12 SQ-HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites

For committee, screen and public [no CON]

Technology appraisal committee A [14th May 2024]

Chair: James Fotheringham

Lead team: Richard Ballerand, Pete Baker, Justin Daniels

External assessment group: Centre for Reviews and Dissemination and Centre for Health Economics, University of York

Technical team: Vicky Gillis-Elliott, Mary Hughes, Richard Diaz

Company: ALK Abello

SQ-HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites

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

NICE National Institute for Health and Care Excellence

Background on allergic rhinitis (AR) and allergic asthma (AA) caused by house dust mites (HDM)

- **Epidemiology**
- Around 19.5 million people in the UK have 'allergic respiratory disease' (ARD) and 4 million people are sensitised to HDM. Around one third (1.32 million) have allergic asthma and allergic rhinitis and two thirds (2.68 million) have allergic rhinitis only
- Multiple symptomatic pharmacotherapies currently available, but a subset with moderate to severe ARD have uncontrolled disease.
- Patients with more severe disease have a higher number of visits to primary and secondary care
- Company estimates 36 % of moderate and 45% severe AR is uncontrolled and 25% moderate and 44% severe AA + AR is uncontrolled

Symptoms and prognosis

- Allergic response occurs when people sensitised to HDM are exposed to HDM. This can include nasal (congestion or runny nose) respiratory (wheezing, chest tightness, cough) and ocular (red, itchy or watery eyes) symptoms

Diagnosis and classification *

- Advanced diagnosis of ARD includes specific allergen sensitisation and type of asthma/ rhinitis.
- Skin prick test and IgE (RAST) blood tests are used in diagnosis. But have different sensitivity and specificity
- Depending upon type of test the diagnosis can be made in primary or secondary care
- AR is classified mild, moderate or severe based on ARIA guidelines and impact on quality of life and combination/ add on therapies are given for persistent symptoms

- *See appendix for
- ARIA classification

NICE

Abbreviations: AA, allergic asthma, AR, allergic rhinitis ARD, allergic respiratory disease; HDM, house dust mites;; IgE, immunoglobin E; FeNO, fractional exhaled nitric oxide; RAST, Radioallergosorbent test

Patient and professional perspectives*

Submissions from Allergy UK, Asthma and Lung, UK and Anaphylaxis UK:

- AR and HDM allergies can be debilitating and affect physical and mental health of people living with them
- AR and AA can impact on all aspects of daily life and people can be excluded from school or work
- Asthma attacks are a serious threat to patient health and the total burden of asthma [including non-HDM asthma] kills 3 people in the UK every day
- Treatment through symptom management works well but can be difficult to manage when allergy triggers are unexpected and do not provide a longer-term health solution.
- 12 SQ-HDM is a much-needed technology and has the potential to reduce emergency admissions and the NHS burden of treating AR and AA in emergency care
- There are side-effect profiles with existing treatments

Submissions from Royal College of Physicians and British Thoracic Society and ARNS professional

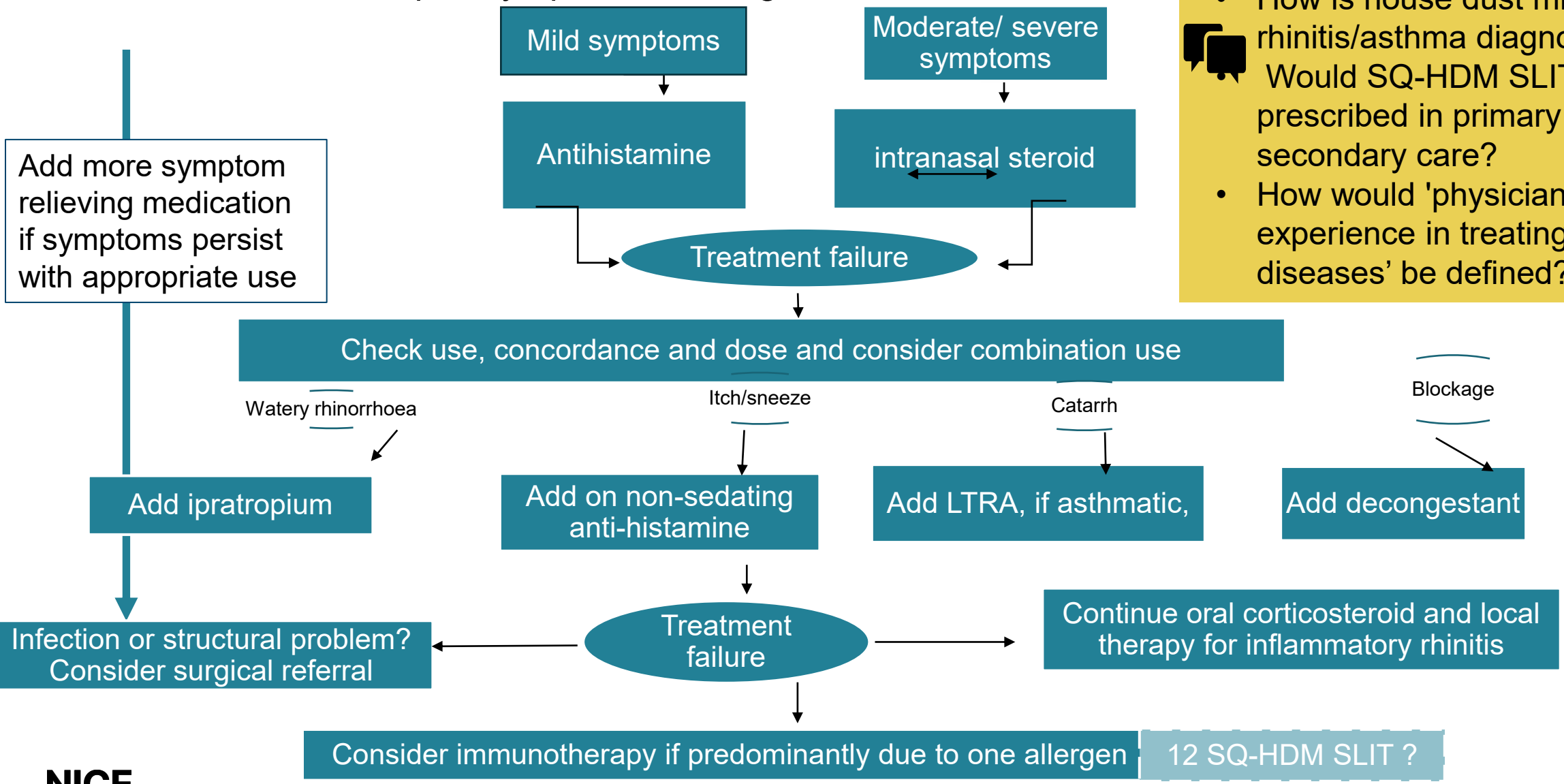
- The technology is a 'step-change' for AR and AA so could address an unmet need
- Immunomodulators can have sustained effects which last for years after stopping treatment, but clarification is needed on evaluation and treatment monitoring
- The use of the technology could result in a substantial benefit in productivity, performance and occupational safety for patients who are taking non-sedative antihistamines.
- More evidence is needed on clinical efficacy and cost -effectiveness to show patient benefit compared to current treatments available and cost effectiveness

* See appendix –Patient perspectives and Clinical perspectives

Abbreviations: AA, allergic asthma; AR, allergic rhinitis; ARD, allergic respiratory; ARNS, Association of Respiratory nurses; HDM, house dust mites; SLIT, sublingual immunotherapy

Allergic rhinitis treatment pathway BSACI

SQ-HDM-SLIT will be used in addition to current treatments in people with persistent moderate-to-severe HDM AR despite symptom-relieving medication



- How is house dust mite allergic rhinitis/asthma diagnosed? Would SQ-HDM SLIT be prescribed in primary of secondary care?
- How would 'physicians with experience in treating allergic diseases' be defined?

NICE

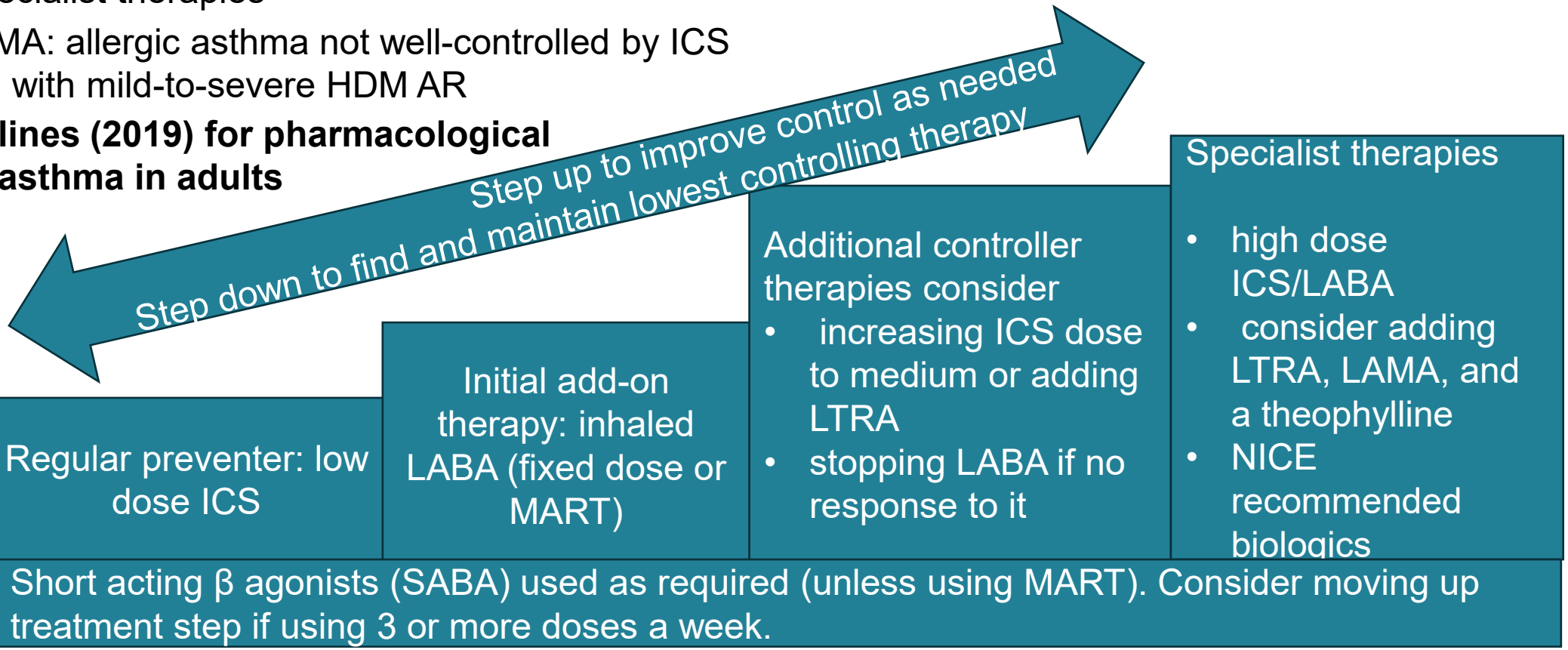
AR, allergic rhinitis; BSACI, British Society for Allergy and Clinical Immunology; LTRA, leukotriene receptor agonist;

