Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis

Part 1 slides for Zoom – redacted

Technology appraisal committee B, 2 July 2025

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Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on severe chronic rhinosinusitis with nasal polyposis

Cause: unknown, but contributory factors include allergies and fungal infection

Epidemiology

- Chronic rhinosinusitis (longer than 12 weeks) common, affects around 10% of UK population
- Of these, up to 30% also have nasal polyps; 476 cases per 100,000 in England (2018)

Diagnosis: people present initially to GP with sinonasal inflammation; if symptoms persist, referred to Ear, Nose and Throat (ENT) or specialised Rhinology clinic for further investigation

Symptoms

- Loss of smell and taste, blocked and runny nose, facial pain and headache, snoring and obstructive sleep apnoea, fatigue; these may last many years
- Severe disease: symptoms rated as VAS score 7 to 10, polyps and mucosal disease on endoscopy
- Comorbidities associated with disease include asthma, allergies and NSAID-exacerbated respiratory disease

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography; NSAID, non-steroidal inflammatory drug; VAS, visual analogue scale

Patient perspectives (1/2)

Submissions from SmellTaste (formerly Fifth Sense), Sinus UK and 2 patient experts

- Loss of smell and taste is one of the most important symptoms, affecting quality of life and mental health - loss of enjoyment but also danger from not smelling smoke or gas
- Inflammation and congestion from nasal polyps and thick mucus causes breathing difficulties, poor sleep, pain, fatigue, and hearing difficulties; despite blockage, people also have a constantly runny nose
- Significantly affects ability to work, affects partners and family
- Frustration at lack of effective treatments; severe lack of treatment innovation for a long time; once first-line nasal sprays no longer work, left with surgery or oral corticosteroids, which can work but only temporarily
- Dismissive attitude of healthcare providers; underappreciated condition
- Significant side effects from treatments, particularly long-term steroid use and repeated surgery
- Unmet need for a long-term solution for people with more severe disease who do not get lasting relief from surgery or who cannot have it

Patient perspectives (2/2)

CRSwNP has taken over my life, I cannot breathe properly, and I am in constant pain... My mood is so low because of it, I am being treated for depression and anxiety

The surgery has always been effective for a matter of weeks but then I lose my smell and taste again

Since starting with dupilumab, my symptoms... are no longer present. My sinuses are completely clear, I can breathe through my nostrils normally, I no longer suffer from mental health issues, socialising is no longer a problem, and life is as good as it can be. I cannot stress just how much taking dupilumab has changed my life in every aspect

Clinical perspectives

Submission from Association of Respiratory Nurses and 2 clinical experts

- Clinically significant response: fewer exacerbations, emergency visits, symptoms (SNOT-22); less need for oral corticosteroids and surgery, improved smell
- Current treatment: ~70% managed with nasal/oral corticosteroids; ~30% have surgery, of these ~20% need revision surgery within 5 years; ~5% need multiple revision surgeries; people with severe asthma may have dupilumab or other biologic
- Unmet need: surgery often relieves symptoms but many do not regain smell, see little benefit or polyps come back quickly; dupilumab a step change in treatment for these people
- Dupilumab an add on to end of current pathway if still very symptomatic and uncontrolled; could significantly improve quality of life for the most severely affected
- More evidence on dupilumab needed; some data from asthma patients with polyps who have benefited
- Patients on dupilumab (for asthma, or privately): high responder rate, able to avoid further surgery, often report minimal symptoms

ENT, ear, nose and throat; SNOT-22, 22-item Sinonasal Outcomes Test

Equality considerations

Noted during scoping

Inequalities exist by geographical location: variability in quality of surgery, and in post-operative pathway; underserved people become more reliant on overstretched primary care services

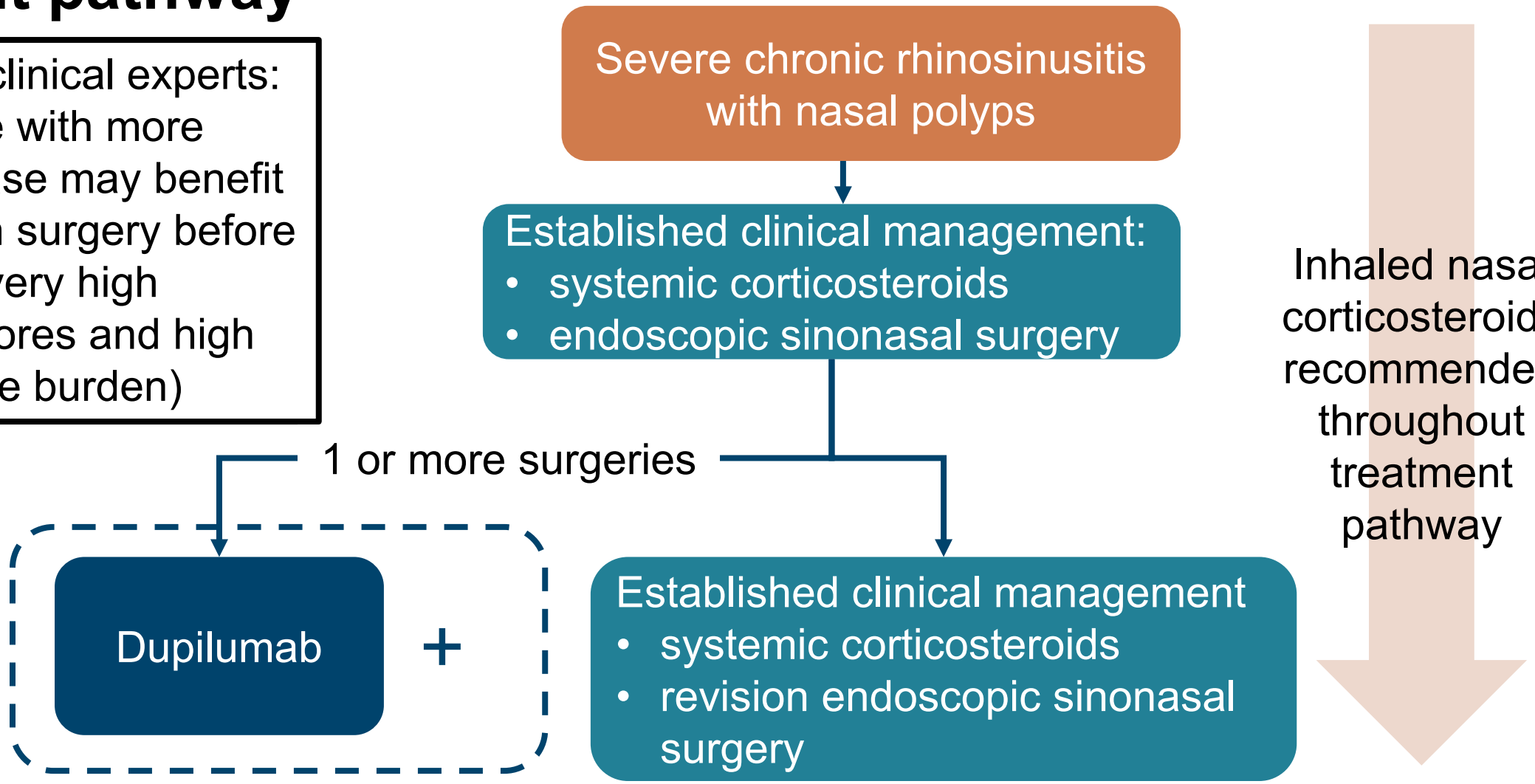
People with multiple comorbidities may not be able to take steroids or have surgery so would not be included in the population (previously treated)

