Single Technology Appraisal

12 SQ-HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites (review of TA834) [ID6280]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

12 SQ-HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites (review of TA834) [ID6280]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from ALK Abello UK**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Association of Respiratory Nurses (ARNS)
   b. British Society of Allergy and Clinical Immunology (BSACI)
   c. British Society of Immunology-Clinical immunology professional network (BSI-CIPN)
   d. National Heart and Lung Institute

3. **Comments on the Draft Guidance from experts:**
   a. Dr Lucy Leeman –clinical expert, nominated by NHS England
   b. Dr Shuaib Nasser – clinical expert, nominated by ALK – Abello UK
   c. Dr Helen Evans-Howells – patient expert, nominated by Anaphylaxis UK

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group critique of company comments on the Draft Guidance**

6. **Patient group and professional group submissions**
   a. Asthma + Lung UK
   b. British Society of Allergy and Clinical Immunology (BSACI)
   c. ENT UK

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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12 SQ-HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites (review of TA834)

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 17 July 2024. Please submit via NICE Docs.

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

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	NA
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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1	**Details of the condition (Section 3.1)** The Company welcomes the committee's recognition that house dust mite (HDM) induced allergic rhinitis (AR), with or without allergic asthma (AA), has a significant impact on the health-related quality of life for patients living in the UK. Without adequate symptom management AR and AA can impact all aspects of daily life, with common symptoms including rhinitis, wheezing, coughing, asthma exacerbations, and difficulty sleeping. All these symptoms have a significant impact on work, schooling, and a patient's ability to participate in usual activities. HDM induced AR and AA are perennial, and avoidance measures are typically ineffective given the prevalence of HDM. The Company also recognises the committee's conclusion that there is a significant unmet need in patients for whom current symptomatic medications are inadequate. Allergen immunotherapy is the only disease-modifying treatment for HDM induced AR and AA, with 12 SQ-HDM sublingual immunotherapy (SLIT) having proven efficacy in the context of both randomised clinical trials and real-world treatment. Consequently, 12 SQ-HDM SLIT is already used regularly in NHS practice, with [redacted] of integrated care systems with a live formulary currently making it available for patients, based on a significant and robust body of evidence showing the benefits of treatment with 12 SQ-HDM SLIT for patients with AR, with or without AA. More broadly, SLIT products for treating HDM, grass, and tree pollen induced AR are currently available in [redacted] of integrated care system formularies, providing benefit for patients with AR, however access to treatment is not consistent across the UK. Treatment with 12 SQ-HDM SLIT, has the potential to meaningfully improve health-related quality of life and address unmet need for patients living with AR and AA and in the UK, and the Company is committed to the process to improve access to 12 SQ-HDM SLIT for patients with AR, with or without AA.
2	**Clinical management – allergic asthma (Section 3.3)** Treatment with 12 SQ-HDM SLIT in patients with HDM induced AR and AA should be initiated in adults with AA not well controlled by inhaled corticosteroids (ICS) and associated with mild to severe HDM AR. Subsequent to the submission, the Global Initiative for Asthma (GINA) have published updated recommendations, including on allergy immunotherapy (AIT). These recommend that HDM SLIT should now be considered at treatment Step 1 in addition to Steps 2 to 4 in adults sensitised to HDM, with sub-optimally controlled AA despite low-to high-dose ICS (provided FEV_1 is >70% predicted).[1] This updated guidance is also supported by the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA), who suggest that AIT should be used more frequently, and that it is currently only initiated for fewer than 7% of patients who would be indicated for treatment.[2]
3	**Eligibility criteria for people with allergic asthma (Section 3.5)** Initiation of treatment with 12 SQ-HDM SLIT should be considered in patients with HDM AA diagnosed by clinical history and a positive test indicating HDM sensitisation (skin prick test or specific immunoglobin E (IgE)). Of these patients, those eligible for treatment with 12 SQ-HDM SLIT, are those patients not well controlled by inhaled corticosteroids and associated with mild to severe HDM AR, aligned with the summary of product characteristics (SmPC). This could include patients treated with inhaled corticosteroids alone, or in combination with long-acting beta-agonists. HDM AA patients should not be treated with 12 SQ-HDM SLIT if they have a lung function of FEV_1 <70% predicted or have experienced a severe asthma exacerbation within the last three months.

[1] *Global Strategy for Asthma Management and Prevention 2024. Global Initiative for Asthma.*

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[2] *Hellings PW, Lau S, Scadding GK, Bjermer L, Backer V, Chaker AM, et al. EUFOREA summit in Brussels 2023: inspiring the future of allergy & respiratory care. Front Allergy. (2023) 4:1236977. doi: 10.3389/falgy.2023.1236977*

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4	**Applicability of trial data to NHS clinical practice (Section 3.7)** The Company maintains that both the MT-04 and MT-06 clinical trials, designed to assess the efficacy and safety of 12 SQ-HDM SLIT in AR and AA with AR patients, respectively, represent a robust and reliable evidence source that can be used to inform decision making with respect to clinical practice in the UK. Furthermore, to validate the conclusions of the MT-04 and MT-06 clinical trials in the context of UK clinical practice, an online survey was conducted which included responses from 46 UK healthcare professionals. Of these, 48% were allergy or immunology consultants; 13% were ear, nose, and throat (ENT) or respiratory consultants; with the remainder being GPs, nurses, or other healthcare professionals working in the UK. This represents a large proportion of the UK community of allergy clinicians. Of those surveyed, 89% of respondents believed the available clinical trial data supported the use of 12 SQ-HDM SLIT within its licensed indication in UK clinical practice, and 76% believed that the available data supports improved AA control (with 24% responding "maybe", and none believing that it did not support a treatment effect). Following publication of NICE's draft guidance for 12 SQ-HDM SLIT, the Company sought further advice from a panel of 10 UK clinical experts in allergy management, comprising allergy clinical leads, consultant allergists, primary care physicians with a special interest in allergy, and allergy consultant nurses with experience of using allergy immunotherapy. In the advisory board, 100% of those responding believed the clinical evidence for 12 SQ-HDM SLIT described a clinically meaningful improvement for patients and a reduction in AA exacerbations, and 100% of responders reported that treatment with 12 SQ-HDM SLIT resulted in a clinical meaningful improvement in symptoms for patients they had treated. **Inclusion criteria of MT-04** The inclusion criteria of MT-04 is aligned with the SmPC for 12 SQ-HDM SLIT, and also with its anticipated place in therapy in the NHS. 12 SQ-HDM SLIT is indicated for the treatment of asthma in HDM AA patients not well controlled by inhaled corticosteroids and with associated mild to severe HDM AR. Severe asthma is a risk factor for adverse reactions to AIT and treatment should not be initiated in this population, consistent with guidelines for AIT.[1] While SLIT is well tolerated, with few incidents of severe adverse events, SLIT has not been assessed in a patient population with severe asthma. As such, MT-04 did not include patients with Asthma Control Questionnaire (ACQ) >1.5 at baseline, which is consistent with the anticipated use of 12 SQ-HDM SLIT in clinical practice in the UK. **Mandated withdrawal of inhaled corticosteroids in MT-04** MT-04 demonstrated that treatment with 12 SQ-HDM SLIT in HDM AA with AR patients who are not well controlled on an ICS would reduce the risk of an exacerbation by 34% in comparison with those receiving standard of care alone. This is based on the principle that if HDM exposure is driving the respiratory disease, treatment with 12 SQ-HDM SLIT specifically targeting the immunological response to that allergen will show an additional benefit. This was evidenced by an ICS withdrawal period which was intentionally part of the study design. While the Company accept that this would not be consistent with clinical practice in the NHS, ensuring enough events to robustly estimate a statistically significant difference in the primary endpoint of asthma exacerbations for patients treated with 12 SQ-HDM SLIT was required from a regulatory perspective. There is also significant Phase 2 data supporting the AA treatment benefit of 12 SQ-HDM SLIT in addition to MT-04. In a clinical trial of 614 patients with HDM AR with AA randomised to double-blind daily treatment with 1, 3, or 6 SQ-HDM SLIT or placebo, HDM SLIT was effective in reducing ICS dose required for asthma control.[3] ICS use was standardised and adjusted at both baseline and the end of treatment to the lowest dose providing asthma control, consistent with AA management guidelines. Treatment with 6 SQ-HDM SLIT (i.e., a lower dose than 12 SQ-HDM

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SLIT) showed a statistically significant reduction in mean ICS dose of 81 µg/day in comparison with placebo (95% confidence interval [CI], 27-136 µg/day, p = 0.004) when used in addition to standard of care (Figure 1). Reductions are anticipated to be larger for 12 SQ-HDM SLIT based on poorer efficacy for patients treated with 1 SQ-HDM and 3 SQ-HDM in comparison with 6 SQ-HDM SLIT. In the advisory board conducted by the Company following the publication of NICE's draft guidance, 86% of respondents believed that treatment with 12 SQ-HDM SLIT would reduce requirements for corticosteroid use.

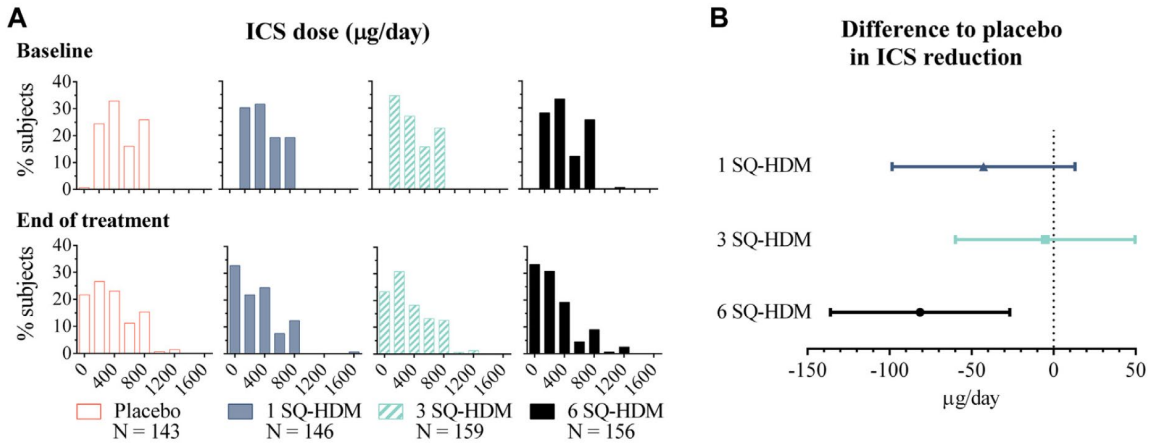

Figure 1: (A) Distribution of ICS dose (µg/day) in each treatment group at baseline and following one year of treatment. (B) Estimated adjusted mean difference (95% CI) between active treatment and placebo in change from baseline to one year in minimum ICS dose required to maintain asthma control. Figure reproduced from Mosbech et al. 2014.

Furthermore, these benefits in improving AA control and reducing the incidence of asthma exacerbations should be considered alongside the benefits of 12 SQ-HDM SLIT in reducing symptoms of AR demonstrated in MT-06. While MT-04 did not capture AR outcomes in patients with HDM AA and AR, an earlier Phase 2 study conducted in an allergen exposure chamber showed a 48.6% reduction in total nasal symptom score (TNSS), a 67.9% reduction in nasal plus ocular symptom scores (TOSS), and a 52.2% reduction in total symptom score (TSS) after 24 weeks of treatment with 12 SQ-HDM SLIT in comparison with placebo in patients with AR with or without AA.[4] Unlike MT-04 and MT-06, this allergen exposure study also showed little or no placebo effect, suggesting that the relative treatment effects observed in MT-04 and MT-06 are likely to be conservative in comparison with the anticipated treatment effect in UK clinical practice.

Primary efficacy assessment outside of the pollen season

Efficacy outcomes for 12 SQ-HDM SLIT, assessed as part of a clinical trial have the potential to be confounded by exposure to other allergens to which the participants may be sensitised. In MT-04 66% of participants were poly-sensitised, and 68% were poly-sensitised in MT-06. Randomisation cannot be used to fully account for the presence of pollen sensitised patients with equal degrees of sensitisation, as specific IgE levels and skin prick test size are not reliable predictors of symptom severity. Consequently, primary efficacy assessments were made outside the pollen season to reduce the potential impact of any imbalances in sensitisation between study arms that could not reliably be accounted for through randomisation. Furthermore, HDM AR and AA symptoms typically peak in the winter months, meaning that assessing efficacy in these months

[3] *Mosbech H et al. J Allergy Clin Immunol. 2014;134(3):568-575*
[4] *Nolte HN et al J Allergy Clin Immunol 2015; 135(6): 1494-501*

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	further reduces variability in patient experience across study arms and results in more robust estimates of comparative efficacy for 12 SQ-HDM SLIT. The results of a post-hoc analysis of HDM sensitised subjects with or without grass and/or tree sensitisation throughout the year (including the pollen season) for the MT-06 primary efficacy endpoint (total combined rhinitis score, TCRS) are presented in Figure 2. Both patients with sensitisation to grass/tree pollen, and those without sensitisation to grass/tree pollen, maintained a consistent treatment benefit throughout the course of the year, with a clear separation in TCRS outcomes for patients treated with 12 SQ-HDM SLIT and placebo. Regardless of the pollen season, patients treated with both 12 SQ-HDM SLIT and placebo show a reduction in the average TCRS score. As such, the timing of the efficacy assessment is not anticipated to bias the estimated treatment effect of treatment with 12 SQ-HDM SLIT in comparison with clinical practice in the NHS.  *Figure 2: Post-hoc analysis of subjects with or without grass and/or tree pollen sensitisation in MT-06* **Prohibition of concomitant medications in MT-04 and MT-06** The company provided specific standard of care medication to participants of MT-04 and MT-06 that patients could use as much or as little as needed depending on how they felt. The medication provided was made up of the majority of. making up the majority of standard of care in clinical practice, which were provided as part of the clinical trials. Only leukotriene receptor antagonists (LTRA), ipratropium bromide, and intranasal decongestants were prohibited in the clinical trials, all of which are infrequently used in clinical practice in the UK for the management of HDM AR. This was validated by healthcare professionals participating in an advisory board following the issuance of NICE's draft guidance, with 100% of those responding believing that the medications used in the clinical trial aligned well with treatments used in clinical practice in the UK. All respondents also believed that the exclusion of LTRA, ipratropium bromide, and systemic corticosteroid from both study arms would not bias results in the context of UK clinical practice. This approach was taken to improve standardisation between study arms and reduce potential confounding due to differences in standard of care medication use. Furthermore, as combined medication scores are often a key endpoint of clinical trials in AR and AA, a standardised set of symptomatic medications is essential in reliably determining treatment efficacy. It is also important to note that the makeup of standard of care for MT-04 and MT-06 was consistent for both study arms, with either 12 SQ-HDM SLIT or placebo being added to the same symptomatic medications.