Treatment pathway: Asthma

See appendix comparison of BTS/SIGN, NICE, GINA. NICE recommended biologics

- Latest British Guidelines are the British Thoracic Society/SIGN guidelines 2019*
- Company submission based on Global initiative in Asthma (GINA) guidelines. GINA has similar approach to stepping up and down treatment (in 5 steps), but algorithm differs. GINA suggest SQ-HDM SLIT would be used in steps before specialist therapies
- SQ-HDM SLIT MA: allergic asthma not well-controlled by ICS and associated with mild-to-severe HDM AR

BTS/SIGN guidelines (2019) for pharmacological management of asthma in adults



Where would 12 SQ-HDM SLIT be prescribed in the asthma treatment pathway?

*Ongoing review of NICE Guideline 80 (2017) in partnership with BTS/SIGN publication date Oct 2024. Abbreviations ICS, inhaled corticosteroids, MART, maintenance and reliever therapy, LABA, Long acting β agonists; LTRA, leukotriene receptor agonist; LAMA, long acting muscarinic antagonists.

12 SQ-HDM SLIT (Acarizax, ALK-Abello)

Marketing authorisation MHRA May 2021	• Adults (18 to 65 years) who have at least one of the following conditions:
	  • Persistent moderate-to-severe HDM AR despite symptom-relieving medication
	  • HDM AA not well-controlled by ICS and associated with mild-to-severe HDM AR
	• Adolescents (12 to 17 years) with persistent moderate-to-severe HDM AR despite symptom-relieving medication
	• Diagnosis by clinical history and positive test HDM sensitisation (skin prick test and/or specific IgE)

Mechanism of action	• An allergy immunotherapy which modifies immune response in upper and lower airways • Increases HDM specific IgG4 antibodies and blocks IgE antibodies from binding to HDM allergens. But exact mechanism of action is not fully understood.
Administration	• 1 sublingual oral lyophilizate daily. The lyophilizate is a tablet which dissolves under the tongue and contains a standardised allergen extract from house dust mites Dermatophagoides pteronyssinus and Dermatophagoides farinae • Once 12 SQ-HDM SLIT is taken swallowing should be avoided ~1 minute • Initiated by physicians with experience in treating allergic diseases, then self-administer • Onset of clinical effect expected 8 to 14 weeks after initiation. Suggested 3-year treatment duration. If no improvement in 1st year – no indication for continuing treatment.
Price (BNF)	• List price per pack = £80.12 per 30 tablets pack • List price for 12 months of treatment = £975.46 per patient

Abbreviations: AR, allergic rhinitis; HDM, house dust mites; IgE, immunoglobulin E; IgG4, immunoglobulin G4; ICS, inhaled corticosteroid

Key issues

Key issues relating to clinical effectiveness

Relevance of data to decision problem
Is the presented clinical evidence appropriate to address the decision problem?

- Are the populations in the trials the same as would have 12 SQ-HDM SLIT in clinical practice?
- Are the treatment pathways in the trials the same as clinical practice?
  - Is 12 SQ-HDM SLIT used in the same way as it would be in clinical practice?
  - Are the treatments used with 12 SQ-HDM SLIT and in the comparator arm similar to what would be used in NHS clinical practice?

Questions around clinical benefit

- Is there a clinical benefit of treatment?
- Would any methodological limitations of the trial affect the size of the benefit?
- Is there expected to be a different treatment effect or effect on quality of life for adults and adolescents with AR?

Is there any further data, not included in the company submission, which could address any uncertainty in clinical effectiveness?

NICE

Abbreviations: AR, allergic rhinitis; SQ, standardised quality; HDM, house dust mite

Key issues

Key issues relating to cost effectiveness

Model structure
Is the structure of the company's models for AA+AR and AR suitable for decision making?

- Does the modelled treatment pathway reflect the treatment pathway in clinical practice?
- Are the health states appropriate?
- Is the data from the MT-04 and MT-06 trials appropriate to inform the models?

Questions around modelling assumptions

- What period of MT-04 should be used in AA + AR model?
- Would a treatment benefit of SQ-HDM SLIT be maintained after stopping treatment?
  - What are plausible treatment waning assumptions?
- Is there appropriate data to model asthma exacerbation rates by treatment arms?
- Would 12 SQ-HDM SLIT reduce primary and secondary care visits? Company or EAG assumptions plausible?
- Should health state utility values be applied or use treatment specific utility values from trial?

If the model is not suitable what alternative model structure is preferred? Could such a model be informed by available clinical data and be suitable for decision making?

Abbreviations, AA, allergic asthma; AR, allergic rhinitis; SQ, standardised quality; HDM, house dust mite

Key clinical trials: overview of trials used in the model

	MT-04 n=834 (AA+AR population)	MT-06 n=992 (AR population)
Design	Phase 3, randomised, parallel-group, double-blind, placebo-controlled multi-centre trial (Europe)	
Population	18 years and over with HDM AA and AR	18 to 65 years with HDM AR.
Intervention	12 SQ-HDM SLIT* n=282 (dose in the MA) 6 SQ-HDM SLIT* n=275 (+ICS* and SABA)	12 SQ-HDM SLIT n=316 (dose in the MA) 6 SQ-HDM SLIT n=336 (+INS, oral/ eye antihistamines as needed)
Comparator	Placebo n=277 (+ ICS** and SABA)	Placebo n=338 (+ INS, oral/eye antihistamines)
Duration	13 to 18 months***	12 months***
Primary outcome	Time to first moderate or severe asthma exacerbation during Period 3 (protocol mandated ICS reduction/ withdrawal period)	Average total combined rhinitis score (TCRS) during the efficacy evaluation period
key secondary outcomes	• Symptoms (change in ACQ) • HRQoL (change in AQLQ)	• Symptoms (change in DSS) • HRQoL (average overall RQLQ score)

- P001 trial (not used to inform model), compared 12-SQ-HDM SLIT (n=741) with placebo (n=741) in people 12 years + with HDM AR for a treatment period of 52 weeks, with efficacy (TCRS) measured in last 8 weeks.
- * different standardised doses of HDM extract **MT-04 had a mandated stopping of ICS in period 3 ***In all trials the treatment durations were less than the recommended immunotherapy use (3 years) in the marketing authorisation.

See appendix for Other relevant trials including P001 trial of SQ HDM in adolescents with AR

Abbreviations: ICS, inhaled corticosteroid; INS intranasal corticosteroid ACQ, asthma control questionnaire; AQLQ asthma quality of life questionnaire; DSS, daily symptom score; IgG4, immunoglobulin G4; HDM, house dust mite; RQLQ, rhinitis quality of life questionnaire

Trial design MT-06: adults with moderate to severe HDM AR

Severity of AR based on the following inclusion criteria:

- Moderate-to-severe HDM AR symptoms during baseline defined as daily total rhinitis symptom score ≥6 or ≥5 with 1 severe symptom in at least 8 days of baseline period
- Symptomatic medication for ≥8 days of baseline period
- 1 or more ARIA QoL items in baseline period
- If have asthma daily use of ICS in line with GINA steps 1 or 2

- People randomised to SQ-HDM SLIT or placebo.
- Could take inhaled corticosteroids, oral histamines or eye drop antihistamines* as needed.

Prohibited medicines: Glucocorticoids, antihistamines, Nedocromil/cromolyn sodium, Leukotriene antagonists, synthase inhibitors, LABA, LAMA, MAOIs, Pizotifene, Theophylline, Beta blockers, Tricyclic antidepressants or antipsychotic with antihistaminic effects

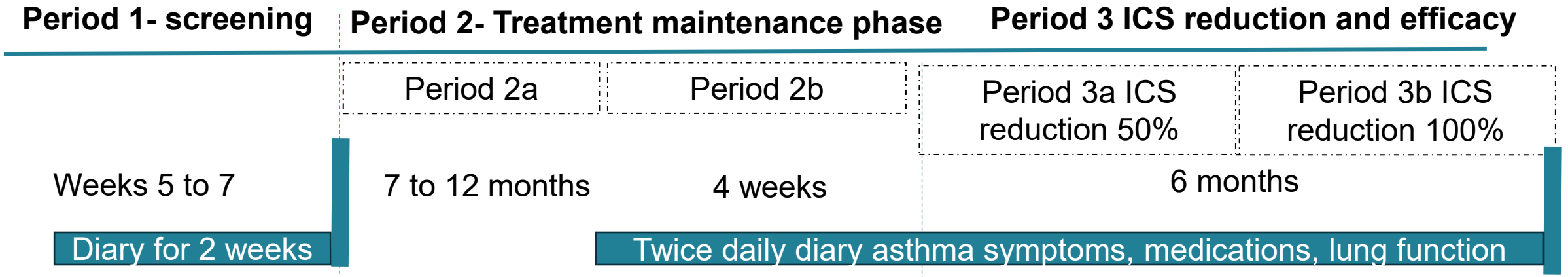
- Primary efficacy assessment periods was outside major pollen season
- Treatment maintenance varied to adjust for pollen season

- Would we allow the prohibited treatments to be used in the UK?
- At what point would we use 12 SQ-HDM in the UK?

