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

For public – CON information redacted

Technology appraisal committee 3 10th December 2024

Chair's presentation

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

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Overview

May 2024 – appraisal committee meeting 1:

12 SQ-HDM SLIT is not recommended, within its marketing authorisation, for the following conditions diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test or specific IgE):

• persistent moderate to severe house dust mite allergic rhinitis in people aged *12 to 65* years* despite using symptom-relieving treatment

• house dust mite allergic asthma in adults (*18 to 65 years*) that:

− is not well controlled by inhaled corticosteroids and

− is associated with mild to severe house dust mite allergic rhinitis

** The marketing authorisation defines an adult population as 18 to 65 years, SQ-HDM SLIT is also indicated for an allergic rhinitis in an adolescent population defined as age 12 to 17.*

November 2024 – appraisal committee meeting 2

- Slides presented with summary of comments on draft guidance and updated analyses from company
- Patient experts provided comments and described survey results. Company noted factual inaccuracies
- Quoracy lost following slide presentation. Meeting stopped – no further transactions permitted when committee non-quorate

Today

- **Start from point of committee discussion**

Key issues for committee discussion 1/3: clinical effectiveness

issue	Questions on slides
How will 12-SQ HDM SLIT be used in clinical practice?	• **Eligibility and starting criteria for allergic asthma** Slide 15 (already discussed at ACM2) • Committee heard (meeting 1) 12 SQ-HDM SLIT would be initiated in secondary care, would follow up and repeat prescriptions also be given in secondary care? (slide 8)
Is there a clinically meaningful benefit compared with established clinical management used in the NHS for • **allergic rhinitis** • **allergic asthma with rhinitis?**	• **Applicability of trial data.** Slides 16, 17, 18 (already discussed at ACM2) • **Clinical meaningfulness of trial results** • Would a 16% reduction in total combined rhinitis score observed in MT-06 suggest a clinically meaningful benefit of 12 SQ-HDM SLIT in AR compared with established clinical management in the NHS? Slide 21 • Is 12 SQ-HDM SLIT expected to improve asthma control compared with established clinical management in NHS? Slide 21 • **Does the presented real-world evidence support a benefit of 12 SQ-HDM SLIT for allergic rhinitis**? Slide 23 • Are people likely to stop taking 12 SQ-HDM SLIT before 3 years, or to a greater extent than the trials? If so, what effect will this have on its clinical effectiveness? Slide 24
Is there class effect of AIT?	• Does the presented real-world evidence support a class effect of subcutaneous and sublingual AIT? Slide 23 (N.B. some long-term modelling assumptions informed by data from subcutaneous allergy immunotherapy)

Key issues for committee discussion 2/3: are the models suitable for decision making?

Issue	Allergic rhinitis	Allergic asthma with rhinitis
After 1st committee meeting both the • allergic rhinitis • allergic asthma with rhinitis models considered inappropriate for decision making	Does scenario including data from people aged 12 –17 years in the AR model suggest model appropriate for decision-making? Slide 26 N.B. company fact check at ACM2 stated that both quality of life and efficacy data from the P001 trial were applied in this scenario	Do the company's revisions make model appropriate for decision-making? Slide 27 and 28 **What committee asked for in draft guidance**: • Allow for stepping up/down of treatments to be modelled • include costs and benefits relating to AR • Consider aligning with previous asthma models (exacerbations, control based on ACQ not GINA) **What company did**: • Made case for a structure based on asthma control being most relevant and changed how modelled concomitant treatments based on control • Included AR costs (EAG said double counting) • New assumptions on exacerbation, but remain based on trial data

Abbreviations: ACM, appraisal committee meeting; AR, allergic rhinitis; HDM, house dust mites; SLIT, sublingual immunotherapy; SQ, standardised quality

Key issues for committee discussion 3/3: committee's preferences on modelling assumptions which have the greatest impact on cost effectiveness results

Issue	Questions on slides
Modelled reduction in secondary care use with 12 SQ-HDM SLIT versus standard care alone EAG estimates smaller reduction than company.	• What is the preferred method of estimating secondary resource use by people with allergic rhinitis and by people with allergic asthma with rhinitis? (slide 30)
Long term assumptions Trial data only for 2 years, then assumptions on effectiveness from Delphi panel. With observational data from REACT study (subcutaneous allergy immunotherapy for allergic rhinitis +/- asthma) to support assumptions. Company and EAG prefer different assumptions.	• Which are the most appropriate long-term assumptions? • Would the treatment effect increase over 2-10 years or stay same as observed at 2 years in trials? • Should a retreatment assumption be included? (slide 32)
Use of treatment specific or health state specific utility values	• At ACM1 committee accepted treatment specific approach to modelling health-related quality of life - has this opinion changed since consultation? (slide 31)

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

- ✓ **Recap from 1st meeting**
- ❑ Consultation responses
- ❑ Applicability of clinical evidence
- ❑ Clinical effectiveness evidence
- ❑ Cost-effectiveness modelling
- ❑ Cost-effectiveness assumptions
- ❑ Summary

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Abbreviations: HDM, house dust mites; SLIT, sublingual immunotherapy; SQ, standardised quality

Draft recommendation

12 SQ-HDM SLIT is not recommended, within its marketing authorisation, for the following conditions diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test or specific IgE):

- persistent moderate to severe house dust mite allergic rhinitis in people aged *12 to 65* years* despite using symptom-relieving treatment
- house dust mite allergic asthma in adults (*18 to 65 years*) that:
  - is not well controlled by inhaled corticosteroids and
  - is associated with mild to severe house dust mite allergic rhinitis

** The marketing authorisation defines an adult population as 18 to 65 years, SQ-HDM SLIT is also indicated for an allergic rhinitis in an adolescent population defined as age 12 to 17.*

Rationale

- Clinical trial evidence is uncertain
  - 12 SQ-HDM SLIT plus standard care may reduce rhinitis symptoms and medicine use and may reduce asthma exacerbations compared with placebo plus standard care.
  - But populations and the way the trials were done does not reflect NHS clinical practice
- There are uncertainties in the economic model structure and does not reflect how people would have treatment in NHS clinical practice

Abbreviations: HDM, house dust mites; IgE, immunoglobin E; SLIT, sublingual immunotherapy; SQ, standardised quality

ACM 1

Key issues

RECAP

Overview

- 12 SQ-HDM SLIT is a sublingual immunotherapy, taken once a day, containing house dust mite extract. Summary of product characteristics suggests treatment for 3 years

Treatment pathway for allergic rhinitis and allergic asthma

- Current treatments for symptoms of allergic rhinitis and allergic asthma are stepped up and down as needed.
- 12 SQ-HDM SLIT is used in addition to established clinical management of symptoms and would continue to be prescribed in secondary care (N.B. although not routinely commissioned, 12 SQ-HDM SLIT is currently being used by some patients in the NHS).
- At ACM1 committee agreed 12 SQ-HDM SLIT expected to be used at end of treatment pathway for AR and before biological treatments for AA+AR.