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	Neither are the prohibited elements of standard of care likely to meaningfully impact patient outcomes. Excluded treatments for AR included leukotriene receptor antagonists (LTRA) which are infrequently used in clinical practice, treatment with ipratropium bromide only reduces rhinorrhoea, and intranasal decongestants do not have a sustained effect in improving patients' symptoms. Oral antihistamines and intranasal corticosteroids remain the cornerstones of AR management, both of which were freely available for use in the context of the clinical trials. Similarly, long-acting muscarinic antagonists (LAMA) are used infrequently as a treatment for AR with AA, and increased doses of short-acting β_2-agonists (SABA) have been established as a risk factor for increased asthma exacerbations[5] and would hence not be used in clinical practice. Additionally, if prohibition of elements of standard of care would meaningfully impact management of a patient's AR or AA, it would be expected that symptoms in patients receiving placebo would increase over time. However, in both MT-04 and MT-06, patients in the placebo arm improved in terms of symptom severity over the course of the clinical trial, suggesting that the components of standard of care included in the clinical trials were at least as effective as whatever treatment a patient was receiving prior to clinical trial enrolment. The placebo effect observed in both trials is anticipated to be due to patients in MT-04 and MT-06 being re-trained on how to use symptomatic medications at touchpoints during period 2. Devices act as a barrier for use and thus clinical and therapeutic effect in chronic disease such as HDM AR and AA. Consequently, this would likely improve adherence to and optimisation of symptomatic medications which would not be realised in clinical practice. The Company also notes that the results observed in MT-04 are in line with other asthma trials, which consistently show substantial improvements in the placebo group. It is likely that this is due to regular visits to a specialist with repeated instruction in the use of ICS and other symptomatic medications which would not occur in UK clinical practice. This means that in effect, the standard of care considered in the clinical trials is likely to overestimate the efficacy of treatment with background standard of care, and correspondingly, underestimate the incremental treatment benefit of 12 SQ-HDM SLIT. Furthermore, as stated in the draft guidance, 12 SQ-HDM SLIT is anticipated to be used in addition to background standard of care. Consequently, any additional components of standard of care that may have limited use in clinical practice and would be relevant for both study arm of MT-04 and MT-06, and any changes in efficacy, would apply equally to both study arms. Consequently, this is not anticipated to have any impact on the estimated efficacy of 12 SQ-HDM SLIT as a treatment for both AR and AR with AA, and indeed, the efficacy of 12 SQ-HDM SLIT is also supported by real-world evidence collected both in the UK and internationally (please refer to Comment 6). **Duration of clinical trials** The recommended duration of treatment with 12 SQ-HDM SLIT is a total of three years. Although efficacy is achieved within a much shorter period of approximately 24 weeks, longer durations of treatment improve the duration of the effect following cessation of treatment with 12 SQ-HDM SLIT. While MT-04 and MT-06 (along with P001, TO-203-31, and TO-203-32) demonstrate the efficacy of 12 SQ-HDM SLIT over shorter durations, real-world evidence and clinical expert opinion support the conclusion that the benefit of treatment is maintained over a significantly longer period following longer durations of treatment (please refer to Comment 9).

[5] *Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting β2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. Eur Respir J. 2020;55(4):1901872. Published 2020 Apr 16. doi:10.1183/13993003.01872-2019*

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5	**Clinical efficacy estimates (Section 3.8 and Section 3.9)** Treatment with 12 SQ-HDM SLIT in MT-06 resulted in statistically significant reductions in AR medication use and symptoms in AR patients, demonstrated by a significant reduction in TCRS compared with placebo in the multiply imputed full analysis set (FAS, absolute difference: 1.09 [95% CI 0.35, 1.84], p=0.004). In addition, 12 SQ-HDM SLIT was associated with a significant improvement in quality of life (QoL), as demonstrated by an improvement in Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score compared with placebo (absolute difference: 0.19 [95% CI 0.02, 0.37], p=0.031) in the FAS population. Similarly, MT-04 demonstrated a statistically significant (34%) risk reduction of a moderate or severe asthma exacerbation compared with placebo (hazard ratio [HR] 0.66, 95% CI 0.47, 0.93, p=0.02). 12 SQ-HDM SLIT was also associated with a reduction in ACQ score in comparison with placebo of -0.12 (95% CI -0.25, 0.01). Although the MT-04 was not designed to capture AR outcomes, these results should be considered in addition to the benefits observed in MT-06, as all eligible patients have AR. The Company notes that mean differences in the trials were impacted by the large placebo effects observed in both MT-04 and MT-06, reducing the relative treatment effect of 12 SQ-HDM SLIT in comparison with placebo. As stated in Comment 4, the placebo effect observed in the clinical trials is believed to be due to participants being re-trained on how to use symptomatic medications during the clinical trial follow-up. Patients also had frequent contact with study clinicians, which would not be expected in routine clinical practice. Consequently, this is expected to improve adherence to and optimisation of symptomatic medications, which would not be realised in clinical practice. This may also be due to confounding due to allergen sensitisation and exposure. Large placebo effects are observed consistently in trials for AIT in AR, and as a result, the US Food and Drug Administration (FDA) has determined that a 15% improvement constitutes a clinically meaningful response in the context of Phase 3 trials.[6] These conclusions were also validated by a survey and advisory board conducted with UK healthcare professionals, with all respondents in the advisory board believing that the clinical evidence for 12 SQ-HDM SLIT described a clinically meaningful improvement for patients and a reduction in AA exacerbations, and also that treatment with 12 SQ-HDM SLIT resulted in a clinical meaningful improvement in symptoms for patients that they had treated. This was supported by a survey of 46 UK allergy specialists, with 89% of respondents believing that the available clinical trial data supported the use of 12 SQ-HDM SLIT in UK clinical practice, and none believing that it did not support a treatment effect. Furthermore, as described in Comment 4, a Phase 2 study conducted in an allergen exposure chamber for patients with AR with or without AA showed a 48.6% reduction in TNSS, a 67.9% reduction in TOSS, and a 52.2% reduction in TSS after 24 weeks of treatment with 12 SQ-HDM SLIT in comparison with placebo in patients with AR with or without AA. Due to the design of the study with controlled exposure to HDM, no placebo effect was observed, and reductions in symptom scores were significantly more than both the 20% and 15% reductions recommended by The World Allergy Organisation and the FDA, respectively. Although 12 SQ-HDM SLIT is not routinely available to patients in the UK and there remains a significant unmet burden and geographic inequality for patients with HDM AR with or without AA, [redacted] of integrated care systems with a live formulary currently make it available for patients. Consequently, there is real-world evidence collected as part of NHS practice which shows that treatment with 12 SQ-HDM SLIT is highly efficacious. The Registry for Immunotherapy (BRIT) is a web-based patient registry that collates immunotherapy treatment data for patients under the care of British Society for Allergy & Clinical Immunology (BSACI) consultants practicing in the UK. Linear mixed effects regression analysis of patient data collected as part of BRIT showed that in [redacted] patients treated in the UK, treatment with 12 SQ-HDM SLIT is estimated to result in a mean

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	change from baseline after one year of [redacted] in the Paediatric Allergic Disease Quality of Life Questionnaire (PADQLQ), and [redacted] in RQLQ, both of which would be considered clinically meaningful on their respective scales.[7,8] In summary, the evidence base from the clinical trials and real-world evidence collected in the UK support a clinically meaningful improvement in AR and AA outcomes for patients treated with 12 SQ-HDM SLIT, and the inherent limitations associated with estimating treatment effect in this area should be considered when interpreting the evidence base.

[6] *Kaur A, Skoner D, Ibrahim J, et al. Effect of grass sublingual tablet immunotherapy is similar in children and adults: A Bayesian approach to design pediatric sublingual immunotherapy trials. J Allergy Clin Immunol. 2018;141(5):1744-1749. doi:10.1016/j.jaci.2017.09.051*

[7] *Roberts G, Hurley C, Lack G. Development of a quality-of-life assessment for the allergic child or teenager with multi-system allergic disease. J Allergy Clin Immunol 2003; 111: 491-7.*

[8] *Juniper EF, Guyatt GH, O'Byrne PM, Viveiros M. Aqueous beclomethasone dipropionate nasal spray" regular versus "as required" use in the treatment of seasonal allergic rhinitis. J Allergy Clin Imunol 1990;86:380-6.*

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6	**Real-world evidence (Section 3.10)** There is extensive real-world evidence describing the efficacy of 12 SQ-HDM SLIT and AIT more generally, including studies which followed patients for up to nine years due to routine use of AIT in other European countries. The Real-world Effectiveness in Allergy Immunotherapy (REACT) study was a retrospective observational, propensity score-matched cohort study using claims data between 2007 and 2017 from a German health insurance fund database. The study aimed to assess the long-term effectiveness of AIT for the treatment of AR with or without AA in a real-world setting. REACT included 46,024 eligible patients treated with AIT, as well as 46,024 matched controls. REACT reported sustained, long-term reductions in the number of severe asthma exacerbations (Year 9, odds ratio [OR] 0.66, p=0.060), and reductions in the prevalence of pneumonia with antibiotic prescriptions (Year 9, OR 0.44, p=0.26), and number of hospitalisations (Year 9, OR 0.72, p=0.04) in the AIT-treated pre-existing asthma cohort. AIT-treated AA patients were also significantly more likely to step down AA treatment, and less likely to step up treatment (Year 9, OR 1.30, p=0.03; OR 0.69, p=0.03). Improvements for patients treated with AIT in comparison with matched controls were maintained over the 9 years, and there was a trend for the treatment benefit to increase over time. However, REACT did not include only patients with HDM AR or AA, and patients were treated with a range of AIT, not specifically 12 SQ-HDM SLIT. As such, the committee questioned whether the results of REACT would be generalisable to treatment with 12 SQ-HDM SLIT specifically. However, REACT did not include only patients with HDM AR or AA, and patients were treated with a range of AIT, not specifically 12 SQ-HDM SLIT. As such, the committee questioned whether the results of REACT would be generalisable to treatment with 12 SQ-HDM SLIT specifically. ALK have conducted a real-world evidence study in 3,584 patients treated with 12 SQ-HDM SLIT, and 3,584 matched controls in Denmark and Sweden with up to five years follow-up. The methodology used was aligned with the REACT study, with propensity matching used to identify suitable control patients. This study shows that reductions in AR prescriptions per subject treated with 12 SQ-HDM SLIT are in excess of those observed in the REACT study, supporting a conclusion that long-term outcomes associated with subcutaneous immunotherapy (SCIT) are likely to be generalisable to SLIT, and are likely to be conservative when assessing the effect of 12 SQ-HDM SLIT in clinical practice in the NHS. Furthermore, the data also show that the effect of treatment with 12 SQ-HDM is not only maintained beyond one year but is anticipated to improve over subsequent years, consistent with the findings of REACT, suggesting that one-year efficacy estimates derived from MT-04 and MT-06 are likely to underestimate the total benefit of treatment with 12 SQ-HDM SLIT (Figure 3).

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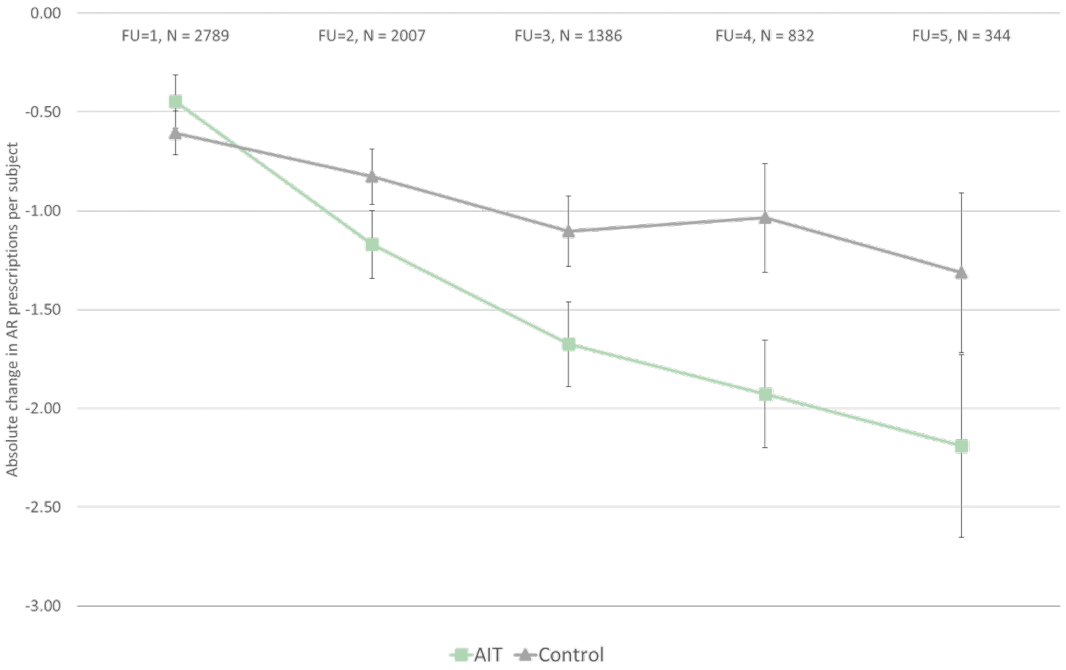

Figure 3: Absolute change in AR prescriptions from baseline for patients treated with 12 SQ-HDM SLIT and standard of care in Denmark and Sweden.