Company, SmellTaste (formerly Fifth Sense)

Introducing dupilumab expected to reduce existing inequalities: access to targeted biological treatment for people with chronic rhinosinusitis with nasal polyps (already approved by NICE for people with other chronic type 2 inflammatory conditions such as asthma and atopic dermatitis)

Treatment pathway

Some EAG clinical experts: some people with more severe disease may benefit from revision surgery before dupilumab (very high SNOT-22 scores and high polyp disease burden)



Does the pathway reflect current UK clinical practice?
Is established clinical management the appropriate comparator?

SNOT-22, 22-item Sinonasal Outcomes Test

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

Key issues

No	Issue	ICER impact
1	Populations for clinical and cost-effectiveness [resolved]	None – prior surgery population used for cost effectiveness model
2	Outcomes for clinical and cost-effectiveness	Small if applied to company base case Large if applied to EAG base case
3	Lack of long-term data	Small
4	Transition probabilities from post-op controlled to uncontrolled health state	Unclear – large effect if extreme scenario applied
5	Health utility values used in the economic model	Large

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

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Key clinical trials

	SINUS-24 [NCT02912468] (n=276)	SINUS-52 [NCT02898454] (n=448)
Intervention	Dupilumab 300 mg once every 2 weeks plus ECM	• Dupilumab 300 mg once every 2 weeks plus ECM • Dupilumab 300 mg once every 2 weeks in first 24 weeks (then once every 4 weeks for next 24 weeks) plus ECM
Duration	24 weeks	52 weeks
Locations	International (n=19 UK)	International (none UK)

Other criteria same for both trials:

- design – phase 3, placebo controlled, double blind, randomised
- population – adults with previously treated severe chronic rhinosinusitis with nasal polyps
- comparator – placebo plus ECM (MFNS 100 micrograms in each nostril twice daily)
- primary outcome – change from baseline in bilateral NPS and NC score at 24 weeks
- key secondary outcomes – changes in HRQoL (SNOT-22 score), sense of smell (UPSIT, LoS score), total symptom score, and sinus opacification

Pooled 24-week results from prior nasal polyp surgery subgroup used in model

HRQoL, health-related quality of life; ECM, established clinical management; LoS, loss of smell; MRNS, mometasone furoate nasal spray; NC, nasal congestion; NPS, nasal polyp score; SNOT-22, 22-item Sinonasal Outcomes Test; UPSIT, University of Pennsylvania Smell Identification Test

AROMA trial [NCT04959448]

Source of longer-term data for dupilumab but not comparative

Design	Observational, open-label, single-arm registry study
Population	Adults with severe chronic rhinosinusitis with nasal polyps
Intervention	Dupilumab prescribed in line with local clinical practice
Duration	24 months
Primary outcome	Descriptive summary of symptoms and HRQoL, including NC score, Lund-Mackay, decreased/loss of smell, SNOT-22 score, TSS, UPSIT, PNIF, ACQ-6 and FEV1
Key secondary outcomes	Treatment patterns, global assessment of disease severity, treatment satisfaction, adverse events
Locations	International (none UK)
Used in model?	Yes – SNOT-22 data to inform treatment effectiveness beyond 1 year (only data available from company submission)

ACQ-6, 6-item Asthma Control Questionnaire; FEV1, forced expiratory volume in 1 second; PNIF, peak nasal inspiratory flow; SNOT-22, 22-item Sinonasal Outcomes Test; TSS, Total symptom score; UPSIT, University of Pennsylvania Smell Identification Test

Pooled SINUS results for prior surgery group at 24 weeks

Dupilumab significantly improves nasal congestion and reduces polyps compared with established clinical management