Clinical evidence and modelling

- Key trials were:
  - MT-04 included adults with allergic asthma with allergic rhinitis (AA + AR)
  - MT-06 included adults with allergic rhinitis (AR)
  - P001 included people 12+ years with allergic rhinitis
- 2 models AA + AR and AR informed by data from MT-04 and MT-06, with assumptions for period beyond trials

Committee heard 12 SQ-HDM SLIT would be initiated in secondary care, would follow up and repeat prescriptions also be given in secondary care?

See appendix for Recap marketing authorisation, recap trial design MT- 06 and MT-04, models for allergic rhinitis and allergic asthma with allergic rhinitis

Abbreviations: AA, allergic asthma; ACM, appraisal committee meeting; AR, allergic rhinitis; HDM, house dust mites; SLIT, sublingual immunotherapy; SQ, standardised quality

ACM1: clinical effectiveness evidence issues

RECAP

Issue	Further evidence requested

Applicability of trial data to NHS clinical practice.
• Both trials prohibited certain concomitant medicines and outcomes were assessed outside pollen season
• The asthma trial
  • included people with an ACQ 1.0 to 1.5 ('partially controlled' symptoms) rather than not well controlled (an ACQ > 1.5 is asthma that is 'poorly controlled')
  • ICS was reduced to induce an exacerbation in a controlled way. In clinical practice 12 SQ-HDM SLIT would be used alongside ICS.
	• Further clinical evidence to determine if 12 SQ-HDM SLIT would provide additional benefits to established clinical management
	
	• Clarification on which people with allergic asthma would have 12 SQ-HDM SLIT in clinical practice

Unclear if trials showed clinically meaningful benefit of 12 SQ-HDM SLIT vs current NHS practice for allergic asthma or rhinitis. **But, anecdotal evidence of effectiveness of immunotherapies in clinical practice** 12 SQ-HDM SLIT and other immunotherapies have benefits reported by clinical experts. Company used data from subcutaneous immunotherapies and immunotherapies against other allergens to estimate longer term benefits of 12 SQ-HDM SLIT	• Real-world evidence for the clinical effectiveness of 12 SQ-HDM SLIT • Evidence for class effect of immunotherapy (immunotherapy delivered SC or sublingually, or for sublingual therapies for house dust mite and other allergens used to treat allergic rhinitis and allergic asthma). • Consider SNOT-22 for patient reported outcomes for allergic rhinitis

Abbreviations: ACM, appraisal committee meeting; ACQ, asthma control questionnaire; ICS, inhaled corticosteroids; SC subcutaneously; SNOT, Sino-Nasal Outcome Test; SQ, standardised quality

RECAP

ACM1: cost effectiveness modelling issues

Issue	Further evidence/modelling requested
AA + AR model structure not suitable for decision making: • Health states based on asthma control for AA +AR model rather than treatment pathway of stepping up and down concomitant treatments • Model did not model rhinitis outcomes and the assumption that exacerbations constant across health states seemed implausible	• Allow for stepping up/down of treatments • AA + AR should include costs and benefits relating to AR • Consider aligning with previous asthma models (e.g. including modelling exacerbations as a health state)
AR model not suitable for decision making: did not include data for young people (12 years +)	AR model should include data relevant to people aged 12 years +
Assumed reduction in primary and secondary care resource use with 12 SQ-HDM SLIT, uncertain and secondary care assumptions [LARGE IMPACT on ICERs]	Additional evidence to support the assumptions of reduction in primary or secondary care visits associated with 12 SQ-HDM SLIT
Utility values. Company use treatment specific utilities EAG preferred health state utility values **[LARGE IMPACT on ICERs]**	Explore if trial measures used fully capture utility with/without 12 SQ-HDM SLIT for the whole population
Long term effectiveness Maximum 2 years of trial data so assumptions + long-term retrospective observational data (immunotherapies) to 9 years used. Persistence of effect based on assumption. No retreatment modelled.	• Clinical evidence on retreatment rates and consider retreatment in model • Evidence for class effect of immunotherapies

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Abbreviations: HDM, house dust mites; SLIT, sublingual immunotherapy; SQ, standardised quality

Consultation responses to draft guidance: overview

Company In its response to uncertainties, company provided data/information from:

- Advisory board report.
- Clinical opinion on company submission from 9 clinicians
- Survey sent to healthcare professionals managing allergic respiratory disease (46 respondents) on their experience of allergic immunotherapies and expected use of 12 SQ-HDM SLIT
- Retrospective analysis of QoL from [redacted] people treated with 12 SQ-HDM SLIT in BRIT registry (BSACI)
- Analysis of Danish and Swedish registry study (RELY) comparing reduction in AR medication in people who had SQ-HDM SLIT compared with propensity matched control cohort with AR
- Phase 2 study of 12 SQ-HDM SLIT

Provided updated model assumptions

Comments on draft guidance received from:

- Allergy UK
- Association of Respiratory Nurses
- British Society of Immunology- Clinical immunology professional network
- National Heart and Lung institute
- British Society of Allergy and clinical immunology
- 2 clinical experts, 1 patient expert
- 17 web comments

Additionally see supplementary appendix for patient and professional group submissions were submitted from **Asthma and Lung, UK and Allergy, UK**, **ENT, UK; British Society of Allergy and Clinical Immunology**