In addition to this, as described in Comment 5, analysis of BRIT registry data showed that treatment with 12 SQ-HDM SLIT is estimated to result in a mean change from baseline after one year of [redacted] in PADQLQ, [redacted] in RQLQ, both of which are more than point estimates derived from MT-04 and MT-06. This again suggests that MT-04 and MT-06 present a conservative estimate of the incremental treatment effect of 12 SQ-HDM SLIT.

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7	**Company's modelling approach (Section 3.11)** The Company acknowledges the committee's preferences with respect to the health economic models for AR and AR with AA, but maintain that both models are fit for decision making regarding the cost-effectiveness of 12 SQ-HDM SLIT. Both models as presented in the submission reflect the impact of HDM AR and AA to both patients and healthcare payers. Nevertheless, the Company has made significant adjustments to both health economic models to explore the uncertainty raised by the committee and demonstrate that these concerns do not have any impact on conclusions of cost-effectiveness in either the AR or AR with AA populations. **Treatment stepping** While the Company acknowledges that treatment stepping is an important part of the management of AA with AR in UK clinical practice, UK clinicians engaged with by the Company as part of submission development confirmed that the primary objective of treatment for AA is disease management, with stepping down treatment only considered once control is achieved. This was further confirmed by a survey completed by 46 UK clinicians, 61% of them being allergy, ENT, or respiratory consultants, where 94% of respondents believed the asthma control was the primary objective of treatment for AA. It was also validated in an advisory board, where 71% of those responding believed that asthma control should be achieved before stepping down symptomatic medications. As such, other model approaches designed around treatment stepping in AA, such as the model published by Parra-Padilla et al. (2020), and advocated by the EAG, in a non-peer reviewed, unvalidated, and un-reproducible approach taken would be unsuitable for decision making. From the perspective of developing a health economic model for 12 SQ-HDM SLIT, only the proportion of patients on each individual element of standard of care is relevant from a costing perspective. The Company believes that the model described in the original submission appropriately captured this component, particularly in the context that cost-offsets with respect to reductions in standard of care medication were not a significant driver of economic value for 12 SQ-HDM SLIT. However, the model has been revised to explicitly model distributions of patients across treatment steps stratified by the level of AA control a modelled patient is experiencing. As such, treatment stepping is implicitly captured in the revised economic model, with patients with uncontrolled AA being on higher treatment steps on average, and conversely, patients with well controlled asthma being on lower treatment steps in expectation. This assumption was validated in the advisory board, where 80% of those responding believed that asthma control level would determine the distribution of patients across treatment steps. As anticipated, these revisions had a negligible impact on estimated cost-effectiveness of 12 SQ-HDM SLIT in patients with AR with AA, reducing the incremental costs associated with treatment in the Company base case from a saving of £2,152 per patient to a saving of £2,179 per patient. As such, modelling treatment stepping in more granularity is anticipated to improve the cost-effectiveness of treatment with 12 SQ-HDM SLIT in the AR with AA population. **Inclusion of AR management costs in the AA patient population** The Company also acknowledges the committee's preference to include standard of care AR treatments costs in addition to AR treatment benefits for 12 SQ-HDM SLIT. The model has been revised to include treatment arm specific AR management costs in the AR with AA patient population, assuming distributions would be consistent with those collected as part of the MT-06 clinical trial. This scenario also nominally improves the estimated cost-effectiveness of 12 SQ-HDM SLIT, increasing cost-savings associated with treatment to £2,241 per patient. **Modelling asthma exacerbations conditional on AA control** The committee believed that it would be more appropriate to model the incidence of asthma exacerbations based on the level of AA control, rather than based purely on treatment arm as

	considered in the originally submitted health economic model. The revised economic model has been updated so that the incidence of exacerbations can be conditioned based on a patient's current AA control level. The relative risk of experiencing an asthma exacerbation is applied to treatment arm specific incidence of asthma exacerbations based on the MT-04 clinical trial, which demonstrated a statistically significant and clinically meaningful reduction in the incidence of exacerbations. This scenario assumes that the event rate observed in MT-04 is representative of the partly controlled health state, with well controlled patients being less likely to experience an exacerbation and uncontrolled patients being more likely to experience an exacerbation. This scenario resulted in improved cost-savings and increased patient benefits in comparison with the submitted base case; estimated cost-savings associated with 12 SQ-HDM SLIT increased to £2,223 per patient. Estimated quality-adjusted life years (QALYs) gained for treatment with 12 SQ-HDM SLIT also marginally improved. **Modelling asthma control based on GINA classification** The Company acknowledges the committee's preference for modelling AA control level based on ACQ score rather than GINA classification. However, the MT-04 clinical trial reported the GINA asthma control level at baseline and at trial end, and consequently, these definitions have been used in the economic model. It is important to note that GINA classification states reported in the clinical trial, and subsequently used in the economic model, were based upon ACQ score. ACQ was collected throughout the trial and consisted of five questions related to symptoms (nocturnal wakening, morning symptoms, activity limitation, short of breath, wheeze), one question related to SABA use, and one question related to about lung function (percentage of predicted FEV_1). These were mapped to GINA 2010 criteria for asthma control of daytime symptoms, limitations for activities, nocturnal symptoms or awakening, need for reliever or rescue treatment, and lung function. As such, results based on the GINA classification used in the model are anticipated to be consistent with estimates if they could be based on direct ACQ measurements available in a format relevant for the economic model.

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8	**Modelling in young people with allergic rhinitis (Section 3.12)** The submitted economic model assumed equivalent outcomes for both adolescent and adult patients with HDM AR treated with 12 SQ-HDM SLIT. This conservative approach was taken as adolescent data was not collected in MT-06, and because study results from P0001 and TO-203-32 showed that adolescents were anticipated to receive the same reductions in AR symptoms and medication use as adults based on subgroup analysis. In addition, there was no significant difference in the tolerability of 12 SQ-HDM SLIT in either population. Furthermore, as noted by the EAG, adolescents experienced a 22.4% reduction in TCRS in comparison with placebo in the P001 study, versus a 19.2% reduction in TCRS in adults. This translates to a relative difference of 16.7% improvement in outcomes for adolescents in comparison with adults and suggests that this assumption is conservative. This was also validated by a survey conducted by the Company, and completed by 46 UK clinicians, with 61% of them being allergy, ENT, or respiratory consultants, where only 2% of respondents believed that a similar or equivalent response to 12 SQ-HDM SLIT would not be observed between adult and adolescent patients. It was further validated in an advisory board, where all participants believed that 12 SQ-HDM SLIT would perform equivalently in adolescent and adult patients. Consequently, the Company believes that the approach taken is both reasonable and likely to be conservative. This is based on both the results of the P001 trial, and a cost-effectiveness subgroup analysis included in the submission which modelled a cohort aged 12 years at baseline, which showed that 12 SQ-HDM SLIT was anticipated to be more cost-effective in adolescents than adults assuming equivalent treatment benefits. However, to reflect the preferences of the committee, an additional scenario has been conducted in the economic model assuming a starting age of 12, and the difference in health-related quality of life collected in P001 adolescent subgroup rather than MT-06. This scenario resulted in significantly improved cost-effectiveness in comparison with the submitted base case, with incremental QALYs gained increasing to 0.64 per patient, and cost-savings increasing to £2,969, resulting in a conclusion of dominance for treatment with 12 SQ-HDM SLIT.

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9	**Long-term effectiveness (Section 3.13)** While both MT-04 and MT-06 were conducted over a period of less than two years, there is extensive experience of using AIT, and SLIT specifically, over a longer follow-up period that confirms a durable treatment effect for treated patients. The REACT study identified as part of the original study demonstrated that there was a persistent treatment effect associated with AIT over nine years following treatment initiation. Over that maximum nine-year follow-up there was also no indication of waning or other loss of treatment effect for patients treated with AIT. In the main analysis cohort, the reduction in AR medication use for those treated with AIT increased from -0.103 per patient in Year 3 to -0.219 in Year 9. Similarly, in the pre-existing AA cohort of REACT, the odds ratio of a ≥ 1 improvement in asthma treatment step improved from 1.15 (95% CI 1.09, 1.22) in Year 3 to 1.30 (95% CI 1.03, 1.64) in Year 9. This trend was observed across the incidence of hospitalisation (0.92 [95% CI 0.86, 0.99] in Year 3 versus 0.72 [95% CI 0.54, 0.98] in Year 9), and asthma exacerbations (0.89 [95% CI 0.81, 0.97] in Year 3 versus 0.66 [95% CI 0.44, 1.00] in Year 9). It is therefore implausible that all treatment effects for 12 SQ-HDM SLIT would be lost immediately after one additional year of follow-up, as per the EAGs preferred scenario. The Company acknowledges that the REACT study was based on a pooled analysis of AIT, with most patients receiving subcutaneous allergen immunotherapy (SCIT) and a variety of allergens, and that the committee would find additional evidence supporting the generalisability of SCIT data to SLIT informative. As described in Comment 6, ALK have conducted a real-world evidence study in 3,584 patients treated with 12 SQ-HDM SLIT, and 3,584 matched controls in Denmark and Sweden with up to five years follow-up. Results showed that reductions in AR prescriptions per subject treated with 12 SQ-HDM SLIT are in excess of those observed in the REACT study, supporting a conclusion that long-term outcomes associated with SCIT are likely to be at least generalisable to SLIT, and furthermore, that this comparison is likely to be conservative when assessing the effect of 12 SQ-HDM SLIT in clinical practice in the NHS. Furthermore, the data also show that the effect of treatment with 12 SQ-HDM is not only maintained beyond one year but is anticipated to improve over subsequent years, consistent with the findings of REACT, suggesting that one-year efficacy estimates derived from MT-04 and MT-06 are likely to underestimate the total benefit of treatment with 12 SQ-HDM SLIT. The findings of these real-world evidence studies support the Company's original assumption of improved efficacy over subsequent years for patients treated with 12 SQ-HDM SLIT following treatment. Furthermore, while the Company agree with the EAG that full treatment benefit would be maintained for at least 10 years, real-world evidence undermines an assumption of immediate loss of treatment effect after 10 years. This assumption is unduly conservative and incompatible with the available data. Furthermore, as stated in the original submission, the assumptions preferred by the EAG also conflict with the opinions of clinical experts with direct experience of treating patients with SLIT in UK clinical practice. The Delphi panel described in the original submission included consensus on the duration of treatment benefit, which was that treatment benefit was anticipated to be maintained for at least 10 years, after which the effect was expected to wane over the following 10 years, but with some patients not losing the treatment effect. The original submission base case was compatible with the opinions of clinical experts in the UK, with other assumptions that fall outside these parameters lacking clinical face validity. The consensus statement was further validated in a survey of 46 UK clinicians conducted by the Company, 44 of which have experience of treating patients with AIT, and 38 of which have direct experience of treating with 12 SQ-HDM SLIT. Of these respondents, only 2% disagreed with the consensus statement around the expected duration of efficacy of 12 SQ-HDM SLIT. Furthermore, in the advisory board conducted following publication of NICE's draft guidance, 88% of participants believed that the available real-world evidence for 12 SQ-HDM SLIT and AIT more generally, supported a conclusion of sustained treatment benefit. There is overwhelming consensus among UK allergy specialists that 12 SQ-HDM SLIT is expected to provide benefits of treatment for patients for over 10 years.

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	Retreatment with 12 SQ-HDM SLIT The Company does not anticipate that retreatment with 12 SQ-HDM SLIT will occur outside some very rare cases. However, the model has been revised to reflect a scenario assuming a proportion of patients will be retreated with 12 SQ-HDM SLIT after 10 years; this scenario increased estimated cost-savings and patient benefits associated with 12 SQ-HDM SLIT treatment. These findings were consistent regardless of the proportion of patients retreated. Consequently, although retreatment is anticipated to happen rarely, it is not anticipated to result in reduced cost-effectiveness of 12 SQ-HDM SLIT.