*Company confirmed loratadine was allowed to be taken as needed

Abbreviations: PEF peak expiratory flow; SABA, short acting B2 agonist; AR, allergic rhinitis; HDM house dust mite; ARIA, allergic Rhinitis and its impact on asthma; QoL, quality of life; GINA, global initiative for asthma; ICS, inhaled corticosteroid; IgE, immunoglobulin E, LAMA, long-acting muscarinic antagonistic; MAOI, monoamine oxidase inhibitors

Trial design MT-04: Adults with HDM-induced AA with AR



During screening people switched from regular medication to ICS and SABA

Severity/ asthma control eligibility criteria

- ACQ score of 1.0 at screening
- ACQ score 1.0 to 1.5 at randomisation

- During treatment maintenance phase people randomised to either SQ-HDM SLIT or placebo, taken alongside ICS and SABA
- **Same prohibited medications as MT-06 .**

- Efficacy outcomes are from period 3
- During period 3 ICS was reduced by 50% first 3 months then completely last 3 months.
- If a person had an asthma exacerbation during period 3b they discontinued from trial.
- Outcomes assessed outside of pollen season

- Why was the ACQ score set at those values?
- Would we allow the prohibited treatments to be used in the UK?
- At what point would we use 12 SQ-HDM SLIT in the UK?

See appendix for Details of ACQ questionnaire

Abbreviations: ACQ, asthma control questionnaire; ICS, inhaled corticosteroid; SABA short-acting β2-agonists

EAG: Key methodological issues with trials

Methodological issues means trials likely over-estimate treatment effect in an NHS cohort

EAG issue	Description
Prohibited treatments	• MT-04 and MT-06 prohibited several treatments which EAG's clinical adviser considered would be widely used in the NHS
Outcomes assessed outside of pollen season	• Asthma exacerbations and rhinitis outcomes only evaluated outside the major pollen season and would have preferred efficacy data from timepoints including the pollen season
Trial duration	• Trials were between 12 to 15 months long. Shorter than standard course of allergy immunotherapy treatment (3 years).
Mandated ICS reduction (AA with AR trial, MT-04, only)	• In phase 3 of MT-04 ICS use was reduced and withdrawn. EAG consider these methods do not reflect NHS practice
Trial eligibility criteria (AA with AR trial, MT-04, only)	• ACQ of 1.0 to 1.5 means some people in MT-04 would have altered usual medication and may have had well-controlled asthma before starting the trial. • May not reflect people whose asthma is not well-controlled taking usual care • People with ACQ over 1.5 are also eligible for SQ-HDM SLIT based on its MA but may be harder to treat

EAG noted other methodological issues (see Appendix). More limitations noted in trials for the AA+AR population

See appendix for
- Full list of EAG methodological issues with all trials
- Symptomatic and prohibited medication in MT-04 and MT-06

NICE

Abbreviations: ACQ, asthma control questionnaire; ICS, inhaled corticosteroid; MA, marketing authorisation

SQ HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites

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

NICE National Institute for Health and Care Excellence

Results AR population- MT-06 trial

SQ-HDM SLIT lowered total combined rhinitis score, a measure of symptoms and medication use, compared with placebo but may not show clinically important difference in this outcome or rhinitis quality of life

	12 SQ-HDM		Placebo		Efficacy 12 SQ—HDM vs placebo			Clinically meaningful difference
	N	Score	N	Score	Absolute difference [95% CI]	p-value	% difference	
Total combined rhinitis score (primary outcome)*	318	5.71	338	6.81	-1.09 [-1.84, -0.35]	0.004	16%	20% difference between placebo and treatment (World Allergy Association)
• **Daily symptom score†**	318	2.84	338	3.31	-0.47 [-0.82, -0.11],	0.001	14%	
• **Daily medication score†**	318	2.32	338	2.86	-0.54 [-1.07,-0.01]	0.003	19%	
Rhinitis quality of life questionnaire period 3 visit 7-8	229	1.41	240	1.61	-0.21 [-0.39. -0.02]	0.031	n/a	0.5, absolute difference (Juniper et al 1999)

*Data from full analysis set with multiple imputation accounting for missing data from period 3. † components of the TCRS, Both scores range 0-12

NICE

Are the observed outcomes clinically meaningful?
Is there a clinical benefit of 12 SQ-HDM for AR

See appendix for
AR population P001 key outcomes
AR population T0203-32 key outcomes
Details of TCRS, DSS, DMS and RQLQ

Results- AA with AR population MT-04

There was a statistically significant reduction in risk of moderate or severe asthma exacerbation for 12 SQ-HDM compared with placebo in the mandated ICS withdrawal period of MT-04. But differences in secondary outcomes of the asthma control questionnaire and asthma quality of life questionnaire may not be clinically meaningful

MT-04 results	12 SQ-HDM		Placebo		Efficacy 12 SQ—HDM vs placebo		clinically meaningful difference
	N	**n (%)**	**N**	**n (%)**	**HR [95% CI]**	**p-value**	n/a
Any moderate or severe exacerbation (primary outcome) FAS -MI	282	59 (21%)	277	83 (30%)	0.69 [0.50,0.96]	0.027	Not available
	N	**score**	**N**	**score**	**Mean difference[95% CI]**		
Asthma control questionnaire score visit 13 (period 3- ICS withdrawal)	204	0.75	208	0.87	-0.12 [-0.25, 0.01]		0.5 (Juniper et al 2005)
Asthma quality of life questionnaire (period 3- ICS withdrawal)	204	6.26	208	6.14	0.12 [-0.02, 0.26]		0.5 (Juniper et al, 1994)

Lung function (peak expiratory flow, forced expiratory flow in 1 second). EAG stated results in clinical study report showed no statistically significant difference

Are the observed outcomes clinically meaningful?

Abbreviations: ACQ, asthma control questionnaire; AQLQ (S), standardised asthma quality of life questionnaire; CI, confidence interval; FAS, full analysis set HR, hazard ratio;

See appendix for AA+AR population T0-203-31 key outcomes

Key issue: Clinical relevance of magnitude of efficacy estimates

Efficacy of trial results should be interpreted with caution

EAG comments

AR population

- MT-06 TCRS based on period 2 (FAS data) and period 3 (FAS-imputed data – which has better internal validity)

AA with AR population

- ACQ score improvements with 12 SQ-HDM was not statistically significant or clinically significant
- No statistically significant improvements in measures of HR QOL or in measures of lung function
- No evidence to support significant improvements in complications of rhinitis (sinusitis).

Other comments

(British Thoracic Society)

- Only 1 clinical trial showed it may be of benefit- but when ICS dose was reduced/ stopped
- In clinical practice we would not stop inhaled steroids
- More evidence is needed on clinical efficacy and cost -effectiveness

(ARNS professional)

- Clinically significant response needs to be identified to show success or failure of treatment.
- Consider FeNO as a measurement tool and symptom-based questionnaire to evaluate treatment
- More clarification needed to patient benefit compared to current treatments available and cost effectiveness.

- Is there a clinical benefit of treatment?
- Would any methodological limitations of the trial affect the size of the benefit?

Abbreviations: AA allergic asthma; ACQ, asthma control questionnaire; AR allergic rhinitis; ARIA allergic rhinitis and its impact on asthma guidelines; ARNS, Association of respiratory nurses; FeNO, fractional exhaled nitric oxide; ICS, intranasal corticosteroid; HRQoL, health-related quality of life; TCRS, total combined rhinitis score. FAS full analysis set

SQ HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites

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

NICE National Institute for Health and Care Excellence

Modelling Issues

- ✓ **Issues specific to the allergic rhinitis model**
- ❑ Issues specific to the allergic asthma with rhinitis model
- ❑ Issues common to both models

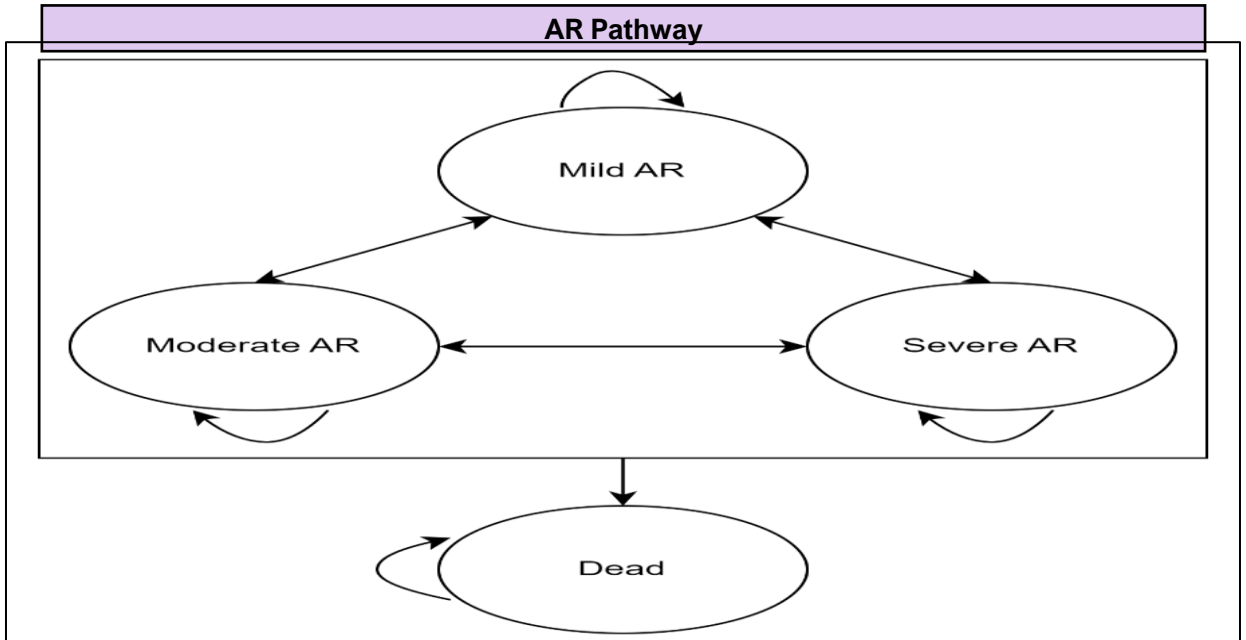
NICE National Institute for Health and Care Excellence

Company's model overview: AR adult population

Both AR and AA with AR models are Markov models, cycle length 1 year. Life-time horizon. Compare SQ-HDM SLIT with standard clinical management to clinical management alone.