Abbreviations: AR, allergic rhinitis; BRIT, BSACI Registry for Immunotherapy; BSACI, British Society for Allergy and Clinical Immunology; HDM, house dust mites; SLIT, sublingual immunotherapy; SQ, standardised quality

Web comments

Patients, carers, family, clinicians and public comments

Impact on people with the condition	12 SQ-HDM SLIT
• Symptoms include severe headaches, persistent congestion, and intense sneezing fits, fatigue, and sleep disturbances caused by severe nasal congestion that made breathing difficult • Impact of AR +/- AA considerable and not captured in model/draft guidance.	• Improvements with 12 SQ-HDM SLIT include reduced absenteeism, decreased need for antibiotics and steroids, better management of symptoms and better quality of life • Useful option if still symptomatic despite maximum medical treatment but not before • Potential class effect of SLIT to prevent disease progression and positive effect on a range of outcomes
Current treatments	**Wider considerations**
• [for] asthma …ICS can step up as well as down • Economic modelling distorted as does not include topical nasal steroid/topical NAH recommended by BSACI and ARIA for HDM AR. Means fewer people need AIT [than modelled] • Ipratropium and nasal decongestants are not relevant • RAST replaced by newer method to detect specific IgE to House Dust Mite species	• 12 SQ-HDM SLIT has already been used and found to be effective but not reported in clinical trials. Clinical experience has not been taken into account • In the NHS, immunotherapy would be used in a different context to that in the trials • Sublingual less expensive than subcutaneous as do not attend hospital for injections • Unmet need for treatment

Abbreviations: AA, allergic asthma; AR, allergic rhinitis; AIT, allergy immunotherapy; ARIA, allergic rhinitis in asthma; BSACI, British Society for Allergy and Clinical Immunology; HDM, house dust mites; ICS, inhaled corticosteroid, IgE, immunoglobin E; NAH, nasal antihistamine; RAST, radioallergosorbent test; SLIT, sub-lingual immunotherapy; SQ, standardised quality

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Definition of allergic asthma not well controlled by ICS

Key issues

Background

MA states that allergic asthma should be 'not well controlled by ICS (inhaled corticosteroid)' but does not include a definition. MT-04 included people with Asthma Control Questionnaire (ACQ) 1.0 to 1.5 at randomisation which implies partially controlled asthma. Clinical expert at ACM1 expected 12 SQ-HDM SLIT would be started when people with not well controlled asthma were experiencing fewer exacerbations

Committee conclusions from ACM1

- Uncertain on eligibility criteria for 12 SQ-HDM SLIT in people with allergic asthma with rhinitis. Uncertainty included if it would be started when asthma not well controlled or started in a period of fewer exacerbations

Company response:

- Allergic Asthma treated with inhaled corticosteroids alone, or in combination with long-acting beta-agonists.
- People should not be treated with 12 SQ-HDM SLIT if they have a lung function of FEV1 <70% predicted or have experienced a severe asthma exacerbation within the last 3 months (N.B contraindication in SmPC)

Other stakeholder response:

- ACQ <0.75 indicates well-controlled asthma and >1.5 indicates poorly controlled asthma
- **BSACI** Uncontrolled asthma means actively symptomatic with ACQ>1.0, using SABA at least every week despite [compliance?] with ICS. Would not start treatment during exacerbation, only after resolved
- **NHLI**: would start 12 SQ-HDM SLIT in GINA step 2-3 if asthma partially controlled (ACQ 1.0-1.5) and no exacerbation needing ICS 6-12 months before
- **Clinical expert** HDM symptoms tend to be worse over winter so start in a season when having fewer symptoms

EAG: No ACQ restrictions in Summary of Product Characteristics. In some studies ACQ <1.5 cited as 'controlled'

Applicability of clinical trial evidence

Key issues

Background

EAG identified methodological limitations of the trials and implications for applicability of results to the NHS:

- In the AA+AR trial (MT-04) inhaled corticosteroids were reduced then stopped - does not reflect anticipated clinical practice, and trial included people with 'partially controlled asthma' (previous slide)
- Measurements taken outside of pollen season (both trials)
- Duration of both trials 12-18 months but recommended duration of immunotherapy in SmPC is 3 years
- Prohibited concomitant medication which would be used in clinical practice

Committee conclusions from ACM 1:

- Evidence was limited in showing how effective 12 SQ-HDM SLIT would be if used in the NHS. It requested further clinical evidence to support decision making
- For AA +AR, 12 SQ-HDM SLIT would be used if symptoms are not controlled by ICS and ICS would not be stopped
- For AR, 12 SQ-HDM SLIT would be used throughout the year with a broader range of symptom-relieving medicines than allowed for in the trials

Abbreviations: AA, allergic asthma; AR allergic rhinitis; HDM, house dust mites; ICS, inhaled corticosteroid; SLIT, sublingual immunotherapy; SmPC, summary of product characteristics; SQ, standardised quality

Applicability of clinical evidence: responses (1)

Key issues

Methodological issues identified with trials (1)

Responses	EAG critique
In MT-04 ICS was reduced and then stopped but committee considered this would not happen in NHS practice	
Company ICS withdrawal was part of the study design. Accept this is not consistent with clinical practice but ensuring enough events to estimate a statistically significant difference in the primary endpoint was required from a regulatory perspective.	• Company's approach does not provide reliable efficacy data • A mandated treatment withdrawal approach means the treatment effect may not have been driven by 12 SQ-HDM SLIT efficacy but by lack of efficacy of restricted routine care • Clinical advice to the company suggested that asthma control would need to be met before stepping down treatment in clinical practice
Duration of clinical trials was 12 to 18 months but recommended duration of immunotherapy is 3 years	
Company Recommended duration is a total of 3 years but efficacy is achieved within a much shorter period of approximately 24 weeks	Company has conducted long-term trials before, to reflect the treatment duration seen in practice e.g. • An asthma preventative trial of SQ grass sublingual immunotherapy in children with grass pollen allergy used a 3-year treatment period followed by a 2-year follow-up period • A trial in adults receiving 3 years of treatment with grass tablet immunotherapy, followed by 2 years of further follow-up