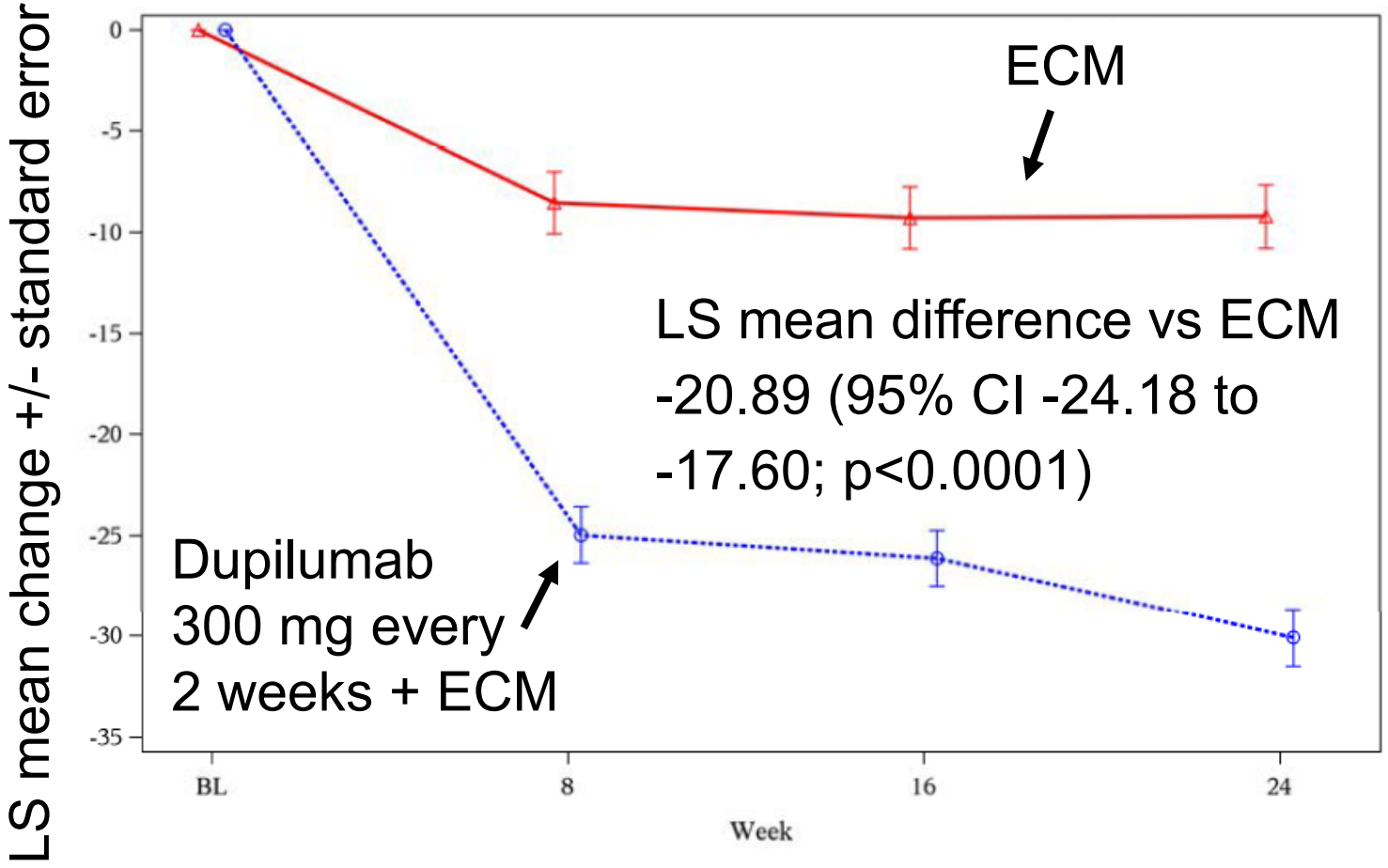
Treatment	ECM (n=187)		Dupilumab + ECM (n=272)		
Primary endpoint	Mean change from baseline (SD)	LS mean change from baseline (SE)	Mean change from baseline (SD)	LS mean change from baseline (SE)	LS mean difference vs ECM (95% CI)
Bilateral NPS	0.13 (1.23)	0.16 (0.14)	-1.89 (1.88)	-1.82 (0.13)	-1.99 (-2.29 to -1.68; p<0.0001)
Nasal congestion score	-0.47 (0.79)	-0.38 (0.07)	-1.38 (0.92)	-1.36 (0.06)	-0.98 (-1.13 to -0.83; p<0.0001)

EAG: both trials at low risk of bias; identical methods and similar baseline characteristics; agrees with company focus on pooled analysis of SINUS-24 and SINUS-52

NICE CI, confidence interval; ECM, established clinical management; LS mean, least squares mean; NPS, nasal polyp score; SD, standard deviation; SE, standard error

SNOT-22

Pooled SINUS results: significantly greater improvement in HRQoL for dupilumab over ECM (prior surgery population) at 24 weeks; similar results at 52 weeks (SINUS-52)



AROMA results for dupilumab (single arm) mean change from baseline:

- 12 months -27.3 points (SD 22.61)
- 24 months -18.0 points (SD 16.63)

EAG: indicates sustained benefit of dupilumab on health related quality of life throughout first year of treatment but AROMA results suggest possible treatment effect waning after 52 weeks

CI, confidence interval; EAG, external assessment group; ECM, established clinical management; HRQoL, health-related quality of life; LS mean, least squares mean; SD, standard deviation; SNOT-22, 22-item Sinonasal Outcomes Test

Pooled SINUS results: NPS and SNOT-22 response in prior surgery subgroup

Company response criteria: change from baseline in NPS ≥1 + SNOT-22 ≥8.9

Response criteria	SNOT-22 total score and NPS (company base case)		SNOT-22 total score only		NPS only	
Intervention	Placebo (ECM only)	Dupilumab + ECM	Placebo (ECM only)	Dupilumab + ECM	Placebo (ECM only)	Dupilumab + ECM
Week 24	N=187	N=272	N=187	N=272	N=187	N=272
Responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 to 52	N=5	N=46	N=35	N=60	N=7	N=54
Responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE ECM, established clinical management; NPS, nasal polyp score; SNOT-22, Sino-Nasal Outcome Test-22