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10	**Primary and secondary resource use (Section 3.14)** There is consistent evidence from both randomised controlled trials and real-world data that AIT treatment reduces healthcare resource utilisation, which applies to both primary and secondary care visits in both the AR and AA with AR patient populations. MT-06 demonstrated a 4.9% reduction in doctor visits from randomisation to the end of trial associated with 12 SQ-HDM SLIT. Similarly, MT-04 showed a 18.7% reduction in GP visits during the treatment maintenance phase, a 38.8% reduction during the final 4 weeks of the treatment maintenance phase, and a 25.8% reduction for all trial visits. Data from the MT-04 study also showed a 60.3% reduction, 79.9% reduction, and 54.6% reduction in emergency visits during the same assessment periods. This is further supported by real-world evidence, with Robaina, Sachez, and Perez, 2016, reporting a significant reduction of 79% ($p<0.0001$) in urgent care visits and a significant 82% reduction in allergist visits ($p<0.0001$)[9]. El-Qutob et al., 2016 reported a significant reduction of 75.4% in emergency visits ($p<0.001$) and a significant 73.5% reduction in outpatient visits ($p<0.001$)[10]. Furthermore, the REACT study showed a consistent reduction in hospitalisations, with odds ratios of 0.72 (95% CI 0.54-0.98), 0.66 (95% CI 0.46-0.93), and 0.85 (95% CI 0.55-1.30) for all hospitalisations, inpatient stays, and outpatient stays, respectively, 9 years after treatment initiation. REACT also showed a reduction in ambulatory visits for patients treated with AIT, with an odds ratio of 0.88 (95% CI 0.49-1.57) after 9 years. While published real-world evidence primarily relates to SCIT treatment, real-world data collected by the Company showed that 12 SQ-HDM SLIT resulted in larger reductions in AR medication prescriptions than observed in REACT. Consequently, the benefit observed for SCIT is likely to represent a conservative lower-bound of the treatment effect associated with SLIT. The impact of treatment with 12 SQ-HDM SLIT on healthcare resource use was also validated in an online survey and an advisory board with UK allergy specialists. In the online survey, only 2% of respondents did not anticipate a reduction in primary or secondary care visits associated with treatment, and only 2% did not anticipate a reduction in hospitalisations. Furthermore, all participants in the advisory board believed that available evidence supported a reduction in healthcare resource utilisation for patients treated with 12 SQ-HDM SLIT. Treatment with 12 SQ-HDM SLIT is anticipated to be entirely cost-neutral to the NHS based on secondary care visit reductions of 37% and 20% for AR and AA with AR patient populations, respectively. Assuming the lowest reduction in secondary care visits identified in the literature (odds ratio 0.72 for all hospitalisation reported in the REACT study) results in an incremental cost-effectiveness ratio (ICER) of £2,613 in the AR population, and dominance in the AR with AA patient population for 12 SQ-HDM SLIT. While there may be uncertainty around the precise estimate of the relative reduction in secondary care visits based on the available data, this uncertainty has no impact on the interpretation of cost-effectiveness for 12 SQ-HDM SLIT, with all available estimates resulting in either highly cost-effective, or dominant ICERs. There is consistent evidence, across all identified data collected in both the real world and clinical trials, that treatment with 12 SQ-HDM SLIT will meaningfully reduce both primary and secondary care use. Introduction of 12 SQ-HDM SLIT is anticipated to be cost-saving to the NHS. Additionally, it is expected to free up primary care appointments and secondary care resources for additional treatments in the NHS. The introduction of 12 SQ-HDM SLIT is expected to provide significant benefits to both patients and NHS service delivery.

[9] *Garcia Robaina J C, Polanco Sanchez C, Estella Perez E. Savings associated with high-dose hypoallergenic house dust mite immunotherapy in rhinitis and/or asthma patients in Spain. Clinicoecon Outcomes Res. 2016;8:235-41.*

[10] *El-Qutob D, Moreno F, Subtil-Rodriguez A. Specific immunotherapy for rhinitis and asthma with a subcutaneous hypoallergenic high-dose house dust mite extract: results of a 9-month therapy. Immunotherapy. 2016;8(8):867-76.*

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11	**Modelling health-related quality of life (Section 3.15)** The Company believes that it is critical that the totality of the benefit associated with 12 SQ-HDM SLIT to patients is represented in the health economic models for both patient populations, with treatment specific (rather than health state specific) utility estimates derived from generic quality of life instruments collected as part of the MT-06 and MT-04 clinical trials. The health states included in both economic models are designed to capture important components of HDM AR and AA, such as standard of care medication use, but they do not represent the totality of the disease burden and consequently cannot be used to exhaustively model health-related quality of life. This is particularly relevant with respect to the AA with AR model, where health states define the quality of life impact of AA only, and do not capture the impact of AR symptoms. The approach preferred by the EAG, which is derived from mapped Asthma Quality of Life Questionnaire (AQLQ) assessment responses collected in MT-04, will not capture the impact of AR on patient outcomes, as the questionnaire is only sensitive to changes in AA symptoms. As such, the treatment specific approach included in the Company submission is the only appropriate approach for modelling health-related quality of life in the economic models, capturing the totality of the disease burden. This approach also better aligns with the explicit preferences stated by NICE in the methods guide, which states that generic measures collected directly from clinical trial data are preferred over mapped utility values,[11] with treatment specific utility estimates being based directly on EQ-5D data collected for the AR patient population and generic SF-36 for the AA with AR patient population. This approach also aligns with the committee's preferences as expressed in the draft guidance, which recognised that AR in addition to AA can affect health-related quality of life.
12	**Cost-effectiveness estimates (Section 3.16)** Treatment with 12 SQ-HDM SLIT is anticipated to be a highly cost-effective or dominant treatment option for patients with HDM AR or AR and AA in comparison with standard of care in the UK NHS. Significant revisions have been made to the health economic model to better reflect the preferences of the committee, with all changes nominally improving the cost-effectiveness of 12 SQ-HDM SLIT. Furthermore, all available estimates of relevant reductions in healthcare resource use translate to cost-effective or dominant ICERs for treatment with 12 SQ-HDM SLIT. While some residual uncertainty remains, as in all economic evaluations, all assumptions that are compatible with available clinical trial evidence, real-world evidence (including data collected in the UK NHS), and UK clinical expert opinion, result in cost-effective ICERs in all patient populations for 12 SQ-HDM SLIT. 12 SQ-HDM SLIT is currently being prescribed by more than 25,000 healthcare professionals (allergy specialists, respiratory specialists, ENTs, dermatologists, and GPs) across North America, Europe, and Asia, with approximately 500,000 patients receiving treatment. Treatment with 12 SQ-HDM SLIT is anticipated to result in improvements to patients' health-related quality of life and alleviate healthcare resource use. It is vital that treatment be made available to patients throughout the UK to help address the significant unmet need associated with HDM AR and AA.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).

[11] *NICE health technology evaluations: the manual. 4.3.12 Measuring and valuing health effects in cost-utility analyses.*

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is [redacted] and information that is [redacted]. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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

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

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Association of Respiratory Nurses (ARNS)

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Nil to disclose
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil to disclose
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The evidence available informs that 12 SQ-HDM “may reduce” asthma exacerbations and “may reduce” rhinitis symptoms and medication – however there is limited data available, and more evidence is needed.

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2	There is relevant evidence on cost for the 3 years suggested treatment, however, it is expensive at £80.12 (ex VAT) for one month's supply especially in comparison to current treatments already used such as inhaled corticosteroids and antihistamines.
3	Clinical data is not available beyond 2 years, although suggested from a retrospective study that it can improve health from 2-10 years however there is limited evidence to prove this long-term benefit.
4	There are suitable guidance recommendations for 2 categories: adolescents (12-17 years) and adults (18-65 years).
5	The appraisal acknowledges people already receiving 12 SQ-HDM treatment can continue to do so if in the patient's interest.
6	Would there be a reason for over 65s to be excluded from treatment and children under the age of 12?
7	More clarity may be useful with regards to treatable traits and exclusion/inclusion criteria.
8	The use of Fractional Exhaled Nitric Oxide (FeNO) measurements before and after treatment could have been a useful tool for assessment, especially for the asthma cohort.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[redacted] BSACI

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	• I received reimbursement from ALK-Abello for contributing to a Modified Delphi advisory panel: Investigating the current treatment landscape and management process of patients with allergic respiratory disease in the UK – £250. This was related to 12 SQ-HDM SLIT. It was a one-off panel, not on-going. • I have received no other funding from the company or comparator treatment companies in the past 12 months.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I feel that additional relevant studies should have been considered. I would suggest evidence from the following studies:

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	Mosbech H et al. J Allergy Clin Immunol. 2014;134(3):568-575 Nolte HN et al J Allergy Clin Immunol 2015; 135(6): 1494-501 Whilst not phase 3 studies, they provide importance evidence of efficacy. Mosbech et al demonstrates the inhaled steroid-sparing effect of 12 SQ-HDM SLIT in asthma. Nolte et al used an environmental exposure chamber study to demonstrate the effect on rhinitis symptoms without being compromised by the very large placebo effect seen in all phase 3 studies of allergen immunotherapy. Here the effect size is close to a 50% improvement versus placebo at 24 weeks treatment.
2	With regards to the summary of clinical effectiveness, I have the following comments: A/ Section 3.5. I think there is confusion concerning asthma control and initiating treatment with 12 SQ-HDM SLIT. An allergist would never start allergen immunotherapy in a patient with severe asthma or with a *current* exacerbation of asthma. A patient with severe asthma would not ever be suitable for immunotherapy, whereas one with a current exacerbation might be suitable, when the acute exacerbation is resolved. Allergen immunotherapy is a good treatment for allergen-induced asthma, but severe or unstable asthma is a risk factor for severe reactions to immunotherapy, including anaphylaxis. This is a standard approach recommended in national (BSACI) and international (EAACI) guidelines on immunotherapy. The data this is based on comes entirely from subcutaneous immunotherapy and is extrapolated to sublingual immunotherapy. Sublingual immunotherapy is, statistically, extremely safe, but no trials have looked at its use in severe asthma, hence the safety-first approach dictated by subcutaneous treatment remains. With regards to which patients would be suitable for 12 SQ-HDM SLIT, I would take 'uncontrolled asthma' to mean: - Actively symptomatic, ACQ>1.0, using SABA at least every week, - Despite concordance with inhaled corticosteroids, - But with FEV1 >70% predicted, low or no requirement for oral prednisolone (maximum 2 courses per year), no history of severe exacerbations in the past 5 years (no inpatient admissions for asthma exacerbations), no history ever of HDU or ITU admission. This addresses a gap in need for patients who do not qualify for biologics but who have symptomatic house-dust mite induced asthma and rhinitis. Some patients may already be on higher doses of inhaled corticosteroids, others may have tried and not achieved improvement. With regard to section 3.7, the reason for not including patients with an ACQ>1.5, or those with more than 3 exacerbations in the run-in period, is for reasons of safety, consistent with the above guidelines on use of allergen immunotherapy. As above, this is historical and based primarily on safety concerns with subcutaneous treatment rather than sublingual. But to say this means all those included had well-controlled asthma isn't correct, the threshold for controlled asthma on the ACQ is 0.75. It is true that in standard clinical practice, inhaled corticosteroids are not reduced without good reason (i.e. clear clinical stability). But the study is proof of principle that 12 SQ-HDM SLIT helps maintain asthma control. Additionally, the clinical effect in practice could be expected to be an achievement of inhaled steroid reduction (see the study by Mosbech et al, referenced above).

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3	B/ Section 3.7. Efficacy outcomes of allergen immunotherapy treatments have to be performed with a view to the effect of other allergen exposures. To measure outcomes during the pollen season would be a huge confounder. Even if active and placebo groups were randomised to include an equal number of tree, grass and weed pollen sensitised patients, with equal levels of sensitisation (itself a huge challenge), specific IgE levels and skin test size are not particularly strong determinants of symptoms severity. This would have been very problematic and doubtless heavily criticised by reviewers. Other medications were not allowed for similar reasons – to allow standardisation between groups. Allergen immunotherapy phase 3 studies in allergic rhinitis are generally conducted in this way, with combined symptom-medication scores as the primary outcome. Intranasal corticosteroids and oral antihistamines are the mainstay and most prescribed treatments. The only additional treatment that is likely to have a meaningful impact would be a combined intranasal steroid and intranasal antihistamine spray. But these are not universally available (NW London CCG refuses to endorse GP prescriptions, for example). The other treatments mentioned in the BSACI rhinitis guideline are either almost universally ineffective (leukotriene receptor antagonists, LTRAs), assist in only one symptom (ipratropium bromide – with running never being patients' main complaint and with unpleasant side effects), or very short term (intranasal decongestants). With regards to asthma medications, to suggest use of higher doses of SABAs as an alternative treatment is potentially dangerous. High use of SABAs is associated with greater risk of severe asthma exacerbations. Long-acting anti-muscarinics have modest efficacy at best and have a place in longer standing asthma with airway-trapping or asthma-COPD overlap rather than in typical allergic asthma. LTRAs (as per rhinitis) generally have minimal or, at best, modest impact – it would be hard to find a clinician managing adult asthma who feels otherwise. So, exclusion of these is not a major concern. Not using ICS-LABAs is, I agree, not in line with guidelines, but given that the study was of inhaled steroid reduction, this would be problematic as isolated use of LABAs (which would have occurred following steroid withdrawal) has also been associated with poor asthma outcomes, including asthma deaths. The trials are of shorter duration because that is what is practicable. It would be foolhardy to run a three-year study before knowing whether a single year works. Extrapolating from other studies of allergen immunotherapy, the efficacy in the second year may well be greater than in the first year, so it is likely that the effect size here underestimates what would be achieved with a longer duration of treatment. The evidence over many years from immunotherapy trials and real-world evidence is that 3 years treatment leads to a persistent clinical benefit. I would expect this to be the case here.
4	C/ Section 3.8. The committee is confusing two completely different scoring systems. Juniper at al 1989 refers to a patient completed questionnaire – the RQLQ – which is entirely different from the TCRS as used in MT-06. The latter is a daily, combined symptom-medication score as recommended for allergen immunotherapy trials. The value of 0.5 as minimally important clinical difference for the RQLQ is not relevant here. Almost all allergen immunotherapy studies in allergic rhinitis have a very high placebo effect, typically in the region of 40%. Reasons for this may include regression to the mean, variations in allergen exposure, a clinical trial effect and possibly other, unknown reasons. It is therefore a very high bar to achieve significant improvement over placebo. The FDA has set a more reasonable figure of 15% in other phase 3 allergen immunotherapy studies, which was met here. It is worth looking at the data from the study mentioned above (Nolte et al) which was a double blind, randomised study of 12 SQ-HDM SLIT for allergic rhinitis +/- asthma with the primary outcome being response to controlled environmental allergen challenge in a chamber. This study had no placebo effect and an almost 50% improvement at 24 weeks in the active versus placebo group in

