities (3/3)

EAG: agrees with use of trial EQ-5D data but concerns remain

EAG critique

- Regression analysis: considered company's original regression method flawed; based on available values EAG used observed change from baseline approach; would have preferred EQ-5D derived from a regression analysis
- Capped utility values: company did not cap values exceeding general population norm because of minimal difference; capped values only used in scenario analysis
- Applying cap slightly increased ICER ([redacted] to [redacted]) because more dupilumab patients in controlled state
- EAG base case includes cap and proportional multiplier to health state utilities

- Is committee satisfied that the company's updated utility values are plausible and derived in line with the NICE reference case?
- Should utility values be capped or not?

EAG, external assessment group; ICER, incremental cost-effectiveness ratio

Company response: transition probabilities (1/2)

Background

- ACM1 conclusion: clarity needed on data and assumptions used to calculate annual rate of revision surgery

Company draft guidance response

- Maintain 42.8% transition from post-op controlled to uncontrolled (see slide for calculation), supported by literature
- Updated annual rate of revision surgery transition probability for uncontrolled to post op controlled = 7.1% (from 14.8%) (see slide for calculation)

EAG comments

Mean time between surgeries represents observed study period only; if 0.4 years assumption does not hold, resulting transition probability will differ

Company response: transition probabilities (2/2)

EAG: uncertainties remain around company calculations

EAG critique

- Incorrect probability conversion: company's annual transition to uncontrolled (42.8%) miscalculated; corrected to 37.2%, increasing ICER by under £[redacted]
- Surgery probability uncertainty: company's updated estimate (7.1%) based on Benson et al; EAG unable to verify calculation – not enough information provided for cross checking;
- Company applied lower rate of surgery in model because EAG previously noted previous value may be higher than expected; EAG still considers this parameter uncertain
- EAG alternative analysis of Benson et al. Kaplan–Meier data (see slide for data): given that 14.5% of people had a 3rd surgery 3 years after the 2nd, assuming a 2 year waiting list, estimated annual transition to uncontrolled health state is 15%, and surgery probability is 39.4%; used in EAG base case to reflect committee preferences from ACM1
- Company values retained in scenario analysis

What transition probabilities are preferred?

- Company: 42.8% post-op controlled to uncontrolled; 7.1% uncontrolled to post-op controlled
- EAG: 15% post-op controlled to uncontrolled; 39.4% uncontrolled to post-op controlled

ACM, appraisal committee meeting; EAG, external assessment group; ICER, incremental cost-effectiveness ratio

Company response: dupilumab adherence

Updated base case uses [redacted] adherence (original base case 99.3% from SINUS trials)

Company draft guidance response

- Adherence to treatment lower in real world than clinical studies
- UK Sanofi homecare adherence data for dupilumab [redacted] for atopic dermatitis, [redacted] for asthma ([redacted] overall); SINUS studies adherence: 99.3%;
- Reasonable that real-world CRSwNP rate for dupilumab similar to asthma
- In SINUS-52 people switched from dupilumab every 2 weeks to every 4 weeks at 24 weeks; little or no worsening of nasal polyp or nasal congestion score (see SINUS trial results) – suggests dupilumab effectiveness could be maintained if small drop in adherence

EAG critique

- Company incorrectly applied lower adherence rate from model start; EAG corrected this
- Despite noting that adherence for dupilumab likely to be similar for CRSwNP and asthma, company applied average rate from asthma and atopic dermatitis; EAG prefers asthma-only rate but applied from year 2 onwards, with SINUS rate for year 1 because SINUS is informing efficacy for that period

Is the company or EAG updated adherence rate preferred?

CRSwNP, chronic rhinosinusitis with nasal polyps; EAG, external assessment group

Company and EAG base case aligned assumptions

Assumption	Company updated base case	EAG base case	Effect on ICER
Utility gain following revision surgery	From Tashman 2024: **0.0644**	Same	n/a - resolved
Population	People with uncontrolled CRSwNP who have had at least 1 surgery **and a SNOT-22 score of at least 50**	Same	n/a
Response criteria	SNOT-22 **total score under 50 or** an at least 8.9 point improvement And an improvement of at least 1 in NPS	Same - disagrees with updated criteria.	Scenario using responder rates from original company base = slightly increased