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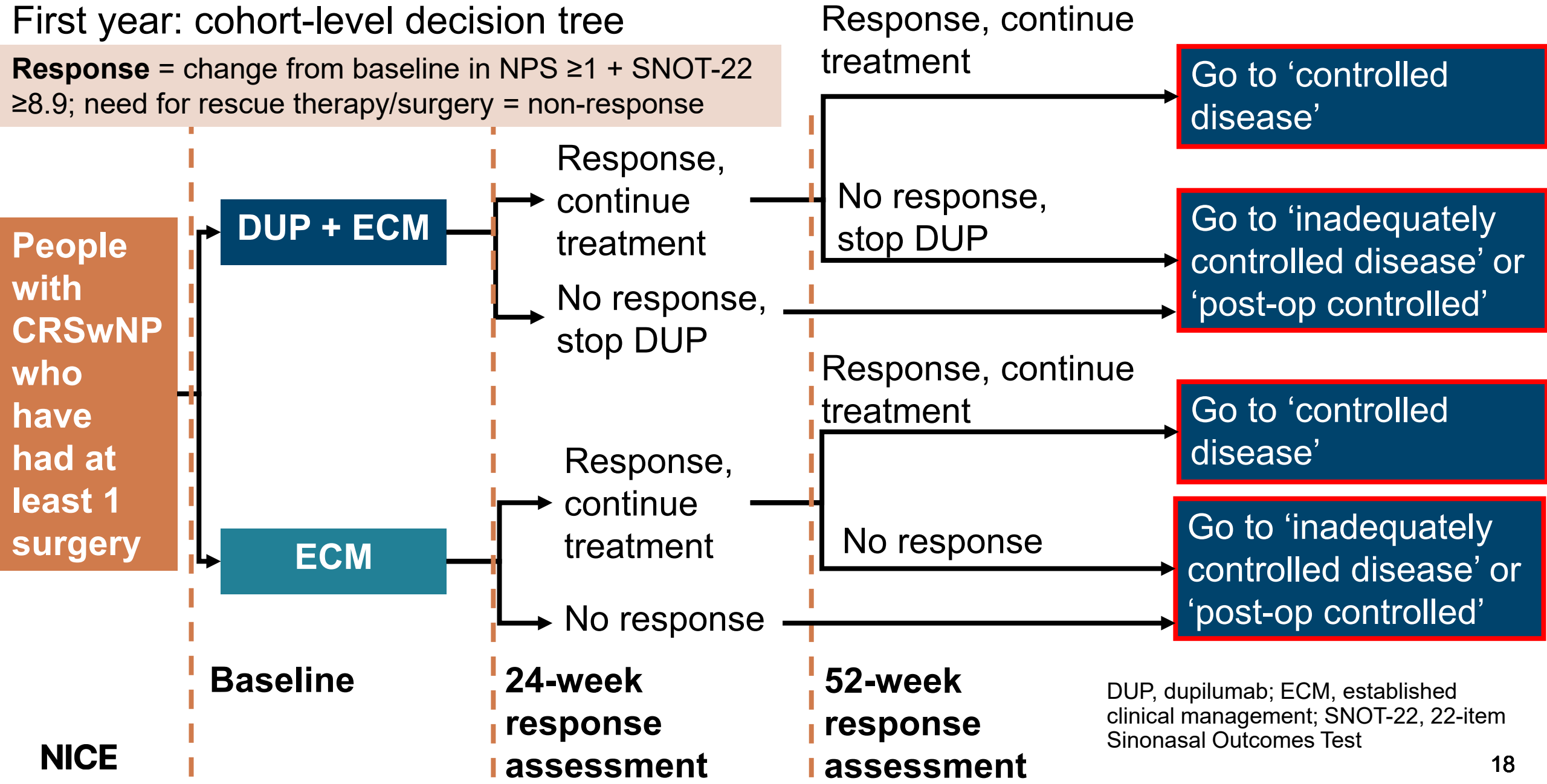
Company's model overview (1/2)

Modelled on SINUS trials

First year: cohort-level decision tree

Response = change from baseline in NPS ≥1 + SNOT-22 ≥8.9; need for rescue therapy/surgery = non-response

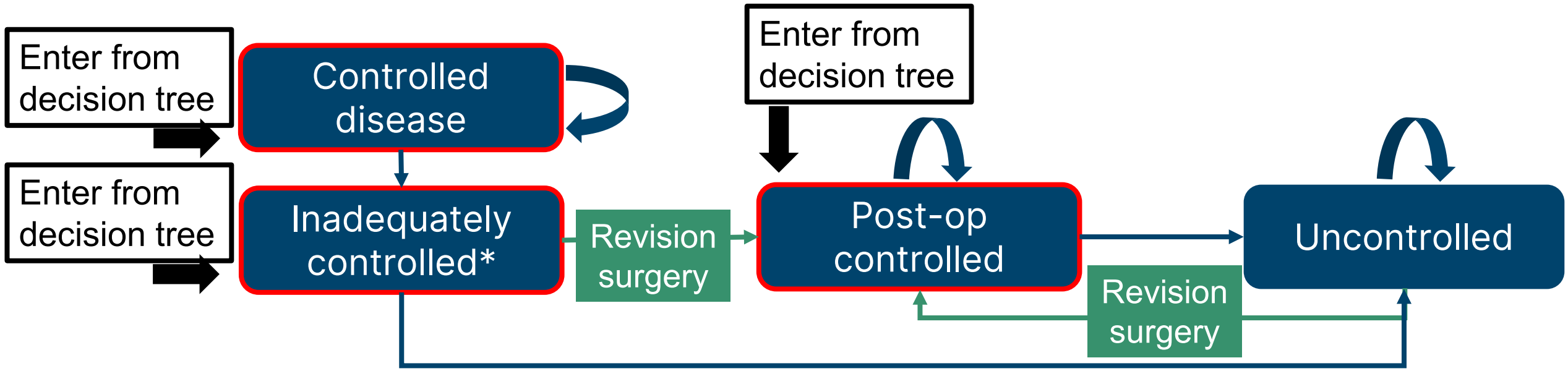


DUP, dupilumab; ECM, established clinical management; SNOT-22, 22-item Sinonasal Outcomes Test

Company's model overview (2/2)

Is the model structure appropriate?

Long-term Markov state transition model – lifetime time horizon with yearly cycle



EAG

- Mainly satisfied that model captures main features of condition
- EAG clinical experts agree with model structure and that currently only revision surgery would result in someone moving out of uncontrolled health state
- 1-year cycle length not in line with dupilumab administration; may not capture timings of key clinical events – but unlikely to have substantial effect on results

*Temporary state for 1 cycle (year) only to capture decline in health-related quality of life before condition becomes uncontrolled

Key issue 2: outcomes for clinical/cost effectiveness

Large effect on ICER

Background:

- Clinical effectiveness assessed using NPS and NC scores from SINUS trials
- Economic model response: change from baseline in NPS ≥1 and SNOT-22 ≥8.9

EAG:

- Using different response measure in clinical to economic analysis could mean differences in cost effectiveness of dupilumab
- Using NPS + SNOT-22 in model meant fewer people in analysis and therefore uncertainty
- EAG clinical experts suggested SNOT-22 commonly used in clinical practice to assess response to treatment – one said would not stop if improved on SNOT-22 but not NPS
- Used company analysis in base case but scenario using only SNOT-22 for response

Company:

- NPS alone does not capture smell loss; SNOT-22 does not fully assess disease control
- Tested with clinicians – combined response criteria in line with clinical practice

Clinical experts: disease control usually = SNOT-22 reduced to mild levels, no OCS or surgery

What criteria would be used in clinical practice to determine response?