Abbreviations: HDM, house dust mites; ICS, inhaled corticosteroid; SLIT, sublingual immunotherapy; SQ, standardised quality

Applicability of clinical evidence: consultation response (2)

Key issues

Responses	EAG critique
Outcomes assessed outside pollen season but symptom relieving medicines would be used all year	
Company: done to reduce imbalances that could not be accounted for by randomisation. Post-hoc analysis of MT-06 (with/ without sensitisation to grass/tree pollen throughout the year) showed consistent treatment benefit maintained in both groups. **Clinical expert**: makes sense to assess outcomes in winter when HDM more prominent [and pollen lower]	• Although treatment benefit appears to be maintained (in post hoc analysis), no error bars or tests of statistical significance presented. • Most concerned about MT-04 where asthma exacerbations were only evaluated outside of the major pollen season but company did not provide additional data from this trial See appendix for company's post hoc analyses of MT-04 pollen season
Prohibition of concomitant medications in MT-04 and MT-06 (such as LABA, LTRA, SABAs and LAMAs)	
Company: To reduce confounding due to differences in standard of care medication. But prohibiting standard of care is not likely to meaningfully impact patient outcomes	• LABAs are routinely used in asthma care • Company response contradictory. Most treatments were excluded due to possible interference with efficacy. • Prohibiting treatments likely biases in favour of 12 SQ-HDM SLIT

Do the responses to consultation change committee's view on applicability to NHS clinical practice of 1) randomised population in asthma trial 2) mandated ICS reduction in asthma trial 3) trial duration 4) measuring outcomes outside pollen season and 5) allowed concomitant treatments in trials?

HDM, house dust mites; LABA, long acting beta-2 agonist; LTRA, leukotriene receptor antagonist, SABA, short acting B2 agonist; LAMA, long acting muscarinic antagonist

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Clinical meaningfulness of trial efficacy estimates

Background

- For AR: differences in outcomes between 12 SQ-HDM SLIT and placebo were statistically significant, but did not meet published cut-offs for a clinically meaningful effect.
  - A 20% reduction in allergic rhinitis outcomes compared with placebo suggested as clinically meaningful by World Allergy Organisation. Trial showed 16% reduction in total combined rhinitis score
  - A 0.5 difference in rhinitis quality of life questionnaire (Juniper et al 1999), Trial showed -0.21 difference
- For AA: statistically significant reductions in exacerbations vs. placebo (during mandated ICS reduction period), but no statistically significant differences in asthma control questionnaire, quality of life or lung function vs. placebo. Asthma control and quality of life questionnaires did not meet 0.5 difference suggested to be clinically meaningful (Juniper et al 2005, 1994)

Committee conclusions from ACM1

- For AR and AA +AR populations: unclear if 12 SQ-HDM SLIT would be clinically effective if it was used as it would be expected to be in the NHS because the trials were not designed to determine this
- 12 SQ-HDM SLIT did not meet clinically meaningful cut offs for important endpoints in both trials, but it was unclear if the 20% cut off for clinically meaningful results in AR was too high
- 40% improvement in symptoms in placebo arm of MT-06 unexplained
- It was not possible to conclude from the evidence submitted that 12 SQ HDM-SLIT would have a clinical benefit for either AR or AA + AR compared with established clinical management in the NHS

See supplementary appendix for trial results from MT-06 (AR), MT-04 (AA + AR)

Abbreviations: AA, allergic asthma; ACM, appraisal committee meeting; AR, allergic rhinitis; HDM, house dust mites; ICS, inhaled corticosteroid; SLIT, sublingual immunotherapy; SQ, standardised quality

Clinical meaningfulness of efficacy estimates responses

Key issues

Responses	EAG critique
Placebo effect	
Company: placebo effect likely due to participants being re-trained in using systemic treatments + frequent contact with clinicians → optimisation may affect efficacy results	Although may be real, would be expected to be same in both arms so would not affect treatment effect
Plausibility of cut-offs for clinically meaningful effect	
Company: AR: FDA states 15% improvement is clinically meaningful in AIT trials AA: Survey of 46 clinical experts, 76% said available data supports improved AA control; 24% said "maybe supports" **NHLI:** • Not relevant to compare between group difference in MT-06 (AR) to the within group MCID [of 0.5] reported by Juniper 1999. • 20% (World Allergy Association) minimal clinically important result was based on expert opinion rather than evidence. **ENT UK:** Trial data is confusing. Including [people with] asthma [in AR trials] seems to have confused things to the detriment of allergic rhinitis [led to not meeting] 20% cut off **BSACI**: Juniper at al 1999 refers to a patient completed questionnaire – the RQLQ – [not] TCRS as used in MT-06. The latter is a daily, combined symptom-medication score as recommended for [AIT] trials.	No specific comment • Would a 16% reduction in total combined rhinitis score observed in MT-06 suggest a clinically meaningful benefit of 12 SQ-HDM SLIT in AR compared with established clinical management in the NHS? • Is 12 SQ-HDM SLIT expected to improve asthma control compared with established clinical management in NHS? (MT-04 results and MCID)

Abbreviations: AA, allergic asthma; AIT, Allergy Immunotherapy Tablet; AR allergic rhinitis; HDM, house dust mites; MCID minimal clinically important difference; RQLQ, Rhinitis quality of life questionnaire; SLIT, sublingual immunotherapy; SQ, standardised quality; TCRS, total combined rhinitis score

Additional clinical data cited in response to consultation

Responses	EAG critique
Further trial data suggested as supporting clinical effectiveness	
Company and BSACI referenced as supportive that MT-04 and MT-06 trials may underestimate benefits of 12 SQ-HDM-SLIT **Allergic rhinitis (with or without allergic asthma)** Nolte et al 2015 phase 2 trial AR +/- AA 12 SQ-HDM SLIT vs placebo (people were exposed to HDM in allergen exposure chamber and measures taken after 24 weeks of treatment). 52% reduction in total symptom score. **Allergic asthma** Mosbech et al 2014. phase 2 trial AA. 6 SQ-HDM SLIT (lower dose) reduced ICS dose vs placebo at 1 year	Comments on Mosbech et al: • Inclusion criterion was "controlled asthma at enrolment" (ACQ score < 1.5). Paper describes trial subjects as having controlled status throughout the trial, with little room for improvement. • Benefits did not relate to exacerbations, but to reductions in ICS dose. • Absence of statistically significant differences for the other assessed asthma outcomes: ACQ score, FEV1, peak expiratory flow and Asthma Quality of Life Questionnaire