CRSwNP, chronic rhinosinusitis with nasal polyps; EAG, external assessment group; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; NPS, nasal polyp score; SNOT-22, 22-item sinonasal outcomes test

Company and EAG base case different assumptions

Assumption	Company updated base case	EAG base case	Effect on ICER
Source of utility values	**EQ-5D data** from pooled SINUS trials based on updated population (SNOT-22 ≥50). Inadequately controlled disease utility value is average between baseline and week 52	EQ-5D data from pooled SINUS trials based on updated population (SNOT-22>50) **with cap applied for general population norms**	Slightly increased
Transition probability for post-op controlled to uncontrolled	Calculated from Benson et al. 2023: **42.8%**	Alternative calculation from Benson et al: **15%**	Substantially increased
Transition probability from uncontrolled or inadequately controlled to post-op controlled	Updated extrapolation of the mean rate of surgery from Benson et al. 2023: **7.1%**	Transition probability from uncontrolled to post-op controlled **39.35%** (also applied to inadequately controlled to post-op controlled)	Substantially increased

Company and EAG base case different assumptions

Assumption	Company updated base case	EAG base case	Effect on ICER
Long-term effectiveness from year 2	Based on analysis of AROMA. Calculated from updated patient population in AROMA matched to SINUS (+rescue therapy censored). **Year 2:** [redacted] **year 3:** [redacted] **year 4+:** [redacted]	Same as company **but using adjusted trendline to exclude data from first 12 months.** Concerns over matching, disagrees with updated response criteria	Slightly increased

EAG, external assessment group; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; NPS, nasal polyp score; SNOT-22, 22-item sinonasal outcomes test

Company and EAG base case different assumptions

Assumption	Company updated base case	EAG base case	Effect on ICER
Percentage of scheduled doses given to patients (adherence)	Extrapolated from real-world data (Sanofi UK homecare): [redacted]	**SINUS pooled trial data in first 52 weeks of the model (99.3%), followed by Sanofi homecare data based on asthma only ([redacted])**	Increased

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EAG, external assessment group; ICER, incremental cost-effectiveness ratio;

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Company response: uncaptured benefits (1/2)

Company: benefits in reducing waiting lists

Background

- Committee ACM1 conclusion: some benefits of dupilumab may not have been captured in the QALY calculation (EQ-5D's possible lack of sensitivity in measuring health-related quality of life in severe CRSwNP; potential for dupilumab to reduce oral corticosteroids use)

Company draft guidance response

- Likely to reduce NHS surgery waiting list: SINUS pooled analysis dupilumab reduced need for surgery 82.6% compared with placebo (HR 0.17; 95% CI 0.07 to 0.46; p=0.0005)
- Explored this in 2 scenarios in which half of people who had had surgery have dupilumab
- Scenario 1: current surgery rates maintained, would 1) eliminate waiting lists within 3 years, 2) potentially free up over 5,500 theatre slots for 5 years or 20,000 over 10 years, opening them up to patients with other conditions
- Scenario 2: surgery rate reduced by number of patients about to have surgery in next year; would 1) reduce the waiting list by 33% to about 16 months 2) free up over 13,500 theatre slots for 5 years

ACM, appraisal committee meeting; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; HR, hazard ratio; QALY, quality adjusted life year

Company response: uncaptured benefits (2/2)

Company: benefits in terms of reduced OCS use and for comorbidities

Company draft guidance response

- Repeated OCS use increases likelihood of developing serious conditions, for example, osteoporosis, Cushing's syndrome, adrenal insufficiency and significant cardiovascular complications
- Dupilumab reduced the proportion of people who needed systemic corticosteroids by 73.9% compared with placebo (HR 0.26; 95% CI 0.18 to 0.38; p<0.0001)
- People with severe CRSwNP typically also have other type 2 inflammatory conditions: up to 60% have comorbid asthma
- For these people, dupilumab could reduce exacerbations and corticosteroid use, and have savings in terms of accident and emergency resources and hospital bed days
- Notes that committee included asthma-related costs in preferred assumptions but says it is at a very conservative level and the positive service impact of this should not be underestimated

CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; HR, hazard ratio; OCS, oral corticosteroids

Company response: acceptable ICER (1/2)

Background

- Committee conclusion at ACM1: middle of range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained)