NC, nasal congestion;
NPS, nasal polyp score;
OCS, oral corticosteroids

Small effect on ICER

Key issue 3: lack of long-term data (1/2)

Background

- To inform dupilumab effectiveness beyond 1 year (Markov model), original company base case used SINUS trials data to inform annual probability of transitioning to inadequately controlled for prior surgery subgroup = [redacted]% (week 24 pooled data from SINUS-24 and SINUS-52 prior surgery subgroup, week 24 to 52 SINUS-52 prior surgery subgroup)
- In response to clarification, company updated base case to use AROMA data (single-arm trial with data up to 2 years, SNOT-22 data only) = [redacted]% for years 1 to 2 then [redacted]% per year

EAG: data used to inform transition probabilities for dupilumab controlled to inadequately controlled health states after 1 year uncertain

Model/scenario	Transition probability for dupilumab + ECM arm controlled to inadequately controlled	Source
Company original (EAG) base case	[redacted]% per year	SINUS data
Company new base case	[redacted]% for years 1 and 2 of Markov model, then [redacted]% per year	AROMA
EAG scenario	15.6% per year after 5 years	Exploratory

EAG, external assessment group; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; SNOT-22, 22-item Sinonasal Outcomes Test

Small effect on ICER

Key issue 3: lack of long-term data (2/2)

EAG comments

- Inappropriate to use AROMA in base case: only SNOT-22 data available from AROMA (NPS + SNOT-22 in first year of model), unclear if rescue treatment/surgery classed as non-response, ECM arm still informed by SINUS data (that is, [redacted] people classed as non-responders in clinical trials) – inconsistent to use 2 different approaches in 2 arms
- AROMA analysis should be formally matched to SINUS trials
- EAG prefers pooled SINUS data; provided scenario: discontinuation of 15.6% after 5 years to test how sensitive results were to higher discontinuation rate because of lack of effectiveness
- EAG clinical expert: expects some waning of treatment effect based on experience of other biologics (EAG noted AROMA results suggest possible treatment waning after 52 weeks)

Company

- AROMA provides real-world evidence of continued benefit
- Sustained benefits of dupilumab observed in other disease areas (asthma and atopic dermatitis) and of dupilumab and other biologics in CRSwNP

EAG, external assessment group; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; SNOT-22, 22-item Sinonasal Outcomes Test

NICE

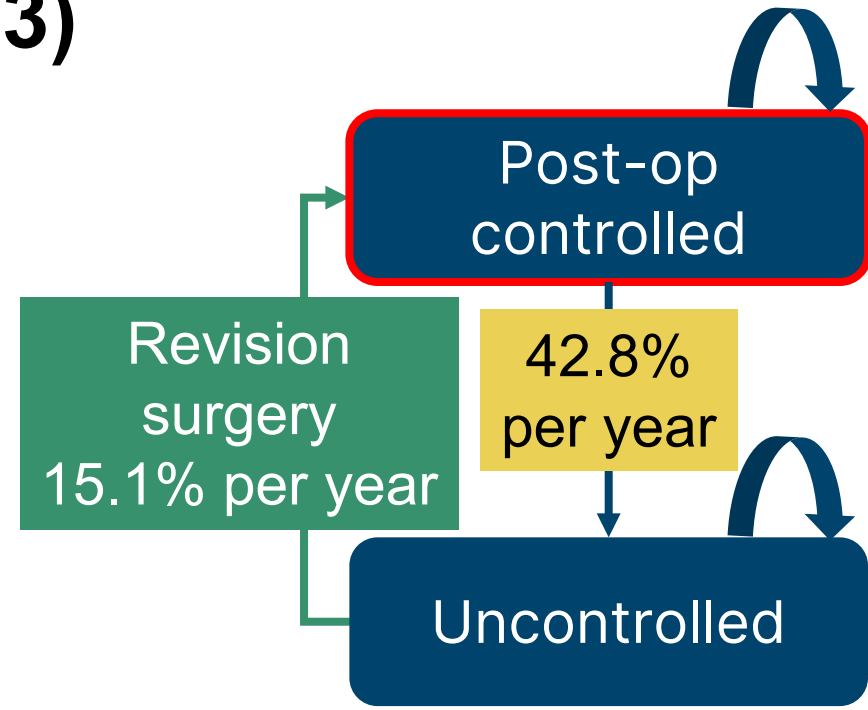
What is the most appropriate data to use to inform dupilumab treatment effectiveness beyond 1 year – SINUS trials pooled data or AROMA data (adjusted or unadjusted)?

Effect on ICER unclear

Key issue 4: transition probabilities from post-op controlled to uncontrolled health state (1/3)

Background

- Proportion in both arms of model have revision surgery
- After surgery people stay in post-op controlled health state until disease becomes uncontrolled again
- Transition probability of moving from post-op controlled to uncontrolled: 42.8% per year based on Benson et al. 2023 (equation using mean time to 3rd surgery 875 days, adjusted based on expert advice that people wait around 2 years for surgery and 40% to 50% will become uncontrolled quickly)