Abbreviations AA, allergic asthma; ACQ, asthma control questionnaire; AR allergic rhinitis; BSACI, British Society for Allergy and Clinical Immunology; FEV1, forced expiratory volume in one second; HDM, house dust mites; ICS, inhaled corticosteroid; SLIT, sublingual immunotherapy; SmPC, summary of product characteristics; SQ, standardised quality

Real world data presented in response to consultation (1)

Key issues

Responses	EAG critique
Company: [redacted] of integrated care systems with a live formulary make 12 SQ-HDM-SLIT available in NHS currently.	

• BRIT database analysis of people with AR +/- AA treated with 12 SQ-HDM SLIT in UK clinical practice mean change from baseline after one year of [redacted] in PADQLQ, [redacted] in RQLQ…more than point estimates derived from MT-04 and MT-06.	Limited data, adds little new to evidence base
	• [redacted] people had measurements
	• 35 had at least 1 subsequent measurement based on same instrument.
	  • Data on RQLQ:[redacted]people and PADQLQ: [redacted]people
	  • % under 12 years, which are outside of MA not known

Data from RE-LY. Presented as evidence that data on reduction of AR prescriptions with subcutaneous immunotherapy (from REACT) over 9 years (used to support long term model assumptions) is generalisable to 12 SQ-HDM SLIT	
• Reduction in AR prescriptions with 12 SQ-HDM SLIT vs. control greater than observed in REACT • Reduced prescriptions maintained over 1 year and increased over 5 years → 1 year data from MT-04 and MT-06 underestimate benefit (supplementary appendix RE-LY results)	• Groups generally well matched, but insufficient information for full critique • Data from people treated with HDM **and** grass SLIT (company: data presented from people treated with HDM SLIT only) • Uncertainty around persistence of treatment and adherence • No results for asthma outcomes

Does the presented real world evidence support
- a benefit of 12 SQ-HDM SLIT for allergic rhinitis?
- a class effect of subcutaneous and sublingual AIT?

Abbreviations: AA, allergic asthma; AIT, Allergy Immunotherapy Tablet; AR, allergic rhinitis; HDM, house dust mites; PADQLQ paediatric allergic disease questionnaire; RQLQ rhinoconjunctivitis quality of life questionnaire, SLIT, sublingual immunotherapy; SQ, standardised quality

Further real-world data identified by EAG after consultation

- EAG concerned with lack of systematic review to identify real world evidence. Identified German database study (Pfaar et al, 2023) which suggested lower persistence to HDM SLIT at 1 year (23-27%) than the 80-90% persistence at 12-18 months follow up from MT-04 and MT-06 trials.
- EAG considers there is uncertainty in the persistence rates of 12 SQ-HDM SLIT over the long term and the impact on long term effectiveness.

Age class (years)	N	Median persistence	Persistence at 1 year (% patients)	Persistence at 3 years (% patients)
12-17	1256	119 days	23.0	5.7
18+	7661	118 days	26.7	7.8

- In company model 12 SQ-HDM SLIT is continued for 3 years. Based on trial discontinuations, 5% people discontinued each cycle (year) to 3 years in the allergic rhinitis model and 8.5% in the allergic asthma with rhinitis model. Company modelled that 50% of people discontinuing before 3 years would have 12 SQ-HDM SLIT benefits

Are people likely to stop taking 12 SQ-HDM SLIT before 3 years, or to a greater extent than the trials? If so, what effect will this have on its clinical effectiveness?

Abbreviations: HDM, house dust mites; SLIT, sublingual immunotherapy; SQ, standardised quality

See supplementary appendix for graph of discontinuation data

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Modelling allergic rhinitis in young people (AR model only)

Background

- Company had originally used MT-06 data (adult population) to model treatment effectiveness in young people.
- This assumed that effectiveness between adult populations and people aged 12 to 17 years was equivalent
- EAG: evidence from P001 suggested larger difference in symptom scores in young people than adults
- So, committee requested additional evidence to resolve uncertainty and that the model considers costs and benefits for whole population for whom 12 SQ-HDM-SLIT is licenced

Company:

- Its ACM1 approach is likely to be conservative – **scenario included as an additional revised base case**
  - Based on subgroup analysis in P0001 and TO-203-32 adolescents were anticipated to have the same reductions in AR symptoms and medication use as adults and there was no significant difference in the tolerability of 12 SQ-HDM SLIT in either population. P001 suggested there was a relative improvement in outcomes for adolescents compared with adults so assumption may be conservative
- Provided a scenario analysis to address uncertainty
  - Assumes a starting age of 12 years and utility values based on difference in HRQoL with 12 SQ-HDM-SLIT from adolescents in P001 not population in MT-06

EAG:

- Source of treatment effectiveness remains the MT-06 trial which included only adults (18-65 years of age).
- Scenario analysis does not overcome absence of treatment effectiveness evidence for the adolescent population in the AR model
- Could not explore the impact use of alternative approaches to HRQoL for the adolescent population

Does the company's scenario analysis resolve uncertainty in modelling AR in an adolescent population/ make this model suitable for decision making?