Model structure overview

- Modelled cohort mean age 32.3 years; 49.8% male (MT-06 data)-
- 3 health states based on AR severity (ARIA classification) and death
- Data from MT-06 used to estimate the proportions of people in each severity health state.
- ARIA score estimated from daily symptom score (as a proxy for troublesome symptoms) and 3 HR QoL scores (sleep disturbance, impairment of daily activities, leisure and/or sport and impairment of school-work) from MT-06
- Does not include data for adolescent population
- Model does not step-up treatment when symptoms persist or step down when well controlled



Modelled treatment effect

- Year 1 (first cycle) informed by post-hoc analysis of proportions in each health state at start and end of MT-06
- Long term (cycle 2 onwards) determined by assumed annual rate of change across health states, with clinical expert validation. Assumption on treatment waning included

Key issue: AR model - adolescent subgroup

Uncertain impact

In the AR model evidence in adults is generalised to the adolescent subpopulation

Background

No data for adolescents related was included in the AR model as informed by MT-06, but P001 trial included people who were 12 years and older.

EAG comments

- EAG clinical advice suggests treatment effectiveness for adolescents compared with adult subpopulations, may differ due to hormonal changes
- Trial results showed a significant improvement in TCRS compared with placebo, regardless of age group
- At clarification company stated no data in P001 would allow for health states in the model to be aligned to definitions of disease severity
- **Impact: EAG is unable to explore the impact of including the adolescent subgroup evidence, from the trials, in the AR model**.

Is there expected to be a different treatment effect with 12 SQ HDM SLIT or effect on quality of life for adults and adolescents with AR?

Abbreviations, AR, allergic rhinitis; TCRS, total combined rhinitis score

Modelling issues

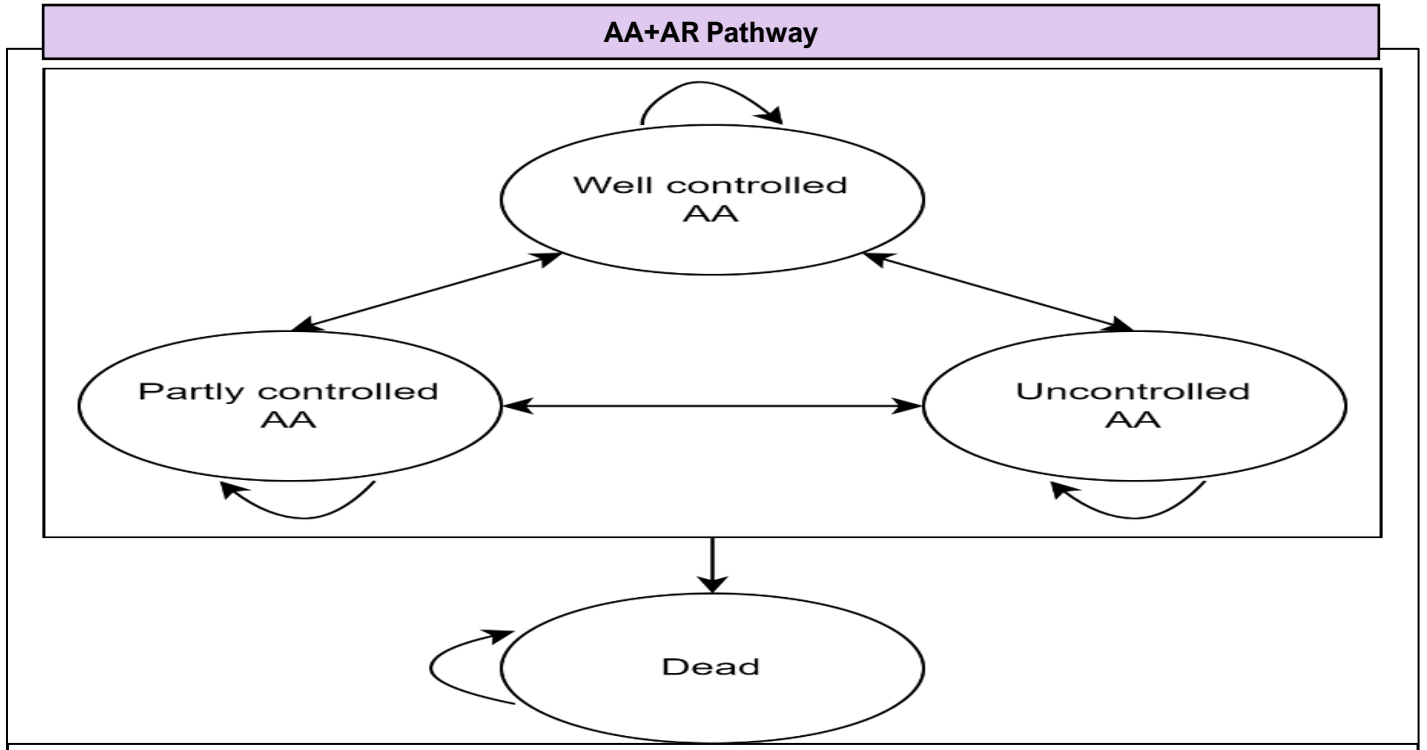
- ❑ Issues specific to the allergic rhinitis model
- ✓ **Issues specific to the allergic asthma with rhinitis model**
- ❑ Issues common to both models

NICE National Institute for Health and Care Excellence

Company's model overview: AA with AR

Model structure overview

- Modelled cohort mean age 33.4 years; 51.7% male (MT-04)
- 3 health states based on GINA guidelines definition of asthma control, or dead
- ACQ data from MT-04 trial was mapped to GINA 2010 criteria for health state distribution.
- AR outcomes not explicitly modelled
- Compares 12 SQ-HDM SLIT with standard clinical management to standard clinical management alone
- Model does not step-up treatment when symptoms persist or step down when well controlled
- Does not model disease progression across asthma steps
- Exacerbations are modelled as events which occur at same rate regardless of health state



Modelled treatment effect

- Transitions between asthma control health states in 1st year estimated using MT-04 ACQ scores at baseline and trial end
- Used data for each arm from MT-04.
- Long term (cycle 2 onwards) based on assumed annual rate of change between health states, with clinical expert validation. Assumption on treatment waning included

Abbreviations: AA, allergic asthma;; AR, allergic rhinitis. EAG, External Assessment Group; QALY, quality-adjusted life year; ACQ,, asthma control questionnaire; GINA, Global initiative for asthma

Key issue: AA with AR model structure

EAG consider company's AA with AR model structure may not be suitable for decision making

Company

- The 3 health states were defined to reflect asthma control, which results from a continual cycle of assessment, treatment adjustment, and review based on GINA guidelines
- Used asthma control data (ACQ) from MT-04 which was mapped to GINA levels of control

EAG comments

- Previous cost-effectiveness studies (Parra-Padilla et al, 2021) used a Markov model to reflect stepping up/ down of treatment, asthma remission and exacerbation and measured effectiveness by reducing medication dose
- Previous models for asthma technology appraisals structured the models around asthma control and exacerbation events in line with BTS/SIGN guideline (which defines asthma control based on ACQ scores)
- Unclear why company did not use ACQ scores directly rather than mapping to GINA criteria
- In BTS/SIGN guidelines an ACQ score of ≥ 1.5 = uncontrolled; <1.5 = controlled. By these definition people in the MT-04 trial would have been considered to have controlled asthma.
- The company's model structure should explicitly account for asthma disease progression over treatment steps
- Model informed by MT-04. EAG is concerned this does not address decision problem (due to methodological issues)
- In absence of better quality evidence, in its base case, EAG uses data from period 2, rather than period 3 (with mandated ICS withdrawal)

- Is the company's model structure for AA+ AR suitable for decision making?
- Are the health states appropriate?

See appendix for model structures in previous TAs

Abbreviations: ARIA, Allergic Rhinitis and its Impact on Asthma; ACQ asthma control questionnaire; GINA, Global initiative for asthma guidelines,

Key issue: AA with AR model -asthma exacerbations

No sizeable impact

Background

- Modelled treatment effectiveness accounted for number of asthma exacerbations in each modelled treatment arm using data from period 3 of MT-04, in which background ICS was reduced and stopped
- Exacerbation rates were converted to annual probabilities for use in the model
- In MT-04 the number of exacerbations was low but reflects trial design where people could stop after first exacerbation or continue in the trial on increased ICS dose

EAG comments

- ICS reduced by 50% (in period 3A) and withdrawn (in period 3B).
- Company's assumption that exacerbation risk is independent of asthma control level and exacerbations do not affect subsequent health states is not clinically supported.
- Annual exacerbation probabilities reflect probability of a first exacerbation during period 3.
- Exacerbation probabilities underestimate total number of events in period 3.
- Previous TAs (TA 479 and TA751 and TA565 and TA880) modelled exacerbations as health states
- ACQ evidence from MT-04 suggested there was similar levels of asthma control between 12 SQ-HDM and placebo in MT-04 and suggests there is a negligible effect on exacerbations compared to placebo in period 2
- EAG scenario: null probability of asthma exacerbations across levels of asthma control in each arm*

Is there appropriate data to model asthma exacerbation rates by treatment arms?