EAG comments

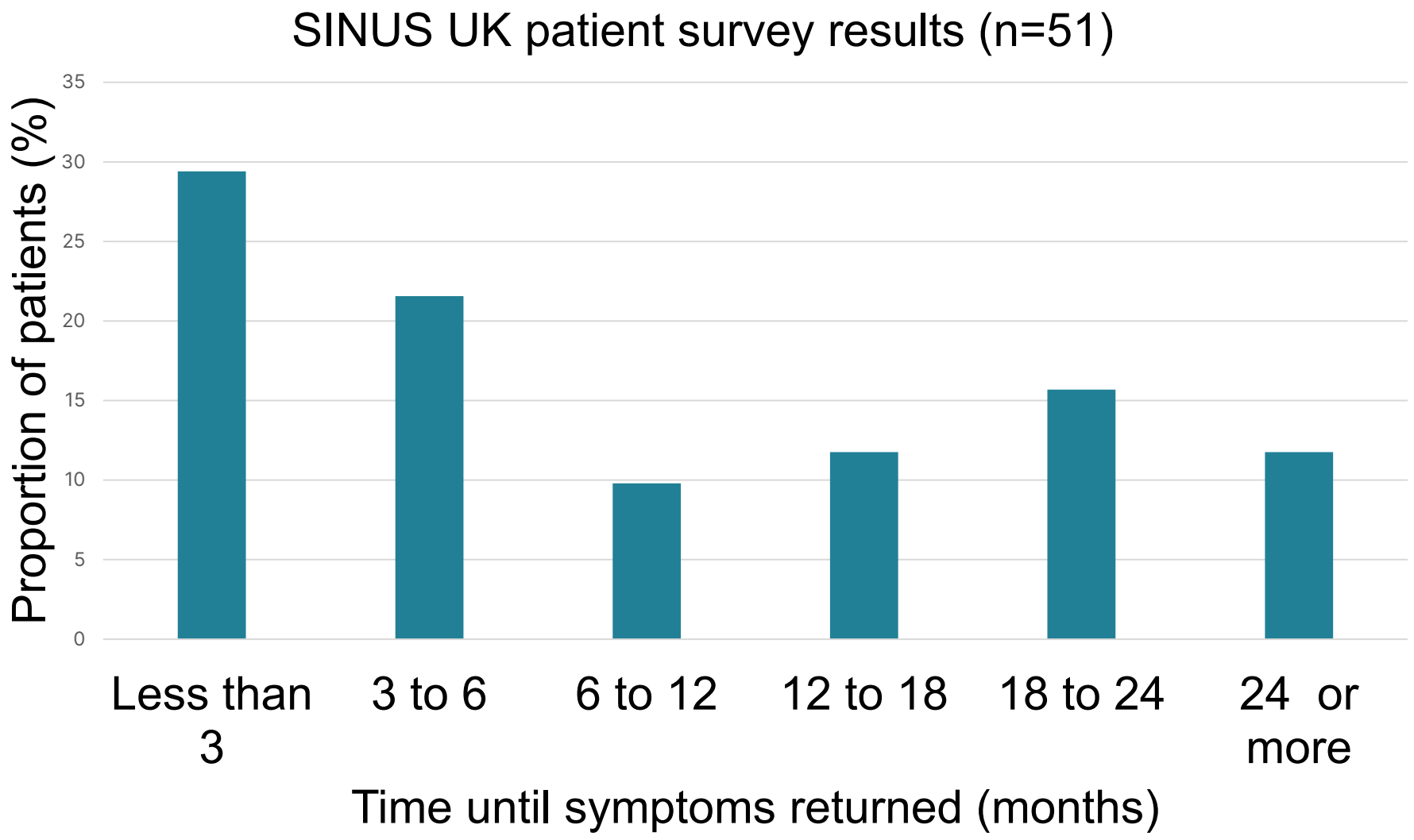
- Clinical experts said rate of loss of control and revision surgery highly variable – waiting lists vary across England, length of control depends on skill of surgeon, type of surgery
- Unable to source alternative value so used company base case
- Exploratory scenario adjusting revision surgery waiting time from 2 years to 1 year: probability reduced to 12.1% per year – upper bound of what ICER might be with lower transition rate

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

Key issue 4: transition probabilities from post-op controlled to uncontrolled health state (2/3)

Effect on ICER unclear

SINUS UK
Survey of 51 patients showed half (26) had symptoms return within
6 months of surgery



ICER, incremental cost-effectiveness ratio

Key issue 4: transition probabilities from post-op controlled to uncontrolled health state (3/3)

Effect on ICER unclear

Company

- Most studies on CRSwNP report recurrence/revision without considering disease severity, number of previous operations, comorbidities (for example asthma) so likely show lower recurrence rates that might be seen in higher-risk patients
- In model, rate of loss of response after revision surgery expected to be higher than general CRSwNP population – people included have had at least 1 surgery, and rate applies after 1 cycle in model before entering post-op controlled state – hence rate for at least 2 operations from Benson et al.
- Studies also usually evaluate disease control based on more restrictive EUFOREA/EPOS guidelines, which are more restrictive than response criteria used in model – 40% rate conservative

What is the most plausible wait time for revision surgery?
Is the company's rate of 42.8% per year becoming uncontrolled after revision surgery reasonable?

EPOS, European Position Paper on Rhinosinusitis and Nasal Polyps; EUFOREA, European Forum for Research and Education in Allergy and Airway Diseases; ICER, incremental cost-effectiveness ratio

Key issue 5: health state utility values used in the economic model (1/4)

Large effect on ICER

Background

- Health-related quality of life collected in SINUS trials using EQ-5D (NICE reference case)
- Company did not use this data to inform model health state utility values, instead used SNOT-22 data from the SINUS trials mapped to EQ-5D
- Company: 0.051 utility gain from revision surgery from Soler et al. 2011 (SF-6D, out of date)

EAG comments

- Use of SNOT-22 instead of EQ-5D not justified; NICE reference case says varying from EQ-5D must be justified by synthesis of peer-reviewed literature – does not consider this has been done
- If EQ-5D does not capture quality of life in CRSwNP, same problem if SNOT-22 mapped to it
- **NICE DSU technical support document 22**: *Mapping to EQ-5D is not appropriate if EQ-5D is considered inappropriate for measuring health benefits in the condition under consideration*
- Choice of utility values main driver of ICER

NICE DSU, NICE Decision Support Unit; ICER, incremental cost-effectiveness ratio; SNOT-22, 22-item Sinonasal Outcome Test

Key issue 5: health state utility values used in the economic model (2/4)

	Company – pooled trial SNOT-22 mapped to EQ-5D		EAG – pooled trial EQ-5D capped at general population values	
Health state	**Dup + ECM**	**ECM only**	**Dup + ECM**	**ECM only**
Decision tree				
Week 0 to 12	0.524	0.524	0.782	0.782
Week 13 to 24	0.727	0.596	0.827	0.775
Week 25 to 52 responders	0.793	0.734	0.856	0.832
Week 25 to 52 non-responders	0.673	0.587	0.791	0.762
Markov model				
Controlled disease	0.809	0.809	0.866	0.866
Inadequately controlled disease	0.594	0.594	0.752	0.752
Uncontrolled disease (assumed baseline)	0.524	0.524	0.732	0.732

NICE

Dup, dupilumab; EAG, external assessment group; ECM, established clinical management; SNOT-22, 22-item Sinonasal Outcome Test

Large effect on ICER

Key issue 5: health state utility values used in the economic model (3/4)