Abbreviations: AA, allergic asthma; AR, allergic rhinitis; HDM, house dust mites; HRQoL, health-related quality of life; SLIT, sublingual immunotherapy; SQ, standardised quality

Company updated base case AA + AR

The company addressed some, but not all model requests

Key issues

Background

- EAG had concerns with model relating to it being informed by data from MT-04 and its structure
- Committee did not consider AA + AR suitable for decision making, requested revisions to model
  - Allow for stepping up/down of treatments to be modelled
  - AA + AR should include costs and benefits relating to AR
  - Consider aligning with previous asthma models (exacerbations, control based on ACQ not GINA)

Company response

- Treatment stepping is an important part of the management of AA with AR in clinical practice…[but] the primary objective of treatment for AA is disease management, with stepping down treatment only considered once control is achieved.
- Confirmed by survey of clinicians (N= 46): 94% believed asthma control was primary objective of AA treatment.
- Validated in an advisory board: 71% of those responding believed asthma control should be achieved before stepping down symptomatic medications

Company have not changed overall structure, but presented updated approach to estimating concomitant treatments in health state (next slide), including AR costs and modelling exacerbations. Did not update modelling asthma control based on ACQ instead of GINA criteria

For AA + AR and AR model structures see supplementary appendix

Abbreviations: AA, allergic asthma; ACQ, asthma control questionnaire; AR, allergic rhinitis; GINA, global initiative for asthma

Company's updated modelling of AA + AR model

Key issues

Parameter	Company revision and rationale	EAG critique
Treatment stepping	No longer informed by relative increase in ICS use between AA levels of control in MT-04 trial. Instead apply an assumed shift of distributions of treatments towards higher steps when level of AA control changes from 'well controlled' to 'partially controlled' to 'uncontrolled'	• Direction of shift may have clinical plausibility, but magnitude of shift is uncertain • Assumption in revised base-case is not supported by any additional empirical evidence
Capturing AR costs in people with AA	Included AR treatment costs by model arm	Unclear why company took this approach: • Original model already included costs of AR with costs weighted by AR severity level informed by Delphi Panel so now double counts AR costs • Still does not address AR outcomes not being modelled which was Committee's issue
Modelling AA exacerbations	Assumes differences in exacerbation incidence by AA control level, based on exacerbations in MT-04 • partly controlled AA = MT-04 • controlled AA= 50% more and • uncontrolled AA= 50% less	EAG remains concerned that exacerbations during the ICS reduction phase in MT-04 is not reflective of clinical practice. Would have been more consistent with model structure to model exacerbations by control (rather by treatment arm using data from MT-04)

Do the company's revisions to the AA + AR model make it appropriate for decision-making?

See appendix for distribution of treatments across steps and asthma exacerbation probability

Abbreviations: AA, allergic asthma; AR, allergic rhinitis; ICS, inhaled corticosteroids

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

- ❑ Recap from 1st meeting
- ❑ Consultation responses
- ❑ Applicability of clinical evidence
- ❑ Clinical effectiveness evidence
- ❑ Cost-effectiveness modelling
- ✓ **Cost-effectiveness assumptions**
- ❑ Summary

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Abbreviations: HDM, house dust mites; SLIT, sublingual immunotherapy; SQ, standardised quality

Modelling secondary care resource use (AR and AA + AR model)

Key issues

LARGE IMPACT

Background

- ACM1: relative reduction in secondary care resource with 12 SQ-HDM SLIT vs. standard care
  - AA + AR model: company assumed 54.58% based on number of emergency visits in MT-04 (between randomisation and end of trial);
  - AR only model: company assumed 73.53%, based on El Qutob et al. (2016) (before/after study of HDM SCIT for allergic rhinitis and asthma)
  - EAG preferred 7.35% for AA + AR and 4.9% for AA, based on estimates of primary care reduction using data from trials (n.b used data from maintenance period without mandated ICS reduction for AA +AR)
- Committee concerned secondary care costs overestimated. Big model driver.

Company:

- Maintain its original assumptions in base case. Reiterated there is RCT evidence and real-world data to show that AIT reduces healthcare resource utilisation. Clinicians surveyed concurred: 2% would not expect reduction in primary and secondary resource and 2% would not expect reductions in hospitalisation
- Carried out scenario analysis
  - In both models the lowest reduction in secondary care visits identified from literature was assumed based on REACT data (odds ratio 0.72 for all hospitalisations equating to a 28% risk reduction)
  - Determined risk reduction of secondary care resource use required to make 12 SQ-HDM SLIT cost neutral

EAG: Could not comment on generalisability of scenario results to 12 SQ-HDM SLIT because REACT did not present estimates of effect on hospitalisation separately for i) SCIT and SLIT or ii) by allergen

- A key uncertainty is around the magnitude of effect of treatment on health care resource use

What is the preferred method of estimating secondary resource use?

Abbreviations: AA, allergic asthma; ACM, appraisal committee meeting; AIT, allergy immunotherapy tablet; AR, allergic rhinitis; HDM, house dust mites; RCT, randomised controlled trial; SCIT, Subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SQ, standardised quality

Modelling health-related quality of life (AR and AA +AR model)

Key issues

LARGE IMPACT

Background

- Company's original base case assumed treatment-specific approach to HRQoL because it could capture other factors beyond allergic control and in the AA with AR model would allow the effect of 12 SQ-HDM SLIT on HRQoL associated with AR to be captured
- Committee accepted this approach but considered the models should represent the full population in the MA

Company:

- Maintains a treatment specific approach is the only appropriate approach for modelling HRQoL and captures the totality of the disease burden
- Treatment specific utility estimates were based directly on EQ-5D data collected for the AR patient population and generic SF-36 for the AA with AR patient population and aligns with NICE methods to apply measures collected directly from clinical trial data over mapped utility values

EAG:

- Still considers the appropriate approach to modelling HRQoL is to consider health-states utility values in both models
  - Assuming constant treatment specific utilities across asthma control levels and rhinitis severity, has no clinical validity
  - SF-36 data could have been used to capture health-state specific utilities in the company model

At ACM1 committee accepted treatment specific approach to modelling health-related quality of life - has this opinion changed since consultation?