See appendix for
- Exacerbation rates from MT-04 used in AA+AR model

*EAG scenario was an additional analysis to their base case
Abbreviations: AA, allergic asthma, AR allergic rhinitis; ICS, intranasal corticosteroid

Key issue: AA with AR model standard of care treatment costs

Company's approach may overestimate costs of standard of care

small impact

Background

- Standard care treatments for each health state are based on BTS/SIGN, with the distribution of patients across management steps from CARIOCA study (a 1-year French longitudinal study of SQ-HDM)
- Weighted cost ratios based on ICS use in maintenance MT-04 is used to factor in the increased costs for SoC in partly controlled and uncontrolled health states vs costs for SOC in well-controlled health state
- 68% eligible for biologics - equal spread (omalizumab, mepolizumab, dupilumab, tezepelumab)
- Assumes 22% reduction in people who are in step 5 (includes biologics) in 12 SQ-HDM SLIT arm

EAG comments

- Reiterated overarching issues with MT-04 and model structure not reflecting clinical practice of stepping up and down treatments
- Company conflated all asthma management steps (1-5) in each of 3 asthma control health states and assume a proportional difference in costs based on MT-04 evidence on ICS dose differences in maintenance period of MT-04. Implausible to assume ICS use between levels of control directly translates to increase in costs across all asthma medications (EAG removes this assumption in base case)
- Biologic treatments included in the company's standard of care cost may not reflect clinical practice. Assumption that 12 SQ-HDM reduces biologic use not validated. Biologics not permitted in MT-04

* See table 25 of EAG report for summary of costs in the company's base case analysis for the AA+AR population

How should medication use be estimated?

Abbreviations: AR, allergic rhinitis; AA, allergic asthma; SOC, standard of care, ICS inhaled corticosteroid

See appendix for
Weighted approach to SoC costs
TA recommendations for biological treatments for asthma

Modelling issues

- ❑ Modelling issues specific to AR model
- ❑ Modelling issues specific to AA with AR model
- ✓ **Modelling issues common to both models**

NICE National Institute for Health and Care Excellence

Key issue: AA with AR and AR models Short term effectiveness

There is uncertainty in the short term (1 year) modelled effectiveness of 12 SQ-HDM SLIT vs standard care because it relies on post hoc analyses of the trial data and does not reflect stepping up and down treatment

Company

AA with AR model

- ACQ data from MT-04 used to estimate proportions of people in asthma control health states and transition probabilities between health states in 1st cycle in post hoc analyses

AR model

- Post hoc analysis of MT-06 used to estimate proportions of people in AR severity health states and transition probabilities in 1st cycle

EAG comments

- In both models, trial data and model structure do not reflect clinical practice of stepping up/down treatment.
- Adjusted post-hoc analysis adds considerable uncertainty
- Company assume distributions across asthma control levels (AA with AR)and rhinitis severity levels (AR model) at baseline and trial end are fixed, so the uncertainty in the transition probabilities in the first cycle is not considered.
- EAG applied a Dirichlet distribution to address parameter uncertainty of transition probabilities in probability analysis. This assumed:
  - People do not get worse from baseline to year 1
  - People in partly controlled/moderate health states at baseline transition to well-controlled/mild health state in year 1

Abbreviations, AA, allergic asthma; AR, allergic rhinitis; ACQ, asthma control questionnaire; GINA, global initiative for asthma; BTS, British Thoracic Society; SIGN, Scottish Intercollegiate Guidelines Network

Key issue: AA with AR and AR model Management costs- secondary care

Model driver

Assumptions on the extent to which 12 SQ-HDM SLIT may reduce secondary care costs are highly uncertain and have a large impact on the ICER

Company

- Used HES data to inform the number of secondary care visits in both models but explored other sources
- AA with AR - Relative reduction for 12 SQ-HDM SLIT vs SOC (54.58%) in AA + AR model based on emergency room visits in MT-04
- AR - Specialist visits in MT-06 assumed to be GP so relative reduction (73.53%) based on El Qutob et al (a study of subcutaneous HDM immunotherapy for rhinitis and asthma)

EAG comments

- Reduction in secondary care visits with 12 SQ-HDM SLIT drives cost savings but considerable uncertainty
- Concerned with El-Qutob to inform relative reduction in secondary care visits in AR model
  - Before and after design to estimate the treatment effects, may result in biased estimates.
  - Intervention is subcutaneous immunotherapy, so it is unclear whether the treatment effects are generalisable to 12 SQ-HDM SLIT(a sublingual immunotherapy)
  - MT-06 comparative evidence was available for outpatient visits
- Due to uncertainty, EAG assumed relative reduction in secondary care visits with 12 SQ-HDM SLIT vs. SOC was equivalent to relative reduction in primary care visits. (7.35% for 12 SQ-HDM SLIT for AA+AR model [using data from period 2 of MT-04] and 4.92% for the AR model [using data from MT-06]).
- This EAG assumption resulted in large increase in ICER in both models

- Would 12 SQ-HDM SLIT reduce primary and secondary care visits?
- Are either Company or EAG assumptions plausible?

Abbreviations: AA, allergic asthma, AR, allergic rhinitis; CE, cost-effectiveness; HES, hospital episode statistics; SCIT, subcutaneous immunotherapy treatment

See appendix for Primary and secondary care visits in Company and EAG base case

Key issue: AA+AR and AR models - Long term effectiveness (1)

Company's long term effectiveness assumptions are highly uncertain

Wide ranging impact – high uncertainty

Background

- Both models assume the transitions across health states over 4 time periods; 2-5 years, 5-10 years, 10 -20 years and 20+ years
- There is some modelled improvement in health from 12 SQ-HDM SLIT up to Year 10, with treatment waning from Year 10 to 20 and no improvement from Year 20 onwards. Long term health is stable in standard of care arm (stay in same health states)
- REACT study showed that over 9 years allergen immunotherapy reduced AA and AR medication prescription
- Company stated 2 modified advisory panels of clinical experts specialists agreed 12 SQ-HDM, is likely to have a sustained and clinically significant effect for 10 years with potential waning over the following decade.

EAG comments

Company applied arbitrary rates of change to reflect medium to long-term effectiveness. Limited evidence for a lifetime horizon. It is not clear if company's clinical experts validated annual rate of change across health states

  - Long term assumptions highly uncertain
  - Lifetime horizon is uncertain and previous publications reported shorter time horizons of 5 to 9 years
- EAG preferred assumptions based on existing published evidence up to 10 years in its analyses **(small impact) But exploratory assumptions in sensitivity analyses had wide ranging impact increasing ICER**

Would treatment benefit of 12 SQ-HDM SLIT be maintained after stopping treatment? Does the disease, technology and mechanism support these assumptions?

See appendix for

- Assumptions in AA+AR and AR models and in published evidence

NICE

Abbreviations: AA, allergic asthma; AR, allergic rhinitis, HRQoL

Key issue: AA with AR and AR models - Long term effectiveness (2)

Wide ranging impact – high uncertainty

Treatment waning may occur after stopping treatment with SQ-HDM

Background

- Company's treatment waning assumption: treatment waning in modelled 12 SQ-HDM SLIT arm starts at 15 years and by 20 years 80% of people in this arm match the distribution of people having standard care alone across health states
- People in the 12 SQ-HDM SLIT arm cannot decline to a worse state than those having standard of care alone
- Company stated 2 modified advisory panels of clinical experts specialists agreed 12 SQ-HDM SLIT, is likely to have a sustained and clinically significant effect for 10 years with potential waning over the following decade.

EAG comments

- Treatment waning assumption arbitrary and highly uncertain
  - Treatment effect will continue to wane and unlikely to completely disappear, though no evidence on when and how it declines
- Clinical advisory boards noted that waning was unlikely to completely disappear
- Assumption that people in 12 SQ-HDM SLIT arm cannot decline to a worse state than standard of care lacks clinical validity

- Would a treatment benefit of 12 SQ-HDM SLIT be maintained after stopping treatment?
- Does the disease, technology and mechanism support these assumptions?

See appendix for
- Assumptions in AA+AR and AR models and in published evidence

NICE

Abbreviations: AA, allergic asthma; AR, allergic rhinitis, HRQoL

Key issue: AA with AR and AR- Utility values

Large impact

Company applies treatment-specific utility values, EAG prefers utility by health state

Background

- Treatment-specific utilities rather than health state specific utilities applied
- **AA with AR model** utilities estimated from SF-36 scores from a post-hoc analyses of MT-04. Mean differences between 12 SQ-HDM SLIT and placebo at baseline and the end of trial were used to derive a utility of 0.785 for 12 SQ-HDM, and 0.753 for standard care
- **AR model** EQ-5D data from a post-hoc analyses of MT-06 was used to estimate average treatment utility in each arm
- **Both models,** multiplicative utilities applied to adjust for age-associated decline in QoL (Ara and Braz, 2010)

EAG comments Prefers health-state specific utilities approach-

- Treatment-specific approach does not align with model structures developed for AA with AR and AR models
- EAG preferred health-state specific utilities. Estimates from post-hoc analysis of MT-04 -Briggs et al, 2021 (mapped AQLQ data to EQ-5D-5L for asthma control health states) for AA with AR model and MT-06 for AR model (company scenario) reduced incremental QALYs in both models
- No AE-related utility decrements were applied in either model
- EQ-5D-5L is only validated for adults and may not be appropriate for adolescents (AR model). Also potential for quality of life to differ in adolescents and adult

Should health state utility values be applied or treatment specific utility values from trial?