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	the primary outcome (rhinitis symptoms). The FDA are considering allowing such studies to be used in place of phase 3 field studies given the challenges the latter pose. I would suggest this is considered here.
5	D/ Section 3.9. As seen in many of the biologics trials in asthma, improving symptom scores (and, for that matter, other parameters such as FEV1, PEFR etc.) has rarely been achieved. All these studies are primarily powered on achieving a reduction in exacerbations, as is the case here. To focus on the ACQ is unfair, the focus should be on exacerbation rate.
6	E/ Section 3.10. The SNOT-22 is not a validated outcome tool in allergic rhinitis – it's for chronic rhinosinusitis. To use it in allergic rhinitis would be a mistake, it has not been validated and contains questions which are not relevant. Either the RQLQ or the miniRQLQ (both by Elizabeth Juniper) should be used. But, as per guidelines on allergen immunotherapy trials for allergic rhinitis, the combined symptom-medication score is recommended as the primary outcome, not RQLQ etc.
7	F/ Section 3.10. The REACT study used propensity score matching to match subjects and controls with equal chances of receiving allergen immunotherapy at baseline, including matched use of other treatments prior to starting immunotherapy.
8	G/ Section 3.12. It is generally accepted that allergen immunotherapy in all its forms has a greater effect earlier in the course of disease. I believe the vast majority of allergists would expect that, assuming equal concordance with treatment, the adolescent group would do as least as well as adults on this treatment.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[redacted] (member of British Society of Immunology-Clinical immunology professional network; [BSI-CIPN]

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Insert disclosure here]
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Desensitisation therapy is a standard of care for venom allergy, other forms of allergic rhinitis (grazax), and more recently food allergy (oral peanut desensitisation), with proven efficacy and safety when used with the correct restrictions and by clinicians with the correct experience. There

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	is a wealth of anecdotal experience in the benefits of sublingual desensitisation therapy for grass pollen rhino conjunctivitis. Other than standard treatments such as antihistamines, steroid nasal sprays, sodium cromoglicate eye drops, there are no other treatment options for patients with house dust mite allergy. Complete avoidance is not possible. To date, anecdotal experience with acarizax has been positive, being well tolerated and initial benefits seen.
2	Prescribing practice; It would be envisaged that acarizax would be initiated in secondary care with ongoing prescription in primary care to complete the desensitisation program. Access to secondary care for patients being treated with acarizax would be available for patients who require review/develop complications.
3	Acarizax would only be initiated if asthma control was optimal
4	Acarizax considered as a step up of treatment in those who are intolerant or inadequately controlled with standard medical care for allergic rhinoconjunctivitis (anti histamines, nasal spray etc)
5	Anecdotally we see benefit in patients with severe AR secondary to grass pollen prescribed grazax
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	National Heart and Lung Institute

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
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1	Committee point 3.5 We agree that 12SQ-HDM should be started at GINA Step 2-3 on top of inhaled corticosteroid in patients partially but not well controlled (ACQ 1-1.5). Eiligible patients for 12 SQ-HDM would need to wait a period of 6-12 months after asthma exacerbation requiring oral corticosteroids before initiation of 12 SQ-HDM.
2	Committee point 3.7. MT-04 included participants **who were not well controlled**, but partially controlled (ie ACQ 1-1.5) but without exacerbations in the previous defined interval)
3	Committee point 3.7. Whereas it is true that 'mandated steroid withdrawal' is not a usual part of clinical practice, **the supervised reduction of inhaled corticosteroids to observe impact on control** is frequently used in order to ensure the minimal effective dose of inhaled corticosteroid to maintain control and minimise steroid side effects. In this sense we consider that introduction of 12 SQ HDM- at a time of inhaled steroid withdrawal is a valid model of usual clinical practice. The model enabled a proof of principle to test the ability of 12Q-HDM to reduce asthma exacerbations. This approach was accepted as valid by the GINA committee who have recommended 12 SQ HDM in their asthma guidelines (GINA 2020-2023)
4	Committee point 3.7 Whereas the recommended immunotherapy duration is for 3 years, this is in order to induce long-term tolerance and persistence of clinical benefit for years after discontinuation (as confirmed for Grass pollen sublingual immunotherapy and likely true for HDM immunotherapy). However, onset of efficacy is within 2-4 months with maximal effect within 1 year as confirmed for all Grass immunotherapy trials and for 12 SQ-HDM in an environmental chamber study within 6 months**. The use of a 12-month study period in MT-04is therefore justifiable in the context of the 12SQ-HDM trials presented**
5	Committee point 3.8. The World Allergy Organisation recommendation of at least 20% for allergen specific immunotherapy for respiratory allergy as a minimal clinically relevant result was empirical and based on expert opinion rather than evidence. The corresponding recommendation for the US Federal Drug Administration for a minimal clinically relevant difference was 15% difference, with a 95% confidence interval lower bar greater than 10% for immunotherapy compared to placebo, (and this would include the 16% reported during period 3 of the MT-06 trial as valid). For trials of grass pollen SLIT, the reported combined symptom medication scores are frequently >30% for trials in adults. A lower % improvement in HDM immunotherapy trials compared to grass pollen is to be expected owing to the increased difficulty in selecting optimal participants due to the many confounding causes of perennial symptoms in patients with perennial rhinitis and a positive IgE test/Skin test to HDM. This is in contrast to seasonal grass allergy where the attribution to pollen is more clear cut.
6	Committee 3.8 The Juniper 'rhinitis quality of life' study (Juniper 1999 as referred to by the committee) reports a minimal clinical important difference (MCID) absolute difference of 0.5. However, this refers to WITHIN group changes not BETWEEN group changes. The difference between 12SQ-HDM and placebo was reported in MT-06 of -0.21. It is therefore not relevant to compare the between group difference in MT-06 to the within group MCID reported by Juniper. The between group MCID for the Juniper RQLQ questionnaire remains to be determined.
7	Committee 3.8. Re the 40% treatment effect noted for the placebo group, this is comparable with many immunotherapy trials and is due to several factors: regression to the mean (patients come in to trials when they are ill and get better as part of the fluctuation of their disease), clinical trial effect (Haldane effect) but most important because both placebo and active treated patients have free access to usual optimal pharmacotherapy (topical corticosteroids and antihistamines) so the placebo group improves by 40 -50% v baseline , compared to 70-80% v baseline for immunotherapy -treated participants ie giving between group differences of around 15-30%.
8	Committee 3.10. Real World Evidence. The SNOT-22 is an outcome measure used for chronic rhinosinusitis (CRSS) and may not be relevant for assessing perennial allergic rhinitis where the symptom profile is completely different from CRSS.
9	Committee 3.12. Based on trials of grass pollen immunotherapy, where more data is available for adolescents, we would not anticipate a difference between adolescents and adults in their response to HDM Immunotherapy

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10	Committee 3.13. There is strong evidence for long-term benefits of pollen immunotherapy in children and adults for years after discontinuation. There is preliminary data for long term effects also for HDM immunotherapy. Immunotherapy, unlike biologics and symptomatic treatments, can modify the cause of the disaes e long-term.

Insert extra rows as needed

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Insert disclosure here]
Name of commentator person completing form:	Lucy Leeman

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
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1	Are the recommendations sound and a suitable basis for guidance to the NHS?

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	I think 12 SQ-HDM SLIT should be recommended on the basis of patient benefit. Certainly for AR there are no long-term, meaningful additional treatment options beyond standard antihistamines, nasal steroid sprays, eye drops, and HDM avoidance. This is a high impact condition, sub=optimally controlled in a cohort of patients. The treatment can be beneficial if appropriately targeted and monitored.
2	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? no
3	committee-discussion, Allergic rhinitis, 3.2 In our practice we ensure that all other appropriate treatments have been tried but also that they have been tried using the correct administration technique, with good concordance, and appropriate combinations of treatments before considering 12 SQ-HDM SLIT and I think this is an important element to include.
4	committee-discussion Setting for prescribing 12 SQ-HDM SLIT 3.4 The radioallergosorbant test has largely been replaced by a newer method so the term RAST is obsolete. The key investigation is the detection of Specific IgE to House Dust Mite species, of which there are 2 main ones in the UK.
5	Setting for prescribing 12 SQ-HDM SLIT Setting for prescribing 12 SQ-HDM SLIT 3.4 Absolutely agree this treatment would be for secondary care only
6	committee-discussion, Eligibility criteria for people with allergic asthma, 3.5 Our practice focuses on the treatment of Allergic Rhinitis. We would expect the asthma control to be stable on whatever step the patient was on for a period of 2 months, and there to be no indication that the patient warrants a higher step treatment such as biologics. For example, if the asthma exacerbations were escalating and the patient was eligible for a higher step asthma treatment then this would be pursued first. However, asthma is a variable condition, patients often display variable symptom control throughout the year. With HDM allergy symptoms are usually worse over the winter, which gives the opportunity to start treatment with SLIT outside this period and observe benefit later in the year. There will be patients who continue to have a stable level of symptoms and a stable frequency of exacerbations on their asthma treatment who are not eligible for biologics, and whose asthma is clearly linked to HDM sensitization. These patients may not reasonably expect improved outcomes from their current step and 12 SQ-HDM SLIT would be appropriate. This treatment is also only appropriate if the patient also has allergic rhinitis.
7	committee-discussion, Clinical evidence, 3.6 MT-04 - this study design makes sense. It assesses efficacy of 12 SQ-HDM SLIT during the time of year when the HDM allergen is more prominent and when any symptoms related to other aeroallergens are likely to be at their lowest, ie in winter, outside the pollen season. It also made sense to try and withdraw regular corticosteroids to assess whether asthma exacerbation rate was reduced by the previous HDM desensitization. It is standard to try to de-escalate treatment where it is appropriate to do so
8	committee-discussion, Applicability of trial data to NHS clinical practice, 3.7 An ACQ score of <0.75 indicates well-controlled asthma, a score >1.5 indicates poorly controlled asthma. The group in the middle naturally have partially controlled asthma and asthma control can vary overtime, especially for HDM driven symptoms which although present throughout the year, are worse during winter. If asthma is poorly controlled then consideration should be given to whether treatment escalation to biologics or short term stabilisation is appropriate. De-escalating asthma treatment if 12 SQ-HDM SLIT was effective could certainly be considered in clinical practice. In this trial, withdrawal of inhaled corticosteroids enabled demonstration of the efficacy of the drug.

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12 SQ-HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites(review of TA834)

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 17 July 2024. Please submit via NICE Docs.

	To assess efficacy in the pollen season would likely have confounded results as some patients are polysensitized and SLIT is allergen specific. In our practice we use 12 SQ-HDM SLIT when it is judged that HDM is the dominant allergen, although desensitization for more than one allergen can be considered. In our practice we assess efficacy of 12 SQ-HDM SLIT and Grazax (Timothy grass pollen SLIT) after 12 months. If there has been no benefit then treatment is stopped. This is based on long-term experience with Grazax.
9	committee-discussion, Allergic rhinitis, 3.8 In our practice 12 SQ-HDM SLIT is used for allergic rhinitis secondary to HDM as the dominant allergen, although polysensitization is common. We restrict this treatment to patients who have optimised their standard therapies and still have confirmed severe symptoms (we use the SNOT22 score). At this level of symptoms and treatment there is significant distress and impact and any relief is welcomed by the patients. HDM is prevelent all year round and HDM reduction techniques are only minimally effective.
10	committee-discussion, Real-world evidence, 3.10 In our practice we have started 12 SQ-HDM SLIT for 41 patients over 2 years. We have long term (>12 months) reports from a subset of 25 of these patients. 8 patients stopped treatment within the first year, however 2 chose to return to treatment at a later date. Treatment was stopped due to side effects rather than lack of efficacy. Most patients report symptomatic benefit in follow up clinic and SLIT is a commonly requested treatment for both HDM and Timothy grass pollen. We treat approximately 30 new patients a year with Grazax for up to 3 years. It is rare for a patient to stop due to side effects or non-efficacy. We use the same entry criteria regarding symptom severity and treatment optimisation. We use a small amount of SCIT for both HDM and pollen allergens. While effective, the treatment includes a significant healthcare utilisation and treatment burden. SLIT (where available) is the preferred treatment modality in our Unit from a patient perspective and from a Service point of view. Anecdotally SCIT and SLIT are very similar in terms of patient outcomes.

Insert extra rows as needed

Checklist for submitting comments

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Insert organisation name]

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NIL
Name of commentator person completing form:	DR SHUAIB NASSER

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	SCIT and SLIT are comparably effective treatments for adults with allergic rhinitis – this was mentioned during the committee meeting but appears to have been omitted from the draft consultation (REF- . *Laryngoscope*, 132:499–508, 2022)

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2	House Dust Mite immunotherapy is likely to improve multiple allergic conditions in the same patient ie allergic rhinitis, sinusitis, asthma control and progression etc and therefore treatment specific (rather than health state specific) utility values derived from generic instruments are likely to give a better representation of total treatment benefit from the technology – this was mentioned during the committee but was not satisfactorily answered and does not appear to have been captured by the draft consultation – this should be addressed
3	
4	
5	
6	

Insert extra rows as needed

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
Name of commentator person completing form:	Dr Helen Evans-Howells

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Although the research data does not show the impact Acarizax has on reduced appointments, prescribing; it would be my clinical experience and I think that of my allergy and asthma colleagues that this would be the case. Acarizax is already widely used within a NHS and private

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12 SQ-HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites(review of TA834)

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	setting for those with uncontrolled rhinitis despite maximal treatment. Often within the first year of treatment, patients start having an improvement. Over the time, this then leads to less requirement to have medications prescribed such as Fexofenadine/ other antihistamines / nasal sprays /montelukast/ increased inhalers. They also arrange fewer consultations with their GP's /out of hours doctors as their symptoms become manageable. I fully appreciate we do not have the tangible data to support this, but our experience shows this to be the case, which is why the BSACI guidelines support treatment for those with uncontrolled symptoms. A 3-year treatment plan, for those at the severe end of disease, will not only improve their quality of life, attendance at school or work, but also, reduce prescription charges from other long-term medication use and medical appointments. I feel this cost benefit has been underestimated and is something we witness within allergy clinics as we see medication use decrease.
2	Many patients with uncontrolled rhinitis will seek to use both oral or intramuscular steroids (accessed privately as not recommended) to improve their symptoms. For frequent asthma exacerbations, both children and adults are prescribed courses of oral steroids, higher doses of oral inhalers and intranasal steroid sprays, and Acarizax greatly reduces this steroid burden as their symptoms become manageable. Again, whilst not demonstrated, we know this will bring with it a benefit to the NHS as the harm from long term steroid use will lead to increased need for medical care and treatments -such as for osteoporosis, diabetes etc.
3	Currently only a few centres in the UK offer sublingual or subcutaneous immunotherapy, meaning that access to care is postcode dependent. Having a NICE approved medication will encourage centres to look at how they can implement this treatment to help patients struggling across the country.
4	In my experience, when patients have uncontrolled asthma, frequent exacerbations, steroid use, increasing treatments- AND have environmental allergies/ house dust mite allergies- addressing their allergies and optimising treatment for this, including immunotherapy, reduces their asthma symptoms. This then will reduce hospital stays, attendances and GP/out of hours attendances. This is often a key component which is overlooked by GP's and having consideration of immunotherapy as a treatment option for asthma, will serve to ensure this important factor is addressed.
5	
6	

Insert extra rows as needed

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Single Technology Appraisal

12 SQ-HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites (review of TA834) [ID6280]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	[redacted]
Other role	Not specified
Organisation	Cambridge University Hospitals NHS Foundation Trust
Location	Not specified
Conflict	None
Notes	None

Comments on the DG:

- Has all of the relevant evidence been taken into account?