Company draft guidance response

- Says it has resolved uncertainties around:
  - data used to estimate treatment effectiveness beyond 1 year in the model
  - transition probabilities in the model for people moving from the post-op controlled to the uncontrolled health state (explained estimates, validated against additional sources)
  - utility values used in the model (improving definition of severity, re-calculated EQ-5D data; no longer lack face validity; updated post-surgery utility gain)
- Shown that real-world adherence for dupilumab in the UK is high and provided evidence that including an adherence estimate in the model based on homecare data should not reduce effectiveness (confirmed at the first committee meeting by clinical expert who described how outcomes are similar at lower dosing rates)
- Suggests acceptable ICER should now be at the upper end of the threshold

ACM, appraisal committee meeting; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life years

Company response: acceptable ICER (2/2)

EAG critique: number of key uncertainties remain

Key uncertainty	EAG explanation
Update population to a more severe group	• Differs from population agreed at ACM1 and relevant to NHS • Resulted in exclusion of half the patients in the original submission • Required the breaking of randomisation
Definition of treatment response	• Does not appear to reflect clinical practice in the NHS • Considerably greater treatment effect when applied to new population • Applied in model despite uncertainties of application in clinical practice
Methods used to match AROMA trials to the pooled SINUS trials and application in the economic model	• Could not adjust for important measures of disease severity (NPS) or any other unmeasured confounders • Based on original ITT population not the updated severe population • Low patient numbers beyond 12 months of treatment • Different response criteria for year 2+ than used in 1st year decision tree • Uncertain if rates have been inappropriately transformed to probabilities
Transition probabilities used in the model	• Obtained from unclear calculations to inform probability of surgery • Rely on strong assumptions about waiting lists and patients becoming uncontrolled within a specific timeframe

Dupilumab for treating severe chronic rhinosinusitis with nasal polyps

- ❑ Recap from first appraisal committee meeting
- ❑ Consultation comments
- ❑ Company response and EAG critique
- ❑ Other considerations
- ✓ **Summary**

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Company updated base case results

Deterministic base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ECM only	[redacted]	[redacted]	-	-	-
Dupilumab plus ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Probabilistic base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ECM only	[redacted]	[redacted]	-	-	-
Dupilumab plus ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

EAG's exploratory analyses applied to company base case

ECM only compared with dupilumab plus ECM (deterministic)

Preferred assumption	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
EAG corrected company updated base case	[redacted]	[redacted]	[redacted]
EQ-5D trial-based utilities with cap applied for general population norms	[redacted]	[redacted]	[redacted]
Adherence based on SINUS for first year then asthma homecare data	[redacted]	[redacted]	[redacted]
Dupilumab loss of response beyond 52 weeks informed by extrapolation of trial-derived probability	[redacted]	[redacted]	[redacted]
Exclude first 12 months of AROMA data from linear trendline	[redacted]	[redacted]	[redacted]
Alternative model transition probabilities based on Benson et al.	[redacted]	[redacted]	[redacted]
Responder rates based on original population and response criteria	[redacted]	[redacted]	[redacted]

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EAG, external assessment group; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

EAG updated preferred model assumptions

Results for dupilumab plus ECM vs ECM alone (cumulative, deterministic – probabilistic results similar)

Preferred assumption	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Corrected company base case	[redacted]	[redacted]	[redacted]
SINUS trial derived EQ-5D utility values with a general population cap	[redacted]	[redacted]	[redacted]
Adherence beyond first year based on asthma Sanofi UK homecare data	[redacted]	[redacted]	[redacted]
Re-estimation of linear trendline fit to AROMA data to exclude first 12 months	[redacted]	[redacted]	[redacted]
Transition probabilities based on alternative data from Benson et al. and 2-year waiting list	[redacted]	[redacted]	[redacted]
EAG preferred base case	[redacted]	[redacted]	[redacted]

EAG, external assessment group; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SNOT-22, Sino-Nasal Outcome Test-22

EAG's exploratory analyses applied to EAG base case

ECM only compared with dupilumab plus ECM (deterministic)

Preferred assumption	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
EAG updated base case	[redacted]	[redacted]	[redacted]
Transition probabilities derived from Benson et al. as used in the company base case model	[redacted]	[redacted]	[redacted]
Utility gain from surgery based on Remenschneider et al. 2015	[redacted]	[redacted]	[redacted]
Responder rates based on original population and response criteria	[redacted]	[redacted]	[redacted]

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EAG, external assessment group; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

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Thank you