Abbreviations: AA, allergic asthma; AR, allergic rhinitis; HDM, house dust mites; HRQoL, health-related quality of life; MA, marketing authorisation; SLIT, sublingual immunotherapy; SQ, standardised quality

Modelling long-term effectiveness (AR only and AA + AR model)

Key issues

LARGE IMPACT

Background

- Clinical trial data for the effectiveness of 12 SQ-HDM SLIT was only available for up to 2 years
- Company had supplemented its long-term effectiveness assumptions with evidence from REACT (a real-world study of people who had or had not received SCIT or SLIT AIT against various antigens over 9 years)
- Company had assumed that 12 SQ-HDM SLIT would improve health to 10 years and wane from 15 years
- But committee requested additional evidence to support the assumption

Company:

- Reiterated REACT had shown persistent effect (cited prescription reductions, asthma exacerbations, hospitalisations) of AIT over 9 years and no indication of waning
- Considers long-term outcomes associated with SCIT are likely generalisable to SLIT because RELY suggested greater reduction in AR medication than REACT (over 5 years)
- RELY showed effect (on AR prescription reductions), maintained over 1st year and increased over next 4 years
- Includes retreatment scenario, but does not expect to happen

EAG:

- Assuming increasing improvements in health for 12 SQ-HDM SLIT for up to 10 years are not justified by REACT data which suggest there is no clear evidence to support an increment in the effect of treatment over time
- RELY of limited use because includes people with AR [caused by] HDM and grass allergen, but no HDM specific subgroup data also considers RELY data may contradict REACT which shows AR prescriptions for SQ HDM SLIT increased over time
- No new evidence to address long term effectiveness from 10 to 20 years. Agrees with company on retreatment
- EAG presented scenarios to address long-term effectiveness, with assumptions on impact of persistence

Which are the most appropriate long-term assumptions? Would the treatment effect increase over 2-10 years or stay same as observed at 2 years in trials? Should a retreatment assumption be included?

See appendix for generalisability of SCIT to SLIT

Abbreviations: AA, allergic asthma; AR, allergic rhinitis; AIT, allergen immunotherapy; HDM, house dust mites; ICER, incremental cost effectiveness ratio; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SQ, standardised quality

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

- ❑ Recap from 1st meeting
- ❑ Consultation responses
- ❑ Applicability of clinical evidence
- ❑ Clinical effectiveness evidence
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- ❑ Cost-effectiveness assumptions
- ✓ **Summary**

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Abbreviations: HDM, house dust mites; SLIT, sublingual immunotherapy; SQ, standardised quality

Summary of assumptions used in both AR and AA + AR models

LARGE IMPACT

Assumption	Company base case* ACM1	EAG base case ACM1 and ACM2	Company base case ACM2
Secondary care costs reduction with SQ-HDM	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)	• As ACM1 but scenarios around secondary care costs (28% reduction)
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	• As ACM1 but scenarios around retreatment and long term effectiveness
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	No change from ACM1

NICE Abbreviations: AA, allergic asthma; ACM, appraisal committee meeting; AR, allergic rhinitis; HDM, house dust mites; SOC, standard of care; SQ, standardised quality

Summary AA + AR model specific assumptions

Assumption	Company base case* ACM1	EAG base case ACM1 and ACM2	Company base case ACM2
Asthma exacerbations	Exacerbation probabilities from MT-04 period 3 (12 SQ-HDM = 36.02% moderate; 8.01% severe)	No asthma exacerbations modelled Conservative assumption because MT-04 does not reflect clinical practice	Assumes differences in exacerbation incidence by AA control level, based on exacerbations in MT-04
Treatment costs (biologics)	Equal spread by each biologic (omalizumab, mepolizumab, dupilumab, and tezepelumab)	Only relevant biologic treatments (omalizumab and tezepelumab)	Same as ACM1
Treatment stepping	Stepping up/down of treatments not modelled. Background treatment costs informed by relative increase in ICS use between AA levels of control in MT-04 trial	Same as company (but disagreed with model structure)	Shifts treatment distribution towards higher steps when level of AA control declines
AR costs	Costs weighted by AR severity level informed by Delphi Panel	Same as company	AR costs added by treatment arm
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)	Same as ACM1

* Included EAG model corrections n.b. company base case does not include all EAG corrections

Cost-effectiveness results

	Allergic rhinitis			Allergic asthma with rhinitis		
	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Company	-£2,899	0.26	12 SQ-HDM SLIT dominates*	Confidential	0.37	12 SQ-HDM SLIT dominates*
EAG	£2,536	0.05	£50,479	Confidential	0.02	>£100,000

- The company base case in both the allergic rhinitis and allergic asthma with rhinitis models is that 12 SQ-HDM SLIT dominates (it is cost-saving and more effective than) standard care
- Costs and ICERs in the allergic asthma with rhinitis are confidential because of confidential discounts of other treatments in the model- all results will be discussed in Part 2 of this meeting
- The impact of the different assumptions used by the company and EAG will be discussed as well as scenarios around re-treatment and using quality of life data from people aged 12-17 with allergic rhinitis in the model (smaller impact) and assumptions on discontinuing 12 SQ-HDM SLIT before 3 years and assumed impact on its benefits (larger impact)

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Abbreviations: HDM, house dust mites; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; SLIT, sublingual immunotherapy; SQ, standardised quality

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Thank you.