The impact of this disease does not appear to be presented strongly enough. To be constantly blocked up with congestion and secretions, unable to breath through the nose, means children cannot concentrate at school and adults at work. Both with resulting cost. Patients have distrubed sleep due to nasal obstruction and discomfort. Headaches are common; secondary sinus infection can occur.
Desperate patients may have unhelpful ENT surgery is an attempt to do something (which unfortunately does not provide benefit)
Clinical trials do not capture the wider impact.
In clinical practice, this is an effective and much needed drug; and there is no alternative.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The impact of HDM allergic rhinitis +/- asthma is considerable. Symptoms are year round (unlike hay fever) with cumulative and greater disability. This should be emphaised. In addition there are systemic effects – tiredness, inability to concentrate, inability to function, mouth breathing, etc. The cohort being considered for SLIT have severe disease.

This is the only disease modifying treatment for this condition. Re cost effective arguments, it adds great value. The committee seemed doubtful about this. Symptoms are considerably reduced (compared to all other available treatments) : the result is i. patients are able to function and ii. long term medication use is reduced ; iii. repeat visits to GPs or allergists/

ENT/ respiratory specialists is reduced iv. Loss of time from work and school is reduced

SLIT is much more cost effective than SCIT as only 1 treatment visit is required, compared to multiple hospital visits. Providing access to SLIT reduces discimination.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

The disease is severe. This drug has very considerable benefits and improves control when fully optimised 'medical treatment' has failed. It has an impressive effect in a difficult to manage chronic condition.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

In UK access to immunotherapy is poor (a significant reduction compared to other developed countries). SLIT means that patients who live far from an allergy service are able to access treatment, as ony 1 hospital visit for treatment initiation is required. By contast SCIT eg for pollen immunotherapy which involves multiple visits and more cost (to NHS and to patient) is not available to those not close to a service .

This treatment will reduce geographical inequality and discimination.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	None
Notes	None

Comments on the DG:

I was disappointed to see the recommendations of this review - having spent many years treating patient with House dust mite allergy and , as is commonly the case, asthma related symptoms. The outcomes do not resonate with my clinical experience. Of course, I fully appreciate the need for an evidence-based approach but matching data to the many different clinical pathways that allergy patients experience in the UK will always be something of an inexact science.
Having used Acarizax in patients for many years, these recommendations feel like a missed opportunity. My experience has been that the benefits in terms of symptom reduction are very commonly highly significant in terms of their holistic impact on symptoms, care costs, sleep, mood, quality of life as

well as productivity and believe that this effect can be challenging to fully capture simply in symptom or QoL scores. These also miss the potential class effect of SLIT to prevent disease progression. I believe there is good evidence of disease modifying impact and positive effect on a range of outcomes which are not being adequately reflected in the recommendations and in my view they remain an important part of treatment, which reduces reliance simply on symptomatic treatment – an approach I find all of my patients wholeheartedly prefer.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	None
Notes	None

Comments on the DG:

- Has all of the relevant evidence been taken into account?

Yes

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I think based on the evidence presented, it would be reasonable to allow prescriptions of 12 SQ-HDM SLIT to patients with asthma with house dust mite allergy and asthma +/- allergic rhinitis at stage 3 of the current guidance, to reduce risk of exacerbations whilst reducing ICS burden

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The study design of MT04 includes withdrawal of inhaled corticosteroids to 50% for 3 months then complete withdrawal. there is a reduction in moderate/severe exacerbations during the 50% reduction phase which i think is clinically important. Although it would not currently be routine clinical practice to completely withdraw ICS so quickly, I disagree with the conclusion of the committee that any reduction in ICS would not be in keeping with current asthma management guidance- (we step down as well as step up ICS dose). furthermore many house dust mite allergic patients

are using topical steroids to lung, skin and nose and any reduction in total ICS burden would be desirable.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	None
Notes	None

Comments on the DG:

- Has all of the relevant evidence been taken into account?

Cliical experience of the use of acarizax and grazax in the NHS has not been taken into account. Sub lingual inmmunotherapy has been found in general to be a well tolerated treatment which greatly improves quaility of life through better symptom control in patients with allergic rhinitis. The trails are also of shorter duration than the 3 year period that had been used to assess other sublingual immunotherapy such as Grazax

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The cost models do not consider the cost to the NHS of surgical treatments for allergic rhinitis which mostly consist of inferior turbinate reduction techniques. These are much more expensive treatments that have been either avoided primarliy or as recurrent procedures by the use of immunotherapy. Significant allergic disease can be a trigger for inducible laryngeal obstruction which can masquerade as severe asthma and even lead to intensive care admissions. I have had success in controlling this condition when allergy has been better managed by including immunotherapy.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No. As the committee has said the NHS would use immunotherapy in a different context to that in the trials that were assessed. Due to clinical need

it has already been used and found to be effective though not reported in clinical trial frmat that the committee can use for assessment

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	None
Notes	None
Comments on the DG:	
I am a consultant allergy and asthma nurse and use Acarizax regularly within my paediatric clinic. In my experience it is a clear, effective treatment for the management of allergic rhinitis in patients sub-optimally managed on conventional therapy. This improves quality of life, improves sleep and school performance, and prevents unnecessary GP and pharmacy visits. Acarizax is the only licensed treatment available. We have used unlicensed treatment before which have been ineffective, and failure to recommend Acarizax will place patients at risk of being offered inappropriate treatments and wasting both NHS resources and patient time, which would be very disappointing. The BRIT registry (maintained by BSACI) records use of immunotherapy and its effectiveness by means of symptom score Patient reported outcome measures.	

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	None
Notes	None
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

Summary: of comments

1. The review and its' conclusions should probably examine the wider literature in greater detail.
2. The broader economic impact of AR should be incorporated in examining cost-effectiveness than HCRU.
3. The economic modelling does not incorporate the critical step in management of HDM AR, which is the inclusion of the topical nasal

steroid/topical nasal antihistamine as recommended both by BSACI and ARIA. This distorts the picture, as fewer patients would require AIT.

1+2: The committee should be aware that the greater economic impact of AR lies in the negative effect on absenteeism and presenteeism (absence at work due to illness and underperformance at work due to a disease, or it's treatment, respectively), than to a narrow analysis of costs borne by the health care system.
There are many studies performed in the USA which demonstrate the costs of absenteeism and presenteeism, but only one of which I am aware in Europe. The study carried out in Sweden suggested that the cost of AR to the Swedish economy (pop 9.5m) was €1.3 pa (2018)) of which 70% was due to presenteeism (decreased work productivity) Cardell LO, Olsson P, Andersson M, Welin KO, Svensson J, Tennvall GR, Hellgren J. TOTALL: high cost of allergic rhinitis—a national Swedish population-based questionnaire study. NPJ primary care respiratory medicine. 2016 Feb 4;26(1):1-5.

3.In their assessment the EAG have ignored the benefits of combination topical nasal steroids with topical intranasal antihistamines. This omission is relevant as it misrepresents effective guideline advocated therapies which in turn would impact on the need to consider AIT in patients in turn seriously impacting economic modelling associated therewith. This is addressed in greater detail below.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

1. As stated above, the exclusion of the addition of the topical nasal steroid/topical nasal antihistamine step in AR management distorts the calculations
2. Diagnosis is usually made in primary care: Specific IgE testing may be performed (RAST was superceded about 15 years ago)
3. The measurement of exacerbations due to HDM outside the pollen/mould seasons makes clinical sense.

2+3. With regard to diagnosis, usually made in primary care, the history in rhinitis is key; of course Allergic rhinitis (AR) may be caused by many different aeroallergens with seasonal progression. House dust mite is ubiquitous but is more prevalent in the winter months because people do not go outside as often and the internal environment (humidity, carpets, cushions, curtains, central heating, double glazing etc) foster the multiplication of HDM,

Those with PAR (perennial AR) may have exacerbations due to co-existing SAR during the months March to October to a succession of aeroallergens of which grass is the most dominant. AIT (allergen immunotherapy) for House dust mite will not effect these responses. By default the effects of

evaluating HDM AIT are best done in the winter months to reduce confounders.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

1. The proportion of patients who might require treatment is not addressed
2. Optimisation of management of AR is not adequately addressed.
3. The EAG should appreciate that the confirmation of the safety of administering AIT to more the population with more severe asthma reduces the contraindications to prescription.
4. There is not a reasonable outline of patient selection (treatment failure is predicated by inappropriate selection)
5. The EAG limit their statements to the current state of allergy services in the UK
6. Including reference to ipratropium and nasal decongestants is of no relevance.
7. The EAG have ignored the maladaptive pathways which have developed as a result of the poor services which exist in the UK currently

As mentioned above, an holistic assessment of the economic impact fo treatment of AR probably should include the wider impact on the economy.

1.The committee should understand that rhinitis may be acute/Seasonal (SAR) or chronic/ persistent (PAR). Perennial allergic rhinitis (PAR) may co-exist with searonal allergic rhinitis. (SAR)
Rhinitis is thus: Allergic (consisting of SAR and PAR) in roughly 50% of sufferers: and Non allergic (NAR) (approx 25-30%) or mixed allergic-non allergic rhinitis) In patients with mixed disease (AR and NAR) any form of therapy will experience reduced efficacy to any form of pharmacological treatment as this has limited impact on the NAR component.

2. In their assessment the EAG have ignored the benefits of combination topical nasal steroids with topical intranasal antihistamines. This omission is relevant as it misrepresents effective guideline advocated therapies which in turn would impact on the need to consider AIT in patients in turn seriously impacting economic modelling associated therewith.

HDM AIT will of course demonstrate it's greatest benefit outside of the pollen season when people spent more time outdoors, houses are better ventilated and the conditions for the multiplication of the HDM are less favourable to it. For this reason it makes sense to design a trial which measures the impact of its' efficacy outside the pollen season. Incidentally, it is thought that one of the many reasons asthma and allergy have become more prevalent is due to adoption of western style housing (poorer ventilation, central heating, increased humidity, double glazing etc) which facilitate the proliferation of HDM.

4. The statement:

• Further clinical evidence, if available, to allow the committee to determine if 12 SQ-HDM SLIT would provide additional benefits to established clinical management alone in NHS clinical practice ….

requires a more specific response, which lays bare some of the weaknesses of current NHS clinical practice: I hope EAG find this response informative.

The current model of management of AR in the UK trivialises the severe impact of moderate/severe AR on patients and their families. NHS England have dictated that AR be managed by Pharmacists. Approximately 50% of sufferers' disease is managed well with OTC medication. A recent pharmacist led study from Belgium suggests that this approach is problematic (Scheire S, et alRhinitis control and medication use in a real-world sample of patients with persistent rhinitis or rhinosinusitis: a community pharmacy study. The Journal of Allergy and Clinical Immunology: In Practice. 2024 Apr 25).
This confirms the findings of other studies Kritikos V, et al. The burden of self-reported rhinitis and associated risk for exacerbations with moderate-severe asthma in primary care patients. Journal of asthma and allergy. 2020 Oct 6:415-28.

Most patients with moderate/severe AR (approx. 40% of sufferers) see the GP. Diagnosis is usually made on symptoms alone. Specific IgE testing for sensitisation may be performed, but in many ICBs this avenue is denied to GPs as access to them is denied. It is also the case that GPs are not confident of interpreting the results when they are received. Ryan D, et al Results of an allergy educational needs questionnaire for primary care. Allergy. 2017 Jul;72(7):1123-8.

6.Nasal decongestants, also advocated in the draft document as additional therapy may be helpful in the first few days of SAR and certainly during the common cold. However, they exhibit tachyphylaxis, limiting use to 7 days. It is frequently misused leading to the condition known as rhinitis medicamentosa which is not amenable to treatment, high-lighted by Scheire above
Intranasal ipratropium is useful only in vaso-motor rhinitis a form of NAR. It has no role in AR.

There is also no evidence that adding an antihistamine to a topical nasal steroid (ICS) is effective (or vice versa) and what evidence there is suggests that (counter-intuitively) any benefit is marginal.
On the other hand, the next step advocated by both ARIA and BSACI guidelines is the addition of topical ICS/intranasal (ICS/INAH) combination therapy which has been demonstrated to have a highly significant effect over a two week period in seasonal AR (Klimek L, et al Effectiveness of MP29-02 for the treatment of allergic rhinitis in real-life: results from a noninterventional study. In; Allergy and asthma proceedings 2015 (Vol. 36,

No. 1, pp. 40-470). Using this therapy, the number of patients requiring further intervention is small. Unfortunately, many ICBs in the UK make it impossible for clinicians to prescribe these highly effective medications.