See appendix for

- Approach to HRQoL in AA+AR and AR models
- Mapped utility scores from Briggs

Summary of company and EAG base case assumptions

Assumption	Model	Company base case* AA+AR model	EAG base case	Impact on ICER
Asthma exacerbations	**AA with AR model only**	Exacerbation probabilities from MT-04 period 3 (12 SQ-HDM= 36.02% moderate; 8.01% severe)	Null probability of asthma exacerbations Conservative assumption because MT-04 does not reflect clinical practice	No sizeable impact
Treatment costs		Biologic treatments • Equal spread by each biologic (omalizumab, mepolizumab, dupilumab, and tezepelumab)	Only relevant biologic treatments (omalizumab and tezepelumab)	Small
Short-term effectiveness source of data		MT-04 period 2 and 3 (baseline to trial end)	using MT-04 period 2 only (does not include period of trial with mandated ICS reduction)	No sizeable impact
Secondary care costs reduction with SQ-HDM	**Both models**	Secondary care visits reduction for 12 SQ HDM (AA with AR 54.58% and AR 73.53%)	Secondary care visit reduction was equivalent to primary care relative reduction (7.35% AA+AR, 4.92% AR)	Large
Long term effectiveness		Waning assumptions based on Delphi panel and advisory panel • Improvement 2 to 5; 5 to 10 yrs • Waning starts at 15 years, 80% of people in same health states as SOC arm at 20 years;	Evidence based waning assumptions • sustained effect of 12 SQ-HDM from 2 to 10 yrs • Post 10 yrs 12 SQ-HDM to match SOC arm health state distribution	Large
Utilities		Treatment-specific utilities in MT-04 and MT-06 AA with AR 0.785 for 12 SQ-HDM and 0.753 for SOC AR 0.919 for 12 SQ-HDM and 0.898 for SOC	Health state specific utilities	Large

See table 33 of EAG report for issues which were not possible to address in EAG exploratory base case

* EAG corrected company base case AA, allergic asthma; AR, allergic rhinitis; SOC, standard of care SQ, standardised quality; HDM, house dust mite; BTS, HES, hospital episode statistics

Cost effectiveness results summary

For both the AR and AA + AR populations the company base case is that 12 SQ-HDM SLIT dominates standard care. This means it costs less and is more effective.

For the AR population the EAG exploratory base case produces an ICER of £50,479 per QALY gained. The model estimates that the total costs of SQ-HDM are higher than standard care alone. There are fewer incremental QALYs with 12 SQ-HDM vs standard care alone (0.05) in the EAG's exploratory base case than the company base case (0.26).

For the AA+ AR population the exact ICER for the EAG's exploratory base case cannot be reported because some biologic treatments included in the model have confidential prices. The ICER is over £100,000 per QALY gained. There are fewer incremental QALYs with 12 SQ-HDM vs standard care alone in the EAG's exploratory base case than the company base case.

SQ HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites

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

NICE National Institute for Health and Care Excellence

Equalities

No equalities issues were identified

Company:

- No known equality issues
- But a large burden of ARD for both patients and NHS, and a lack of accessible and well-resourced specialist services for ARD patients.
- As the first dose of 12 SQ-HDM is administered in secondary care, this may be considered to represent a barrier to some patients for whom allergy services are less accessible

Patient expert:

- Language barriers: Understanding treatment which may lead to compliance issues.
- Disability: if people cannot open treatment packaging
- Access: There are very few allergy centres that provide immunotherapy country wide, with large geographical variation in provision,
- GP's may have little allergy knowledge to refer people who fit the criteria for HDM SLIT.
- Cut off age for immunotherapy and people who are pregnant would not start immunotherapy

NICE

Abbreviations: ARD, allergic respiratory disease, AA, allergic asthma; AR, allergic rhinitis

SQ HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites

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

NICE National Institute for Health and Care Excellence

Questions for committee

Clinical effectiveness

- Are the treatment pathways in the trials the same as clinical practice?
- Is SQ-HDM used in the same way as it would be in clinical practice?
- Are treatments used with SQ-HDM or in the comparator arm similar enough to what would be used in NHS clinical practice?
- Is there a clinical benefit of treatment? Would any methodological limitations of the trial affect the size of the benefit?

Cost effectiveness

- Is the company's model structure for AR and AA+AR suitable for decision making? Are the health states appropriate?
- Is there expected to be a different treatment effect or effect on quality of life for adults and adolescents with AR?
- Is there appropriate data to model asthma exacerbation rates by treatment arms?
- What period of MT-04 should be used in AA + AR model?
- Would a treatment benefit of SQ-HDM be maintained after stopping treatment? What are the plausible assumptions?
- Would SQ-HDM SLT reduce primary and secondary care visits? Are either Company or EAG assumptions plausible?
- Should health state utility values be applied or treatment specific utility values from trial?

Abbreviations: AA, allergic asthma; AR, allergic rhinitis;

SQ HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites [ID6280]

Supplementary appendix

NICE National Institute for Health and Care Excellence

Patient perspectives

Allergic asthma and allergic rhinitis are long-term conditions that can impact on daily activities and quality of life

Submissions from Allergy UK, Asthma and Lung, UK and Anaphylaxis UK

- There is an unmet need and there are currently no effective long-term treatments available on the NHS to reduce the severity of an allergic reaction
- There is a lack of awareness of longer-term solutions within the patient and carer community,
- Cause of disease is unknown and change in QOL becomes the new normal
- Because exposure to HDM occurs all year round, medication also needs to be taken all year round, often for many years. People often find this challenging and side effects can be a problem

"When we received the HDM allergy diagnosis, it was completely overwhelming, because of the list of things we had to do, we had to change our daily habits"

"My allergies were virtually year-round, the physical symptoms also affected my sleep and my ability to feel like I was functioning during the day and this also affected my mood."

Link to Patient and clinical perspectives*

Abbreviations: AA, allergic asthma, AR, allergic rhinitis, HDM, house dust mite, QOL, quality of life

Clinical perspectives

SQ HDM-SLIT has the potential to improve long term outcomes for people with AA and AR but more data is needed

Submissions from Royal College of Physicians and British Thoracic Society

- Using allergen immunotherapy for asthma is in the Global Initiative for Asthma guidelines as well as the EAACI Guidelines on Allergen Immunotherapy: But this has yet to be translated to national guidelines and so access to this is limited
- The trial measured exacerbations once inhaled steroids were reduced and then stopped. There is only a single trial; more evidence is needed
- This technology is suitable to be used as an add-on treatment for mild asthma or to prevent escalation of treatment to biologicals, immunosuppressive agents or low dose corticosteroid.

Access to allergen immunotherapy is limited due to limited access to funding for treatment as well as limited centres in England which provide this service"

"We would not recommend stopping inhaled steroids in a patient who has asthma- this is outside standard guidance and can result in asthma death."

Link to Patient and clinical perspectives*

Abbreviations: AA, allergic asthma, AR, allergic rhinitis

ARIA classification

Mild symptoms
No affected items

Moderate symptoms
1 to 3 affected items

Severe symptoms
4 affected items

Affected items include:

- Troublesome symptoms (sinusitis, conjunctivitis, oral allergy syndrome, repeat respiratory infections)
- Sleep disturbance
- Impairment of school or work
- Impairment of daily activities, leisure and/or sport

Recommendation based on 2016 revision of ARIA	
1a	In patients with SAR, a combination of an ICS with an OAH or an ICS alone
1b	In patients with PAR, an ICS alone rather than a combination of ICS with OAH
2a	In patients with SAR, either a combination of an ICS with an IAH or an ICS alone
2b	In patients with PAR, either a combination of an ICS with an IAH or an ICS alone
3a	In patients with SAR, a combination of an ICS with an IAH rather than an IAH alone
4a	In patients with SAR, either an LTRA or an OAH
4b	In patients with PAR, an OAH rather than a LTRA
5a	In patients with SAR, we suggest an ICS rather than an INH
5b	In patients with PAR, we suggest an ICS rather than an INH
6a	In patients with SAR, we suggest either an INH or OAH
6b	In patients with PAR, we suggest either an INH or OAH

Based on conditional recommendations; source ARIA (2016) Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines—2016 revision - Journal of Allergy and Clinical Immunology (jacionline.org)

ARIA, Allergic rhinitis and its impact on asthma; IAH; intranasal H1-antihistamine; ICS, intranasal corticosteroid; LTRA, leukotriene receptor antagonist; OAH, oral antihistamine; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis;

Recommended treatments and steps in different guidelines

	Recommended treatment options and steps	
GINA (2022)	Reliever: ICS-formoterol as needed Steps 1-2: as-needed low dose ICS-formoterol Step 3: low dose maintenance ICS-formoterol Step 4: medium dose maintenance ICS-formoterol Step 5: add-on LAMA, consider high dose maintenance ICS-formoterol, consider anti-IgE, anti-IL5/5R/4R, anti-TSLP	Reliever: SABA as needed Step 1: ICS whenever SABA taken Step 2: low dose ICS Step 3: low dose maintenance ICS-LABA Step 4: medium/high dose maintenance ICS-LABA Step 5: add-on LAMA, consider high dose maintenance ICS-LABA, consider anti-IgE, anti-IL5/5R/4R, anti-TSLP
	HDM SLIT can be considered as a controller option at Steps 2, 3, and 4 for the treatment of suboptimally controlled asthma with allergic rhinitis.	
BTS/SIGN (2019)	Reliever: SABA as needed Regular preventative therapy: low dose ICS Initial add-on therapy: low dose ICS-LABA Additional therapy: medium dose ICS-LABA, consider adding LTRA Specialist therapy: high dose ICS/LABA, consider adding LTRA, LAMA, and a theophylline. Biologic therapy may be considered in eligible patients with high oral corticosteroid burden. NICE guidance on Omalizumab, Mepolizumab, Reslizumab, and Benralizumab to be considered.	
NICE NG80 (2017)	Reliever: SABA as needed 1 First-line therapy: low dose ICS 2. Second-line therapy: low dose ICS plus LTRA 3 Next step therapy: low dose ICS-LABA with or without LTRA 4. Next step therapy: medium dose ICS-LABA with or without LTRA 5. Next step therapy: consider high dose ICS-LABA with or without LTRA, OR consider medium dose ICS-LABA with or without LTRA plus LAMA or theophylline 6 No commentary on specialist therapies including biologics and immunotherapies (* see next slide for NICE recommended biologics through TA programme)	