EAG comments cont'd

- Model used for mapping (Crump et al.) inappropriate – people with chronic rhinosinusitis awaiting surgery (that is, uncontrolled), 2 of Crump models suggest anosmia and lack of sleep improve quality of life – model chosen by company obscures this relationship by combining with other component, for example facial pain/pressure
- Substantial QALY gain for dupilumab ([redacted]) despite no demonstrated survival gain
- Requested scenario: utility values derived from trial using observed CFB EQ-5D data capped at general population age and sex-matched utility values and multiplier applied to subsequent health states to retain proportional differences between states – used in EAG base case
- CFB analysis best of data available but preferred option would be regression model excluding SNOT-22 because it is not an independent variable
- EAG base case uses 0.08 utility gain from revision surgery based on Remenschneider et al. 2015, derived from more recent data and based on EQ-5D-5L rather than SF-6D

CFB, change from baseline; EAG, external assessment group; SNOT-22, 22-item Sinonasal Outcome Test

Large effect on ICER

Key issue 5: health state utility values used in the economic model (4/4)

Company

- EQ-5D utility values were higher than age and sex-matched general population values for patients responding to treatment
- EQ-5D poor at capturing quality of life for people with CRSwNP – particularly as anosmia and sleep not covered by it
- SNOT-22 most widely used CRS-specific patient reported measure to record quality of life
- Acknowledges that population in Crump et al. somewhat different to that in model

Patient organisations

- SNOT-22 robust means of capturing health-related quality of life – covers symptom severity, social and emotional impact, productivity, and sleep consequences
- Survey of 184 people CRSwNP asked if EQ-5D captures impact on quality of life:
  - no 92
  - yes 57

EQ-5D and SNOT-22 examples

NICE

CRS, chronic rhinosinusitis; SNOT-22, 22-item Sinonasal Outcomes Test

What is the best source of quality of life data for the model?
What utility gain from revision surgery is most appropriate?

Company and EAG base case assumptions – key issues

Assumption	Company base case	EAG base case
Treatment effectiveness – transition probability of controlled to inadequately controlled – key issue 3	AROMA SNOT-22 data	Pooled SINUS response data from prior surgery subgroup (NPS + SNOT-22; scenario with 15.6% beyond 5 years)
Source of health state utility values – key issue 5	SNOT-22 data from the SINUS trials mapped to EQ-5D	Based on observed CFB EQ-5D SINUS trial data, with cap on responder utility values at general population and multiplier applied to retain proportional differences between states
Surgery utility gain – key issue 5	Long-term improvement in utility 0.051 QALYs from Soler et al. 2011	Long-term improvement in utility 0.08 QALYs from Remenschneider et al. 2015

NICE

CFB, change from baseline; EAG, external assessment group; NPS nasal polyp score; QALY, quality-adjusted life year; SNOT-22, 22-item Sinonasal Outcomes Test

Other differences in company and EAG base case assumptions

Assumption	Company base case	EAG base case
General population mortality	Based on Office for National Statistics (ONS) life tables 2021 to 2023	Based on ONS life tables 2017 to 2019 (in line with NICE DSU guidance)
Difference in asthma-related mortality between treatment arms	Increased mortality for people with asthma	No increased mortality for people with asthma
Post-op controlled state utility values	Post-revision surgery dupilumab non-responders have higher utility than ECM non-responders	Same post-revision surgery utility regardless of previous treatment
Costs related to asthma control	Different costs for people with asthma	Differences in costs for asthma removed
Costs related to help with dupilumab administration	100% of people can self administer dupilumab	5% have help provided by a nurse home care visit
2 year follow-up costs post-revision surgery	Only cost of 1 follow-up visit included	All costs included from Clarke et al. 2022

Company base case results

Deterministic incremental 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]	23,410

Probabilistic incremental 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]	23,793

ECM, established clinical management, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SNOT-22, 22-item Sinonasal Outcomes Test

EAG preferred model assumptions (1/2)

Results for dupilumab plus ECM vs ECM alone (probabilistic, cumulative)

Preferred assumption	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Corrected company base case	[redacted]	[redacted]	**23,499**
General population mortality based on ONS life tables 2017-19	[redacted]	[redacted]	23,542
Controlled to inadequately controlled transition based on SINUS 24/52 responders – key issue 3	[redacted]	[redacted]	23,960
No asthma mortality included	[redacted]	[redacted]	24,356
Utility values based on observed trial based EQ-5D (change from baseline) – key issue 5	[redacted]	[redacted]	53,497
Revision surgery utility gain based on Remenschneider et al. 2015 – key issue 5	[redacted]	[redacted]	57,087

NICE

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

EAG preferred model assumptions (2/2)

Results for dupilumab plus ECM vs ECM alone (probabilistic, cumulative)

Preferred assumption	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Utility values for post-op controlled disease do not differ between treatment arms	[redacted]	[redacted]	56,683
Removal of differences in costs related to asthma control	[redacted]	[redacted]	59,175
5% of people have help with dupilumab admin from nurse home care visit	[redacted]	[redacted]	59,030
Inclusion of 2-year follow-up costs post-revision surgery	[redacted]	[redacted]	59,379
EAG preferred base case	[redacted]	[redacted]	**59,379**

NICE

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

EAG base case results

Deterministic incremental 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]	60,551

Probabilistic incremental 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]	59,379

NICE

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

EAG key issue scenarios – applied to company base case

Results for dupilumab plus ECM vs ECM alone (deterministic)

Preferred assumption	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case	[redacted]	[redacted]	**23,410**
Responder analysis based on SNOT-22 response only – key issue 2	[redacted]	[redacted]	28,128
Annual probability of transitioning from controlled to inadequately controlled in dupilumab arm beyond 5 years = 15.6% – key issue 3	[redacted]	[redacted]	24,288
Transition probabilities from post-op controlled to uncontrolled adjusted based on a 1-year wait time – key issue 4	[redacted]	[redacted]	25,643

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

EAG key issue scenarios – applied to EAG base case

Results for dupilumab plus ECM vs ECM alone (probabilistic)

Preferred assumption	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
EAG base case	[redacted]	[redacted]	**59,379**
Responder analysis based on SNOT-22 response only – key issue 2	[redacted]	[redacted]	76,832
Annual probability of transitioning from controlled to inadequately controlled in dupilumab arm beyond 5 years = 15.6% – key issue 3	[redacted]	[redacted]	61,488
Transition probabilities from post-op controlled to uncontrolled adjusted based on a 1-year wait time – key issue 4	[redacted]	[redacted]	72,073

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

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Other considerations (1/2)