7.A word of caution also concerning the use of depot steroid injections, sought by patients who are highly symptomatic and suffering impairment of quality of life in the absence of access to ICS/INAH as the next step. These are very effective and indeed not expensive but at the risk of extensive side effects to patients is significant. Depot steroids are categorically contraindicated in all rhinitis guidelines but are freely available (and advertised as such) from private clinics and prescribing pharmacists alike resulting in the emergence of a maladaptive and harmful pathway, suggesting that established clinical management alone in NHS clinical practice needs reform including the option to receive AIT where appropriate. Thus denying access to HDM AIT on the grounds of current NHS management cannot be considered a legitimate statement.

There are sufficient areas of concern to indicate that these are not a reasonable summary of the evidence or its interpretation coupled with poor interpretation of the current guidelines for asthma and rhinitis.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

The manner in which the four questions is formulated do not permit a broader, more cohesive response. This is itself discriminating. I would not pretend to understand the modelling employed but nonetheless believe that it has shortcomings.

The need of patients with AR is very high. It has been demonstrated that some 50% receive and are content with OTC medication from the pharmacist: these are patients with mild AR whose symptoms do not impact their daily life. In those with moderate to severe disease (by the ARIA definition) there is a larger unmet need as demonstrated by this study from the UK: UK prescribing practices as proxy markers of unmet need in allergic rhinitis: a retrospective observational study: DB Price, et al- NPJ primary care respiratory medicine, 2016. This study however relates to SAR not PAR but does exemplify the numbers of appointments made over the course of time because patients are not getting significant relief from their symptoms, thus placing additional demand and cost on primary care, which needs to be taken into account with the economic modelling. To my knowledge no similar study has been performed for PAR. More briefly, our poor service and innapropraite use of medications and failure to use appropriate medications makes our current service ineffective with resulting impairment on quality of life and reduction in economic efficiency.

The denial of a NICE approval for HDM SLIT would also systematically deny access to treatment of those who are unable to source/afford the treatment in the private sector or seek treatment through maladaptive and ungoverned a pathways as described above.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	None
Notes	None

Comments on the DG:

- Has all of the relevant evidence been taken into account?

Many centres are already using SLIT for managing patients with allergic rhinitis due to HDM allergy (confirmed by history, SPT and or blood results) who are still symptomatic despite maximum medical treatment which should include high dose antihistamines (e.g. fexofenadine 180 mg twice daily) and dymista nasal spray. From clinical experience patients are showing good response. Would be useful to consider getting data from centres already providing this treatment and clarifying when this is offered.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

In comparison to Subcutaneous immunotherapy, sublingual is less expensive as it reduces number of hospital attendance to have the subcutaneous injection.

These are calculations made by our service

Alutard HDM SCIT 3 year course treatment cost £19,500 (14000 for day care activities + 5500 for the treatment)

Tyrosin HDM SCIT 3 year course treatment cost £12,933 (£11,200 for day care activities + £1733.00 for the treatment)

While SLIT NHS would pay only for the treatment and one day case activity as only the first dose is given in hospital. The rest will be done at home unless patient stopped >7 days.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I disagree as SLIT is useful option to offer if patient is still symptomatic despite maximum medical treatment. I would not recommend offering before that.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	None
Notes	None

Comments on the DG:

- Has all of the relevant evidence been taken into account?

While the committee has considered clinical trial evidence, it appears that some crucial real-world evidence and clinical practice observations may not have been fully taken into account. In our clinical practice, we observe significant improvements in patients using 12 SQ-HDM SLIT. These improvements include reduced absenteeism from work or school, decreased need for antibiotics and steroids, and overall better management of symptoms. Additionally, the potential for this treatment to impact primary or secondary prevention of asthma and enhance quality of life has not been thoroughly evaluated. This real-world evidence suggests that the benefits of 12 SQ-HDM SLIT might be more substantial than what the clinical trials alone indicate.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summaries provided seem to focus heavily on uncertainties within the clinical trials and economic models. However, they do not fully reflect the positive outcomes observed in clinical practice. In our experience, 12 SQ-HDM SLIT has shown to be effective in reducing symptoms and the need for additional medications. The quality of life improvements for patients, including reduced absences and better overall health, suggest that the treatment may be more cost-effective in the long run than the summaries indicate. Therefore, the interpretation of the evidence may be unduly conservative, not capturing the full scope of the treatment's benefits.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations, as they stand, may not fully align with the needs and experiences of patients and healthcare providers. Given the observed clinical benefits and the potential for improved quality of life, it may be premature to exclude 12 SQ-HDM SLIT from recommended treatments. More comprehensive and nuanced guidance that considers both clinical trial data and real-world evidence would be more suitable. This would ensure that patients who can benefit from this treatment are not denied access due to a potentially narrow interpretation of the available evidence.
It's also important to highlight that the current recommendation conflicts with the GINA Asthma guideline, which supports the use of immunotherapy for asthma management. Ignoring the potential benefits of 12 SQ-HDM SLIT for asthma patients can lead to suboptimal management of the condition, affecting their quality of life. Considering the broader implications on patient well-being and healthcare resource utilization (e.g., reduced need for antibiotics and steroids) should be a priority in forming the final guidance.

By addressing these points, the NICE guidelines could more accurately reflect the benefits of 12 SQ-HDM SLIT, ensuring that patients receive the best possible care based on both clinical trial data and real-world evidence.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

One area that requires careful consideration is age. The recommendation currently includes people aged 12 to 65 years but does not specify considerations for those outside this age range who might also benefit from the treatment. Ensuring that younger children and older adults are not excluded from potentially beneficial treatments is crucial.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Evelina London Children's Hospital
Location	Not specified
Conflict	Not specified
Notes	Not specified
Comments on the DG:	

- Section 3 – Committee-discussion, point 3.2, ‘Allergic rhinitis’

We also receive many referrals from our ENT colleagues who have had to do surgery to reduce inflamed turbinates which are a long term sign of persistent allergic rhinitis.

We also see a prolonged benefit and many patients report the response to treatment has lasted for years past the end of the course. This is only evident in children who were started younger and remained under our service until they are teenagers however.

This treatment is an absolute life line for our house dust mite allergic patients who are receiving treatment. We have two clinics a week and speak to parents whose children is on Acarizax and they all find the treatment is making a positive difference. Parents report the child's behaviour improves, their sleep improves, and that the children have more energy.

Many parents become obsessed with cleaning and buy expensive products to try and reduce the house dust mite load in the house, which can also lead to parental stress and anxiety and expense.

In the longer term, there is evidence from clinical trials that there is an economic benefit as house dust mite allergic individuals require less prescriptions and are able to attend school and work.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	None
Notes	None

Comments on the DG:

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No: I believe that too much weight is given to the 20% difference specified in the World Allergy Organization guideline. In my view, this threshold is appropriate for the treatment of seasonal allergies with immunotherapy, but not for house dust mite allergic rhinitis, which is a very different disorder characterised by chronic persistent nasal inflammation rather than seasonal exacerbation only in which the symptoms go from zero to a high level for a relatively short finite period.

In my clinical practice, I have found that in highly selected patients, meticulously screened for chronic allergic rhinitis symptoms driven by house dust mite - i.e., supported by a clinical history of clear worsening upon direct house dust mite exposure and improvement in low house dust mite environments, and sometimes reversibility of symptoms with potent nasal steroids or prednisolone (neither of which is tenable as a long-term treatment) - this treatment can be extremely effective and indeed life-changing. I have experience treating many such patients with Acarizax very successfully. However, I do feel that this needs careful evaluation by specialists experienced in treating allergic diseases in the secondary or tertiary care setting, and in my view, would not be appropriate outside this setting. Assessment of response is also vital, with a willingness to stop treatment if insufficient benefit is seen after 6-12 months.

The misery of persistent nasal allergic symptoms due to house dust mite poorly controlled by nasal steroid therapy, cannot be overstated. It should also be borne in mind that these symptoms are frequently comorbid with allergic asthma, and therefore, immunotherapy can successfully address both issues simultaneously. Has this been reflected in the economic modelling?

- Are the recommendations sound and a suitable basis for guidance to the NHS?

In my view, no, please refer to above comment

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	None
Notes	None

Comments on the DG:

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

- Are the recommendations sound and a suitable basis for guidance to the NHS?

More evidence is needed, but safety & initial efficacy data suggests this is better than existing unlicensed (essentially no data, opaque) medications

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

As mentioned below - In real-world, these are major limitations and as clinicians we are conflicted in our advice. Patients may end up stopping treatment that potentially worsens their symptoms due to lack of trial data

- Section 3 – Committee-discussion, point 3.2, 'Allergic rhinitis' 'after all appropriate symptom-relieving medicine had been tried and symptoms continued.'

As clinicians, we recommend continuing on maximal medical therapy when commencing SLIT. This should be made clear.

- Section 3 – Committee-discussion, point 3.5, 'Eligibility criteria for people with allergic asthma' 'It was unclear how 'asthma not well controlled by inhaled corticosteroids' would be defined in clinical practice.'

Respiratory review is recommended, with additional FeNO or lung function tests to define how well-controlled asthma is

- Section 3 – Committee-discussion, point 3.5, 'Eligibility criteria for people with allergic asthma' 'This uncertainty included whether people would start treatment when their asthma was not well controlled, or whether they would need to wait for a reduction in exacerbations before starting treatment.'

Reasonable control of asthma is the minimum expectation as symptoms may be exacerbated if SLIT was started when asthma symptoms are limiting

- Section 3 – Committee-discussion, point 3.7, 'Applicability of trial data to NHS clinical practice' 'The EAG considered that this meant that there was limited data for people whose asthma was not well controlled with inhaled corticosteroids.

This is a major limitation for MT-04

- Section 3 – Committee-discussion, point 3.17, ‘Equality’ ‘But because its recommendation does not restrict access to treatment for some people over others, the committee agreed these were not potential equalities issues.’

In real-world, these are major limitations and as clinicians we are conflicted in our advice. Patients may end up stopping treatment that potentially worsens their symptoms due to lack of trial data

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	None
Notes	None

Comments on the DG:

- Has all of the relevant evidence been taken into account?

Yes treatments are discussed thoroughly and all relevant evidence been taken into account

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes they are reasonable

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

None

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Allergy UK
Location	Not specified
Conflict	Funding from ALK; Nov 2010 Dec 2010 £250 Apr 2015 Apr 2015 £5,000 Oct 2016 Oct 2016 £500 Plus travel exp. Jan 2017 Jan 2017 £500 Plus travel exp. Feb 2018 May 2018 £3,250 plus VAT Sponsorship Agreement Jan 2022 Mar 2023 £72,503 This last amount was for a series of projects which included masterclasses for HCP's, podcasts, video, article, online digital leaflet and top tips for managing asthma.£4,302 which includes VAT to collect comments from people affected by HDM allergy.
Notes	None

Comments on the DG:

Patient experiences of living with and caring for children with house dust mite allergies.

Adult living with HDM allergy
Dust causes me to have horrific asthma attacks. I can be speaking and then all of a sudden, I feel a speck of dust hit the back of my throat, and it feels like I've been shot in the back of the throat and my throat immediately feels like it's closed and lungs like rocks. I can't breathe.

This happened to me most recently, 2024 2 weeks ago late at night after putting my son to bed. Nothing that I did worked and I ended up collapsing from a height while looking for something to take to stop my throat swelling more. I landed on my ribs, which were really bruised, and knocked over the dog food and water. Which is where I was found and treated. It was terrifying.

As I couldn't speak, due to not being able to breathe, I couldn't tell anyone what would help.

It was terrifying. Yes, I still can't get an epi pen. This was not the first time. However, this time, I genuinely thought I was going to die because nothing helped. This stuff has to be taken more seriously.

I have lived with a house dust mite allergy from the age of 21 until my current age of 31. Having asthma from 7 years old my asthma took turn for the worst and became brittle at 21. Since then I have taken montelukast, cetirizine and a daily steroid inhaler Relvar.

Adult living with HDM allergy

Despite taking these medications I still live with a daily HDM allergy that affects my daily life. Every night in bed I have to sleep wearing a cotton mask which I have done for the last 10 years otherwise I wake up with asthma symptoms from my nose and mouth being on the bed sheets, this is despite having hypo allergenic and anti allergen bed sheets and pillows. The other big effect for me is in the winter, once I turn the radiators on I have asthma symptoms as the hot air heats up the carpet and room and I instantly feel allergic to the dust mite allergens that rise on the hot air. This means I very rarely turn the heating on in the winter, I am left with a choice of feeling cold and being able to breathe or turning the radiators on and being warm but feeling tight chested and struggling to breathe. I have been under a secondary care respiratory consultant in the past for my asthma but during covid this came to halt and was never reinitiated. Heaters trigger HDM allergens resulted in me having to give up an office job previously due to be me feeling too ill in the office.

Over the last few years I have searched for treatment options to desensitise my allergies and immunotherapy but have been unable to find anything suitable wither privately or on the nhs. I am aware the nhs has immunotherapy options to reduce allergy and biologics but there are only available to those who are admitted to hospital out of control x amount of times and when I asked for these treatment options in 2019 under consultant care I was ineligible. I'm stuck between a rock and a hard place, I either continue wearing a cotton mask to sleep every night and don't turn my radiators on in the winter to manage my asthma symptoms or I don't do these things and end up sick in hospital with my asthma meaning I may be a le to access allergen reducing medications that could make the difference to my life I mean.

The possibility of a treatment for house dust mite allergen being available on the nhs would be a life changing medication for me and I highly advocate for it.

Adult living with HDM allergy
I wanted to tell my story because I felt that it has been a long and hard struggle for me to even get to the stage that I am at the moment. Firstly, I had asked my GP to refer me for an allergy test and he forgot to do it, after a whole year of waiting and investigating, that's when He came to know that he had not even sent it in the first place after which he sent it. And luckily after my insistent chasing up, I got an appointment and I came to know that I have house due mite and aspergillus which keeps coming up high on the radar but nothing has been done about it even now, I actually had to go to India. Because of the aspergillus, I feel it created a lesion in my lung and it has made me very sick. I was coughing all the time but even now, I have not been seen to as yet. I am not sure when I will be heard by the doctor because he thinks that it is something else when, as a patient he does not want to listen to my. Symptoms which I keep talking about, especially the allergies. I'm not sure who to approach. Or how to go about this? But the only way I thought is since I have access to other country's treatments. I found it easier to go there and that's the only way forward. I'm going at the moment to Abu Dhabi as my

partner lives there. And I will be seeing a doctor there because I don't seem to be getting anywhere with the NHS.