Technology appraisal recommendations for biological treatments for asthma

TA	Technology + mechanism of action	Indication
TA278	Omalizumab (monoclonal antibody that binds to IgE)	Add-on in people aged 6 years and older who need continuous or frequent treatment with oral corticosteroids (4 or more courses in previous year)
TA880	Tezepelumab (monoclonal antibody against TLSP.	Add-on for severe asthma in people 12 years and over, when treatment with high-dose ICS and another maintenance treatment has not worked well enough, if ≥3 exacerbations in last year, or having maintenance oral corticosteroids.
TA671	Mepolizumab (monoclonal antibody against anti-IL-5 receptor alpha)	Add-on for severe refractory eosinophilic asthma blood eosinophil count has been recorded as ≥300 cells per microlitre Or blood eosinophil count ≥400 cells per microlitre and ≥ 3 exacerbations needing systemic corticosteroids in past 12 months
TA479	Reslizumab (monoclonal antibody against anti-IL-5 receptor alpha)	Add-on for severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose ICS plus another drug blood eosinophil count ≥400 cells per microlitre and ≥3 severe asthma exacerbations needing systemic corticosteroids in past 12 months
TA565	Benralizumab (monoclonal antibody against anti-IL-5 receptor alpha)	Add-on severe eosinophilic asthma inadequately controlled in adults despite maintenance therapy with high-dose ICS and LABA
TA751	Dupilumab (monoclonal antibody against IL-4 and IL-13)	Add-on maintenance therapy for severe asthma with type 2 inflammation that is inadequately controlled in people 12 years and over, despite maintenance therapy with high-dose inhaled corticosteroids and another maintenance treatment

Abbreviations: ICS, inhaled corticosteroid; IL, interleukin; IG, Ig, Immunoglobulin; TLSP, thymic stromal lymphopoietin

Decision Problem

	Final scope	EAG comments
Intervention	SQ-HDM SLIT add-on to standard therapy	
Population	• People aged 18 to 65 years with HDM sensitisation and persistent moderate to severe HDM AR despite symptom-relieving medication, or AA not well-controlled by ICS and associated mild-to-severe AR • People aged 12 to 17 years with HDM sensitisation persistent moderate-to-severe HDM AR despite symptom-relieving medication	• AA trials restricted by ACQ score but this would not happen in the NHS
Comparator	Established clinical management CM without SQ-HDM SLIT	Does not represent standard care in NHS
Outcomes	• Severity of rhinitis symptoms†‡, • Complications of AR (sinusitis or middle ear infections) †, • Rhinitis medication use† • Use of ICS‡ • Use of rescue medication‡ • Time to first moderate or severe asthma exacerbation after ICS reduction‡ • Reduction in risk of risk of asthma exacerbation‡ • Lung function‡ • Adverse effects†, ‡ • Health-related quality of life†,‡	• In practice ICS dose would be rather managed using a stepwise approach based on GINA guidance.

† For HDM sensitisation with persistent moderate-to-severe HDM AR despite use of symptom-relieving medications:
‡ For HDM sensitisation with AA that is not well-controlled by ICS and associated with mild-to-severe AR

Other relevant trials

P001- double-blind, multicentre RCT in people 12 years and older with AR/ARC symptoms from HDM

T0-203-31 - double-blind, multicentre RCT including ACQ score of 1.0 to 1.5 and daily ICS use

T0-203-32 - double-blind, multicentre, RCT in people with HDM-induced AR

Relevant outcomes for inclusion from other relevant trials

	P001	T0-203-31	T0-203-32
Primary outcome	Average TCRS*	Time to first moderate or severe asthma exacerbation**	Average TCRS*
Key secondary outcomes	• Average rhinitis DSS * • Average rhinitis DMS* • Average TCS * • Average AR/ARC VAS score *	Time to first moderate or severe asthma exacerbation***	Average AR symptom score (DSS) *

*during last 8 weeks of treatment
**in period 3 measured from randomisation (calculating from the first day of study treatment)
*** in period 3 measured from the Period 3 started date (calculating from the Period 3 started date)

Abbreviations: ACQ, asthma control questionnaire; AR, allergic rhinitis; ARC, allergic rhino conjunctivitis; HDM. house dust-mite; RCT, randomised controlled trial; TCRS, total combined rhinitis score; VAS, visual analogue scale; TCS, total combined rhinoconjunctivitis score

Symptomatic medication in MT-04 and MT-06 6

Concomitant treatments provided at randomisation	Prohibited concomitant treatments (MT-04 and MT-06)
MT-04 - Participants were switched from their regular asthma controller medication (including combination products) to equivalent doses of ICS and short-acting β2-agonists as needed. ICS was provided as budesonide powder for inhalation in strengths of 100 or 200 µg per dose and were used as daily controller treatment of asthma until Period 3B. Throughout the trial, SABA was provided as salbutamol for inhalation in a strength of 200 µg/dose.	Glucocorticoids, antihistamines, Nedocromil/cromolyn sodium, Leukotriene antagonists, synthase inhibitors, LABA, LAMA, MAOIs, Pizotifene, Theophylline, Beta blockers, Tricyclic antidepressants or antipsychotic with antihistaminic effects
MT-06 - For rhinitis symptoms: oral antihistamine tablets (desloratadine tablets, 5 mg – max daily dose of 1 tablet), or nasal corticosteroid spray (budesonide 64 mg per dose - max daily dose of 2 puffs per nostril).	
MT-06 - For conjunctivitis symptoms: antihistamine eye drops (azelastine 0.05% - max daily dose of 2 drops per eye).	

NICE

EAG considers pivotal trials had a lower standard of care and less flexibility of treatment management than in NHS practice

AA+AR population T0-203-31

	TO-203-31 results	12 SQ-HDM		Placebo		Efficacy 12 SQ-HDM VS Slacebo		
		N	n (%)	N	n (%)	HR [95% CI]	Risk reduction	p-value
Primary endpoint	Any exacerbation, moderate or severe (FAS)	276	104 (38%)	274	110 (40%)	0.971 [0.74,1.27]	NR	0.8285
Secondary endpoints	Any exacerbation, moderate or severe (PPS)	240	88 (37%)	225	87 (39%)	0.984 [0.73,1.32]	NR	0.9158
	Any exacerbation, moderate or severe, from Period 3 (FAS-MI)	276/ 238	104 (38%)	274/246	110 (40%)	0.945 [0.73,1.23]	NR	0.6750
	Any exacerbation, moderate or severe, from Period 3 (FAS-OC)	238	104 (44%)	246	110 (45%)	0.924 [0.71,1.21]	NR	0.5653

NICE

AR population P001 key outcomes

			Mean score	Median score [lower, upper]	Relative treatment difference (95% CI)	Hodes-Lehman estimate of shift (95% CI)	p-value
Primary endpoint	**Total Combined Rhinitis Score (TCRS), nonparametric analysis**						
	12 SQ-HDM	566	4.67	4.10 [2.0, 6.4]	-17.2% (-25.0, -9.7)	-0.80 (-1.20, -0.40)	<0.001
	Placebo	620	5.49	4.95 [2.7, 7.6]			
Secondary endpoint	**Rhinitis symptoms score (DSS), nonparametric analysis**						
	12 SQ-HDM	566	3.83	3.55 [1.9, 5.3]	-15.5% (-24.4, -7.3)	-0.60 (-1.00, -0.30)	<0.001
	Placebo	620	4.46	4.20 [2.3, 6.3]			
	Total combined rhinoconjunctivitis score (TCS), nonparametric analysis*						
	12 SQ-HDM	566	6.40	5.50 [2.5. 8.8]	-16.7% (-24.6, -4.0)	-1.10 (-1.70, -0.60)	<0.001
	Placebo	620	7.62	6.60 [3.6, 10.4]			
	Average VAS score, nonparametric analysis						
	12 SQ-HDM	540	42.29	41.40 [24.9, 59.3]	-16.0% (-22.7, -8.3)	-6.10 (-9.10, -3.10)	<0.001
	Placebo	685	47.96	49.30 [29.4, 65.2]			

* Includes conjunctivitis symptoms and medications, company state results are not confirmatory due to prespecified control strategy for this trial

AR population – T0203-32 key outcomes

TO-203-32 results	12 SQ-HDM		Placebo		Treatment effect			p-value
	n	Score	n	Score	Difference of adjusted mean (95%CI)	Ratio of adjusted mean (95%CI)	Relative difference	
Total combined rhinitis score (TCRS) (mean)								
FAS	281	4.14	285	5.14	-0.99 [-1.5,-0.48]	0.81 [0.72,0.90]	19%	0.0001
ITT (MMRM)	307	4.14	317	5.15	-1.00 [-1.49,-0.51]	0.81 [0.72,0.90]	20%	<0.0001
PPS (LMEM)	274	4.16	276	5.12	-0.96[-1.48,-0.45]	0.81 [0.73,0.91]	19%	0.0002
Rhinitis symptom score (DSS) (mean)								
FAS	281	3.87	285	4.75	-0.87 [-1.32,-0.43]	0.82 [0.73,0.90]	18%	0.0001
ITT (MMRM)	307	3.88	317	4.77	-0.89 [-1.32,-0.46]	0.81 [0.73,0.90]	23%	<0.0001
PPS (LMEM)	274	3.90	276	4.74	-0.84 [-1.29,-0.39]	0.82 [0.74,0.91]	22%	0.0003
Rhinitis medication score (DMS) (mean)								
FAS	281	0.1	285	0.15	-0.05 [-0.11,0.01]	0.68 [0.40,1.11]	32%	0.1244
Total combined rhinoconjunctivitis score (TCS) (mean)								
FAS	281	5.3	285	6.64	-1.34 [-2.04,-0.65]	0.80 [0.71,0.90]	20%	0.0002

NICE

Key issue: AA+AR and AR models - Long term effectiveness

Medium to long-term assumptions in AA+AR and AR models

Annual rate of change	Intervention arm AA+AR / AR		Control arm AA+AR / AR	
	Well-to-partly controlled / mild-to-moderate	Partly-to-uncontrolled / moderate-to-severe	Well-to-partly controlled / mild-to-moderate	Partly to uncontrolled / moderate-to-severe
Year 2 to year 5	-5.00%	-5.00%	0.00%	0.00%
Year 5 to year 10	-2.50%	-2.50%	0.00%	0.00%
Year 10 to year 20	2.50%	2.50%	0.00%	0.00%
Year 20 onwards	0.00%	0.00%	0.00%	0.00%