Supplementary appendix

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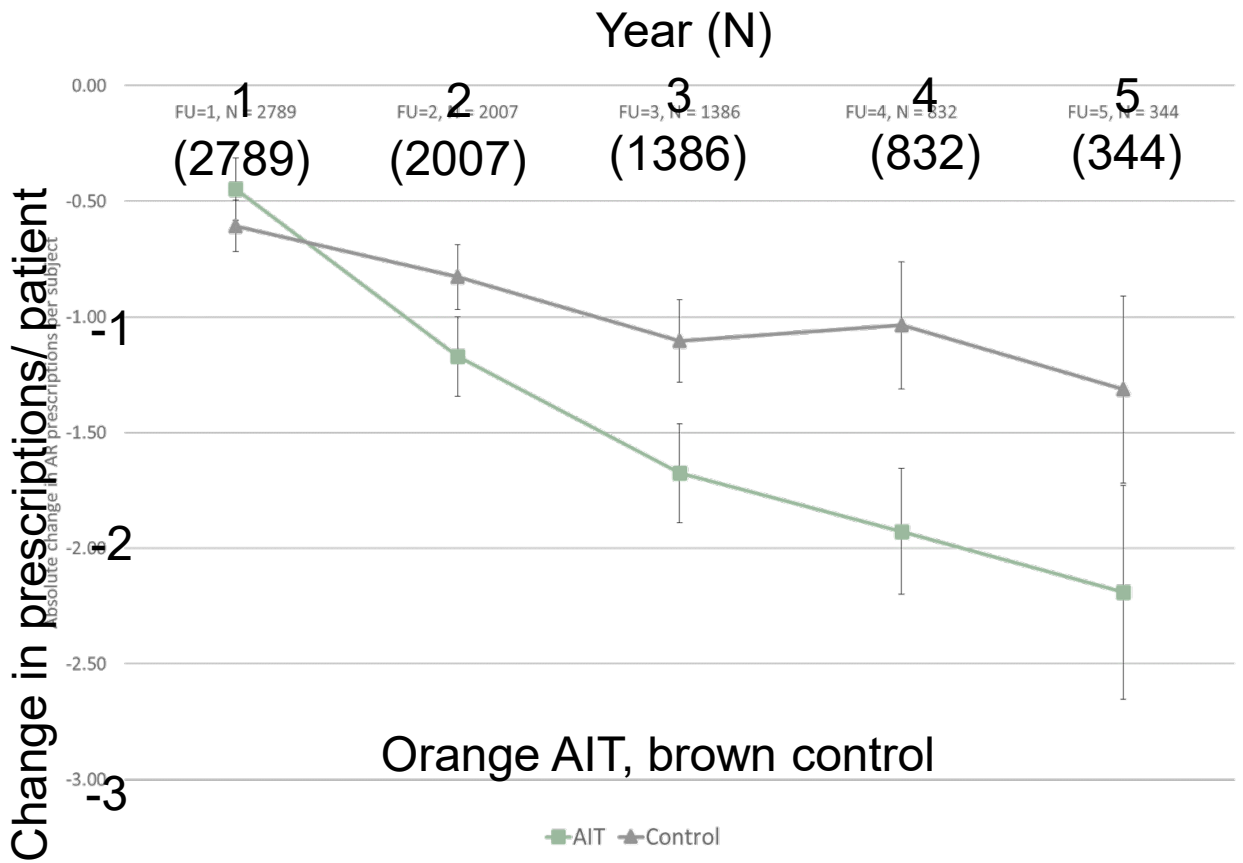
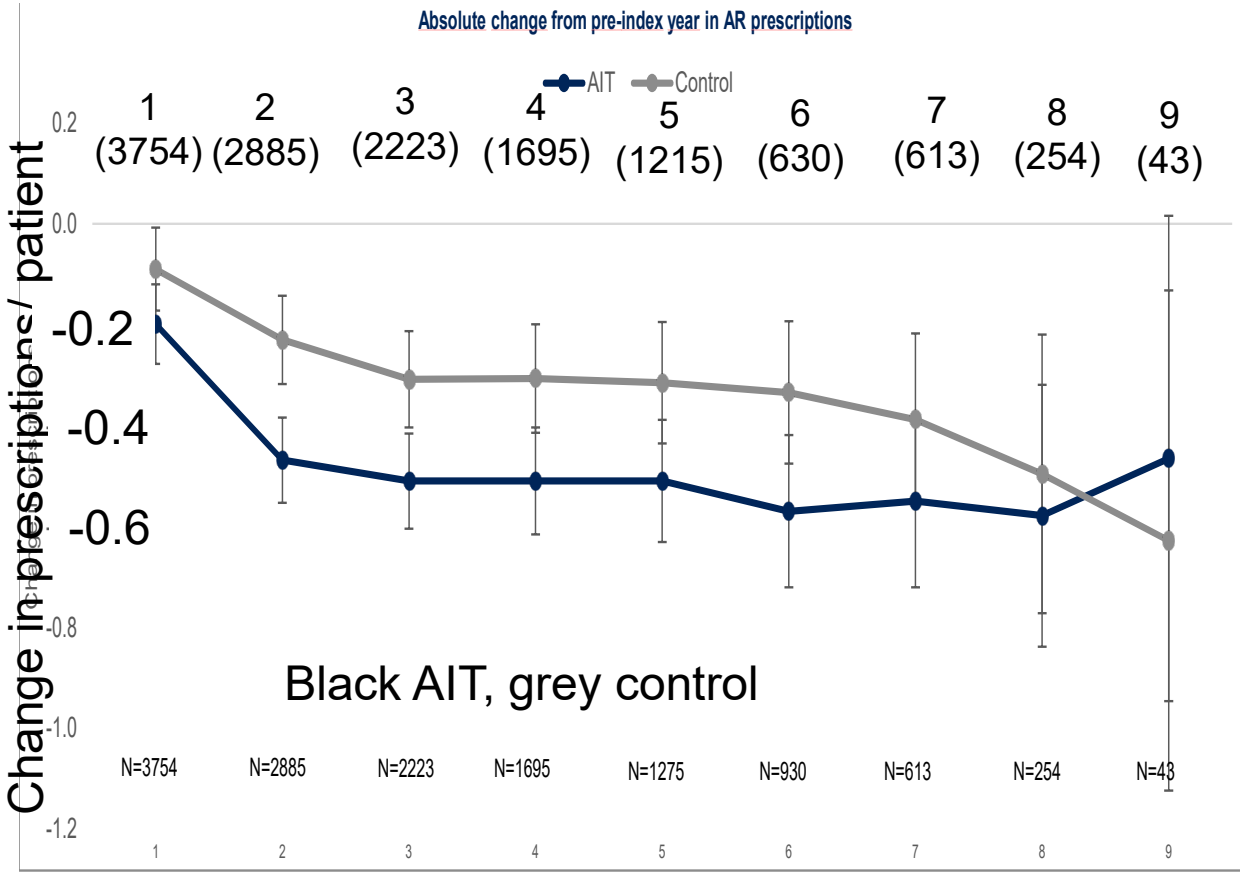
Real world evidence Generalisability of SLIT to SCIT

Real world study showed the absolute change in AR prescriptions from baseline for 12 SQ-HDM SLIT was lower than those having standard of care.

Company suggest long-term outcomes of SCIT are generalisable to SLIT



EAG consider REACT data shows constant change in AR prescriptions in the SLIT-tablet subgroup from year 1 to year 9.
So there is no clear evidence to support an increment in the effect of treatment over time.



See link to real world evidence long-term effectiveness