Uncaptured benefits

- Company
  - EQ-5D unlikely to fully capture symptom relief, in particular around anosmia and sleep (also mentioned in patient organisation submissions)
  - psychological impact, for example around chronic discomfort, embarrassment
  - increased productivity, reduced healthcare use
- Clinical expert
  - surgery costs and complications, delays in operations for other ENT conditions because of need for repeated operations for chronic rhinosinusitis with nasal polyps
  - oral corticosteroid side effects
  - benefits for comorbidities – asthma, eczema, allergic rhinitis
  - dosing could be reduced from every 2 weeks to every 4 weeks at 6 months (not in licence)

Other considerations (2/2)

Multidisciplinary team

- EAG's clinical experts: important that decisions about dupilumab are made in specialist centres, overseen by a multidisciplinary care team with experience in treating chronic rhinosinusitis with nasal polyps
- Preferable to decisions being made by a single clinician, such as a rhinologist; similar to how biologics are prescribed for people with asthma
- No impact on evaluation of clinical effectiveness, but multidisciplinary team appointment is included in company economic base case
- Clinical expert submissions also said treatment should be offered in specialist ENT clinics/tertiary care

Severity
No severity modifier applied

Managed access
No managed access proposal

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues

No	Issue	ICER impact
1	Populations for clinical and cost-effectiveness [resolved]	None – prior surgery population used for cost effectiveness model
2	Outcomes for clinical and cost-effectiveness	Small if applied to company base case Large if applied to EAG base case
3	Lack of long-term data	Small
4	Transition probabilities from post-op controlled to uncontrolled health state	Unclear – large effect if extreme scenario applied
5	Health utility values used in the economic model	Large

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

Dupilumab for treating severe chronic rhinosinusitis with nasal polyposis

Supplementary appendix

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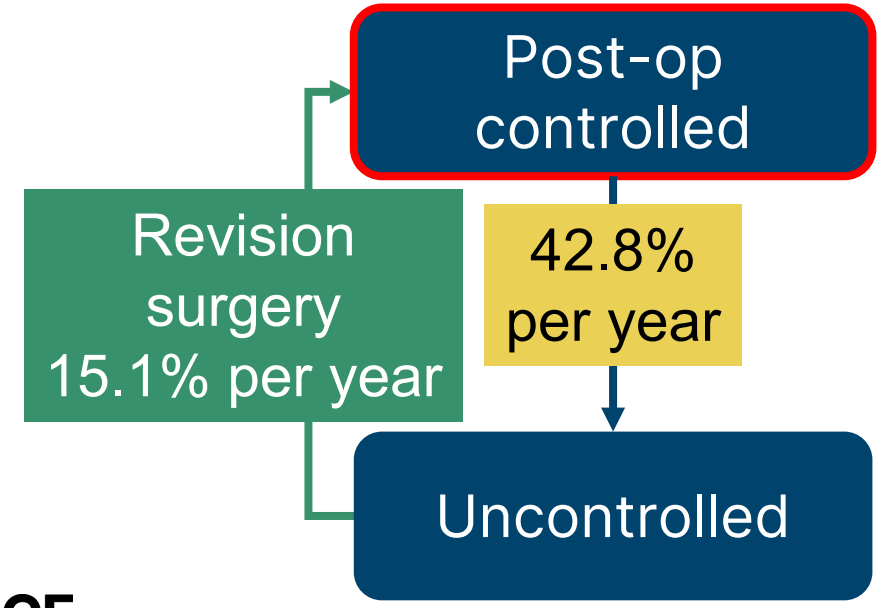
Equation to calculate annual transition probability from post-op controlled to uncontrolled health states

Data from Benson et al. 2023

$$\frac{122 \text{ people with at least 3 surgeries} / 722 \text{ people with at least 2 surgeries}}{(875 \text{ days between second and third surgery} - (365.25 \times 2) \text{ 2 year wait time}) / 365.25}$$

= 42.8%



Key issue 4: transition probabilities from post-op controlled to uncontrolled

EQ-5D and SNOT-22 examples

Under each heading, please choose the ONE answer that best describes your health TODAY.

EQ-5D-3L sample

MOBILITY

- I have no problems in walking about ❑
- I have some problems in walking about ❑
- I am confined to bed ❑

SELF-CARE

- I have no problems with self-care ❑
- I have some problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have some problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am extremely anxious or depressed ❑

I.D.:_____ **SINO-NASAL OUTCOME TEST (SNOT-22)** DATE:_____

Below you will find a list of symptoms and social/emotional consequences of your rhinosinusitis. We would like to know more about these problems and would appreciate your answering the following questions to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems as they have been over the past two weeks. Thank you for your participation. Do not hesitate to ask for assistance if necessary.

1. Considering how severe the problem is when you experience it and how often it happens, please rate each item below on how "bad" it is by circling the number that corresponds with how you feel using this scale: →	No Problem	Very Mild Problem	Mild or slight Problem	Moderate Problem	Severe Problem	Problem as bad as it can be		5 Most Important Items
1. Need to blow nose	0	1	2	3	4	5		○
2. Nasal Blockage	0	1	2	3	4	5		○
3. Sneezing	0	1	2	3	4	5		○
4. Runny nose	0	1	2	3	4	5		○
5. Cough	0	1	2	3	4	5		○
6. Post-nasal discharge	0	1	2	3	4	5		○
7. Thick nasal discharge	0	1	2	3	4	5		○
8. Ear fullness	0	1	2	3	4	5		○
9. Dizziness	0	1	2	3	4	5		○
10. Ear pain	0	1	2	3	4	5		○
11. Facial pain/pressure	0	1	2	3	4	5		○
12. Decreased Sense of Smell/Taste	0	1	2	3	4	5		○
13. Difficulty falling asleep	0	1	2	3	4	5		○
14. Wake up at night	0	1	2	3	4	5		○
15. Lack of a good night's sleep	0	1	2	3	4	5		○
16. Wake up tired	0	1	2	3	4	5		○
17. Fatigue	0	1	2	3	4	5		○
18. Reduced productivity	0	1	2	3	4	5		○
19. Reduced concentration	0	1	2	3	4	5		○
20. Frustrated/restless/irritable	0	1	2	3	4	5		○
21. Sad	0	1	2	3	4	5		○
22. Embarrassed	0	1	2	3	4	5		○

2. Please mark the most important items affecting your health (maximum of 5 items)_____ ↑