Medium to long-term assumptions in published evidence

Study	Time horizon	Treatment	Assumptions (base case)		
Time period			Years 2-3	Years 4-5	Years 6-9
Hahn-Pedersen 2016	9 years	12 SQ-HDM+PhTx	+5%	0%	-5%
		PhTx	0%	0%	-5%
Green 2017	9 years	12 SQ-HDM+PhTx	+5%	0%	-10%
		PhTx	0%	0%	-5%
Green 2019	5 years	12 SQ-HDM+PhTx	+5%	0%	N/A
		PhTx	0%	0%	N/A

Abbreviations: AA, allergic asthma; AR, allergic rhinitis, HRQoL

Key issue: AA+AR model Standard of care treatment costs

	12 SQ-HDM			SOC AA+AR		
	Well-controlled	Partially controlled	Uncontrolled	Well-controlled	Partially controlled	Uncontrolled
Budesonide daily dose	547.00	590.00	712.40	547.60	564.40	715.40
Salbutamol annual total intake	84.91	166.31	339.80	69.17	207.29	484.74

Asthma guidelines	SABA reliever	ICS alone	ICS/LABA	LTRA	Theophylline	Biologics
Step 1	Yes	Low dose	No	No	No	No
Step 2	Yes	No	Low dose	No	No	No
Step 3	Yes	No	Medium dose	Yes	No	No
Step 4	Yes	No	High dose	Yes	Yes	No
Step 5	Yes	No	High dose	Yes	Yes	Yes

Abbreviations: AR, allergic rhinitis; AA, allergic asthma; SOC, standard of care. SABA, short-acting β 2-agonist; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LTRA, leukotriene receptor antagonist.

Summary of sources of data and number of primary care and secondary care visits

Source	GP visits per year		GP reduction associated with AIT
	Established clinical management	12 SQ-HDM	
MT-04	0.2345	0.1741	-25.76%
MT-06	0.1037	0.0986	-4.92%
Demoly et al., (2016)	3.5	-	-
Primary care Delphi	2.2	-	-
Romano et al., (2023)	3.8	-	-
	Pre-treatment with AIT (Num. patients)	Post-treatment with AIT (Num. patients)	
Robaina, Sanchez, and Perez (2016)	-	-	-
El-Qutob et al., (2016)	-	-	-
Source	**Hospital/ED/Allergist visits per year**		**Outpatient reduction associated with AIT**
	Established clinical management	12 SQ-HDM	
MT-04	0.0273	0.0124	-54.58%
MT-06	-	-	-
Demoly et al., (2016)	1.70	-	-
HES data analysis	2.66	-	-
	Pre-treatment with AIT (Num. patients)	Post-treatment with AIT (Num. patients)	
Robaina, Sanchez, and Perez (2016)	91	16	-82.42% (p<0.0001)
El-Qutob et al., (2016)	68	18	-73.53% (p<0.0001)

Abbreviations: AIT, allergy immunotherapy; SQ, standardised quality; HDM, house dust mite; ED, emergency department; GP, general practitioner.;

Key issue: AA+AR model Asthma exacerbations

Company's modelled exacerbation rates from MT-04 used in AA+AR model

Exacerbation severity	12 SQ-HDM			
	N	Events	Probability (180 days)	Annual probability
Any	248	59	-	-
Moderate	-	49	19.76%	36.02%
Severe	-	10	4.03%	8.01%
Exacerbation severity	**Placebo**			
	N	Events	Probability (180 days)	Annual probability
Any	257	83	-	-
Moderate	-	65	25.29%	44.66%
Severe	-	18	7.00%	13.70%

Key issue: AA+AR model Asthma exacerbations

Company's modelled utility scores AA+AR model

	Mean utility score based on SF-36	
	12 SQ-HDM n=172	Placebo n=172
Visit 3	0.728	0.757
Visit 9	0.759	0.763
Visit 13	0.777	0.774
Mean change in utility†		
Visit 3 to 9	0.032	0.006
Visit 3 to 13	0.049	0.017
Baseline utility‡		
Combined all patients	0.736	
Utility score used in model		
Visit 3 to 9	0.768	0.742
Visit 3 to 13	0.785	0.753

Company's modelled utility scores AR model

	Treatment-specific mean utility score	
	12 SQ-HDM n=301	Placebo n=326
Visit 3	0.891	0.884
Visit 8	0.926	0.916
Mean change in utility Visit 3 to 8†	0.029	0.014
Utility score used in model		
Average utility Visit 3 to 8	0.919	0.898

Key issue: AA+AR model Asthma exacerbations

Mapped utility scores used in the model from Briggs et al., 2021

	EQ-5D-3L utility data from Briggs et al., 2021			
	7 days	14 days	21 days	28 days
Well-controlled	0.923 (-0.0007)	0.923 (-0.0007)	0.923 (-0.0007)	0.923 (-0.0007)
Partly controlled**	-0.0252* (-0.0024)	-0.0251* (-0.0024)	-0.0252 * (-0.0024)	-0.0252* (-0.0025)
Uncontrolled**	-0.0634* (-0.0029)	-0.0633* (-0.0030)	-0.0632* (-0.0030)	-0.0633* (-0.0030)
Moderate exacerbation**	-0.0921* (-0.0059)	-0.0876* (-0.0055)	-0.0867* (-0.0054)	-0.0834* (-0.0053)
Severe exacerbation**	-0.163* (-0.0118)	-0.132* (-0.0096)	-0.125* (-0.0095)	-0.115* (-0.0090)

Asthma control questionnaire

- The ACQ consists of 7 questions referring to the previous week.
    - 5 questions are related to symptoms (nocturnal wakening, morning symptoms, activity limitation, short of breath, wheeze)
    - 1 question is about the frequency of SABA use
    - 1 question is about lung function (percentage of predicted FEV1).
- Each question is scored on a 7-point scale from 0 to 6, with higher scores indicating poorer responses. The overall ACQ score is the average of the 7 scores of the individual questions. The range of the overall ACQ score is 0 to 6.
- A score of 0-0.75 is classified as well-controlled asthma; 0.75–1.5 is partially controlled; and a score >1.5 is poorly controlled asthma.
- The minimum clinically important difference for the ACQ is a change of 0.5

Rhinitis outcome measures

Daily symptom score

- 4 rhinitis symptom scores (runny nose, blocked nose, sneezing and itchy nose)
- Measured on a 4 point scale from 0 (no symptoms) to 3 (severe symptoms)
- Range 0-12

Daily medication score

- Sum of total daily scores for all rhinitis medication
- Range 0-12
- Score of 1 for each desloratidine tablet (max 4)
- Score of 2 for each puff of budesonide nasal spray (max 8)

Total combined rhinitis score

- Sum of rhinitis and medication score
- Range, 0-24

Rhinitis quality of life questionnaire

- 28 questions on a 7 point scale (0-6), divided into 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms and emotional)
- Weekly domain scores are the average of all 28 item scores

Key methodological issues across the randomised trials

Trial quality issue ✓Present ×Absent	AA+AR Trials		AR trials		
	MT-04	TO-203-31	MT-06	TO-203-32	P001
Selection of trial population – trial eligibility criteria (A)					
ACQ score must be between 1.0 and 1.5	✓	✓	NA	NA	NA
Prior electronic diary compliance rate must be ≥ 80% at randomisation visit	✓	✓	×	✓	×
Use of usual or concomitant therapies (A)					
Alteration of usual medication prior to randomisation	✓	✓	×	×	✓
Prohibition of a range of concomitant medication available on the NHS	✓	✓	✓	✓	✓
Protocol mandated ICS reduction and withdrawal periods	✓	✓	NA	NA	NA
Outcome assessment (A)					
Primary efficacy assessment period outside of the major pollen season	✓	✓	✓	✓	✓
Censoring following asthma exacerbation	✓	✓	NA	NA	NA
Discontinuation due to ACQ>1.5 at the start of efficacy assessment period	×	✓	NA	NA	NA
Approach to missing data (RoB)					
Primary outcome analyses use LOCF or complete case (observed) data	×	×	×	✓	✓*
Some, or all, secondary outcome analyses use LOCF or complete case analysis	✓	✓	✓	✓	✓
Other (A & RoB)					
Change of outcome measure definition	✓	NE	×	NE	NE

Abbreviations: A: Issue related to applicability to NHS setting issue, ACQ: Asthma control questionnaire, ICS: Inhaled Corticosteroids, LOCF: Last observation carried forward, NA: Not applicable, NE: Not evaluated by EAG, RoB: Risk of bias issue.

*Sensitivity analyses used multiple imputation, last observation carried forward, and longitudinal data analysis model

Model structures used in previous Technology appraisals for asthma

TA	Model structure and composition
TA479 Reslizumab for treating severe eosinophilic asthma	Comprised of six mutually exclusive health states and the cohort were cohort able to transition between the 'Controlled asthma', 'Uncontrolled asthma', 'Moderate exacerbation', and 'Severe exacerbation' states.
TA565 Benralizumab for treating severe eosinophilic asthma	Patients classified as to receiving background therapy or not , then enter the treatment phase. Patients could transition between Controlled Asthma: (ACQ <1.5); uncontrolled Asthma (ACQ ≥1.5), and whether they experience exacerbations (OCS burst; emergency visit or hospital admission
TA751 Dupilumab for treating severe asthma with type 2 inflammation	Patients transition between the "controlled asthma", "moderate exacerbation" and "severe exacerbation" health states according to transition probabilities calculated from clinical trial data,
TA880 Tezepelumab for treating severe asthma	Model divided into five health states: controlled asthma, uncontrolled asthma, uncontrolled asthma with exacerbation, controlled asthma with exacerbation, dead

Company's cost-weighting for SOC costs

AA+AR health state	Cost weighting	Weighted total cost	
		12 SQ-HDM	SOC AA+AR
Well-controlled	100.00%	£285.14	£303.09
Partially controlled	105.46%	£300.72	£319.65
Uncontrolled	130.44%	£371.94	£395.35
Abbreviations: SQ, standardised quality; HDM, house dust mite; AR, allergic rhinitis; AA, allergic asthma; SOC, standard of care.			