I've repeatedly told the specialist That it could be due to my allergies that I am having this problem. But he says that it's not that and he has dismissed it with no further investigation.

I was told by my GP that I should use a hepta filtered hoover and that's all.

I am still waiting for a treatment plan.

Adult living with HDM allergy
I have lived with this for at least 20years. Rhinitis and wheezing being the most prevent symptoms.

People think you have a " cold" Can make you feel quite unwell and particularly worse in autumn & winter when central heating is on.

Always worse in the evenings when the house is closed up despite having windows open permanently.

The only room with a carpet is the lounge. Steam cleaning & shampooing helps a little

I take antihistamines when bad & sometimes have to use steroids inhaler.

Can be difficult when staying in holiday accomodation & friends houses.

I spend most of my time outdoors as that's where I feel healthy.

Adult living with HDM allergy
Diagnosed with severe Atopic Eczema in 1972, progressed to Chronic fixed Asthma from age 4. House dust mite allergy diagnosed over 50 years ago, along with other allergies.

Now 55, on Dupilumab, Methotrexate, 3 inhalers, topicals, antihistamines and long term Prednisalone (throughout my life) with all environments preventions taken (eg no soft furnishings, covers, vacuum, sprays, air filters) but I still have an off the scale, immeasurable allergy to house dust mites.

This has resulted in Steroid induced Adrenal insufficiency and Bipolar disorder , osteoporosis, kidney damage, high blood pressure. I am frequently Suicidal.

All this and my face and neck are still swollen and doctors can't do any more. My meds cost over 30K per year. Im mostly housebound, unable to work for 12 years due to severe symptoms and side affects of meds.

It would be great if anyone could find the cause of such severe allergies or if there we more effective, less damaging treatments.

Adult living with HDM allergy

Chronic undiagnosed rhinitis caused me to retire early from teaching. I had been suffering from poor concentration and broken sleeping patterns, which led to depression and irritability that affected not only my ability to teach, but my family and personal relationships. People would ask me why I was short tempered, always tired and seemed 'different', or not the same. I was also constantly on nasal decongestants from the local chemist or sticking things up my nose in order to promote a sneeze.

This sorry state continued until a friend gave me a 15 minute video tape entitled 'Who's been sleeping in your pillow?', starring Dr David Bellamy and approved by Asthma UK and Allergy UK. The video was all about allergy causing house dust mites, how they lived and bred in pillows and bedding how to avoid them. I took Dr Bellamy's advice and removed the HDM from my sleeping environment. Within weeks I was restored to good health! I had a sound sleeping pattern, energy and positive thinking to towards life, and a much better relationship with family and friends.

However, there are HDM sensitive or allergic people who will not be able to experience this transformation, because of family or work environments, such as cleaners, nurses, primary care attendants, or those restricted by financial pressure or home environments. Within this group are the ultra HDM sensitive patients, some of whom are steroid resistant, who must avoid the mite as it presents real danger.

The invasive major HDM allergen is medically described as an enzyme that can disrupt delicate tissue of the respiratory tract, eyes and on vulnerable skin causing immune reactions. Working to diminish the ability of HDMs to alarm a sensitive immune system is a goal that has been achieved by a simple 'under the tongue' tablet named ACARIZAX®

It is my wish that ACARIZAX® may be made available on the NHS, but add a note of concern. HDMs are carriers of bacteria known to be a risk to human health. The named bacteria (i.e. Staph aureus and E coli) are not allergens but come from the environment that is home to a HDM colony. Therefore, avoidance of excessive exposure to HDMs must be stressed when ACARIZAX® is considered.

Adult living with HDM allergy

After suffering severe atopic eczema since I was 2 years old, after some allergy testing at around 8 years old I got diagnosed with a dust mite and animal allergies. I remember them saying a score of 50 would denote an allergic response and my score for dust was 500.

So for my childhood my mum was amazing washing everything and regularly freezing my teddies and bedding to kill any mites. As an adult it became harder again when I had my own flat. I noticed more allergic symptoms

including developing allergy asthma and allergic rhinitis to add to the eczema and contact dermatitis.

As a 34 year old I have my allergy tablets, tissues and inhaler and eczema cream and gloves on my bedside table every night as bedtimes are usually the worst for the dust allergy kicking off. Cue itchy eyes, itchy hands , wheezy etc. it definitely makes my sleep quality poor.

Adult living with HDM allergy

Since I was a baby I struggled with allergies, mainly HDM. If I am in a place that is not clean and has a lot of dust I can't stop sneezing. And then the running nose comes. If I do not run away from the place, after some time my face becomes red and swollen and I have difficulty breathing. I cannot stay in a place with old carpet and animals, it makes me feel worse immediately.

As a kid I had a runny nose most of the time in the mornings and got better after noon.

My mum did everything she could to help me. I lived in Brazil and I had immunotherapy for many years. Immunotherapy was really helpful, but then I grew up and moved to different countries and I could not find any more treatment to follow and get better.

When I turned my 30ies, I had a lot of stress because of my work and symptoms got really worse, mainly on my skin. The atopic dermatitis showed up and I could not get rid of it anymore. So I had to avoid or reduce some food with cow milk, wheat flour, eggs and shrimp. I was itching the whole evening and then I woke up with a red and swollen face. Sometimes I did not have courage to go to the office, I felt ashamed of my appearance. Doctors only gave me corticoids to make me feel better for a few days, but after this period of prescription, all the symptoms came back. It was really hard to understand my problem and had some kind of relief from my symptoms.

I have lived in the UK for 6 years and I have never received a referral to an allergist.

I use loratadine almost every day but it is not working anymore. Whenever I go to the GP, they just give me a betamethasone cream for the skin and they don't care about my nose symptoms. I have a blocked nose 24x7, all the time. To be honest, I don't know what normal breathing is anymore. I live in a house with carpet. I try to clean it regularly and swap bed clothes regularly but it is almost impossible to be free from house dust. I also cannot use emollients for a long time. It works for a few days and then I start to have skin reactions and I have to stop using them.

My daughter has started having the same symptoms. She had a referral for an ENT but the doctor said she was not too bad to start an allergen immunotherapy and she was discharged.

I am so busy now with my work, children and housework that I stopped insisting on treatment with my GP. I have private health care but they did not accept my case as it is considered a chronic disease. So I gave up temporarily. Hope my daughter has more luck in the near future with new treatments and better health care.

Parent caring for a child with HDM allergy

My 16 year old son suffers from multiple food, environmental and animal allergies (including HDM), as well as eczema and Eosinophilic Esophagitis (EoE). When he was younger, his eczema was so severe that we made every effort to improve his condition. Based on numerous medical sources indicating that carpets can be allergen (HDM) repositories, we replaced all the carpets in our house with hard flooring. This change had an immediate and significant positive effect on his eczema, hay fever and asthma. Although he eventually outgrew his asthma, the other conditions persist, but we remain hopeful.
I believe house dust mites exacerbate my son's eczema and carpets, being difficult to clean, contribute to the problem. I am particularly concerned about the time when he has to go to University. When visiting some dormitories for my older son, I noticed that all have carpets, and I am unsure how accommodating they will be about replacing them. Sadly, I feel there is not enough awareness about this issue.
People often don't realise how challenging it is to live with multiple allergies. House dust mite allergies frequently coexist with other allergies, exacerbating conditions like rhinitis, eczema, asthma. It can also lower tolerance for food allergies, affecting concentration, exam's performance, social activities and potentially, mental health. Despite this, there is little understanding and almost no support.
By sharing our story, I hope to increase awareness of what it is to live with allergies. I also hope for greater compassion in the future, as allergies, eczema and asthma - which can be exacerbated by HDM - can qualify as disabilities, depending on their impact.

Parent and adult

Both my son and I have house dust mite allergy. It has proved impossible to keep the house as dust-free as would be required to alleviate symptoms (although we still try) and so I take an antihistamine every day and use a steroid nasal spray, and my son does these things occasionally too, but mainly just has a snotty nose. I worry that this allergy may progress towards allergic asthma for either of us or both of us, as I think this can be more serious.

I've been to our NHS GP quite a few times about this, and they suggested daily antihistamines plus the steroid nasal spray.

If it was proven to be safe, I would love for my son not to have this allergy. Ideally, it would be great for me not to have this allergy too.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Allergy UK
Location	Not specified
Conflict	Funding from ALK; Nov 2010 Dec 2010 £250 Apr 2015 Apr 2015 £5,000 Oct 2016 Oct 2016 £500 Plus travel exp. Jan 2017 Jan 2017 £500 Plus travel exp. Feb 2018 May 2018 £3,250 plus VAT Sponsorship Agreement Jan 2022 Mar 2023 £72,503 This last amount was for a series of projects which included masterclasses for HCP's, podcasts, video, article, online digital leaflet and top tips for managing asthma.£4,302 which includes VAT to collect comments from people affected by HDM allergy.
Notes	None
Comments on the DG:	
People or parents caring for a child living with house dust mite allergy Receiving a house dust mite allergy diagnosis is overwhelming. My son [redacted] lives with multiple allergies. He was diagnosed with aero allergies at the age of ten. The list of things that we had to introduce and change in our lives when we received the house dust mite diagnosis was extensive. We had to change to adapt a new routine for the whole family. For instance, [redacted] used to have a zoo of soft toys on his bed. They had to go. We had to all have new bedding which was suitable for people living with a dust mite allergy. A new Hoover that was able to pick up any bit of dust in his room and around the house. It also meant that 2 to 3 times a week, I deep clean his room and change his bedding every 5 days. This regime helped bring an improvement in the severity of the house dust mite symptoms, but it is a lot of work. Living with a house dust mite allergy is also costly; there are lots of new appliances – hoovers, bedding, new detergent, just to make your home one which is safe and comfortable for someone to be in.	

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Allergy UK
Location	Not specified
Conflict	Funding from ALK; Nov 2010 Dec 2010 £250 Apr 2015 Apr 2015 £5,000 Oct 2016 Oct 2016 £500 Plus travel exp. Jan 2017 Jan 2017 £500 Plus travel exp. Feb 2018 May 2018 £3,250 plus VAT Sponsorship Agreement Jan 2022 Mar 2023 £72,503

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Notes	None
Comments on the DG:	
[redacted] story is one that resonates with many people living with house dust mite allergy in the UK. Her journey began nearly a decade ago when she and her family moved to Yorkshire to renovate an old house. What started as seemingly innocuous symptoms ended up causing a significant impact her quality of life and day-to-day activities. Initially mistaking her symptoms for seasonal allergies or a cold she just couldn't seem to shake, [redacted] attempted to manage with over-the-counter medicines. However, as her condition worsened, she sought medical advice and was eventually diagnosed with house dust mite allergy. "It was a relief to finally have a name for what I was experiencing" [redacted] recalls, "But it was also the beginning of a challenging journey." [redacted] symptoms were wide-ranging and disruptive. She experienced severe headaches, persistent congestion, and intense sneezing fits - sometimes sneezing 10-15 times in succession. She often experienced fatigue, exacerbated by sleep disturbances due to severe nasal congestion that made breathing difficult. While benefiting from flexible working, there were times she had to adjust her schedule to accommodate the impact of her symptoms. "There were days when I had to step away and nap because I hadn't slept well the night before due to congestion," she explains. Avoidance strategies have been useful in managing her symptoms over the years. [redacted] avoids activities that might stir up dust and often wears her hair up to prevent dust collected on it from reaching her face. The family installed hardwood floors throughout the house to reduce dust mite habitats, in addition to maintaining a rigorous and demanding cleaning routine, including the use of a high-efficiency vacuum cleaner. Like many people with house dust mite allergy, [redacted] symptoms worsen during the autumn and winter months. The Christmas period, in particular, presents unique challenges. "I have to leave the task of retrieving decorations from the loft to another family member," [redacted] explains. "Then, I have to wait for the dust to settle from the decorations and tree before I can take part in the festivities. It's frustrating to not be able to fully engage in the Christmas preparations, as that's all part of the fun" In an attempt to manage her symptoms,[redacted] turned to antihistamines, beginning with over-the-counter tablets and then those prescribed by her GP. Despite this, she still suffered from the symptoms of her dust mite allergy. With [redacted] experiencing little relief from symptoms in her daily life, she was referred to an immunologist for immunotherapy to address the cause of her symptoms. [redacted] began sublingual immunotherapy almost three years ago, a decision she now describes as life changing. "I can't imagine ever going back to how life was before," she says. "The difference is significant." Through one wafer taken each day, [redacted] immune system was better equipped to handle exposure to dust mite allergens, noticing a difference	

within the first three months of starting her treatment. In addition to immunotherapy, [redacted] is also prescribed a nasal spray, though does not use it consistently.

The transformation in [redacted] quality of life since beginning treatment is evident. "When I look at old photos, I can see just how unwell I was," she reflects. "I look and feel like a different person now."

While [redacted] has found a routine that works for her, she emphasises the ongoing nature of living with house dust mite allergy. “It’s not something that goes away completely,” she says. “But through finding the right treatment and management strategies that work for you, I’ve found that it’s possible to reclaim your life and enjoy special moments– even during dusty Christmas preparations.”

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Evidence Assessment Group's Critique of the Company's Response to the Consultation of the Draft Guidance Document

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

Produced by	Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE) Technology Assessment Group, University of York, Heslington, York, YO10 5DD
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Date completed	15/10/2024

Note on the text

All confidential (CON) data have been highlighted in blue and underlined.

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1 OVERVIEW OF THE COMPANY'S RESPONSE TO THE DRAFT GUIDANCE DOCUMENT

The company provided 12 comments in response to the Consultation of the Draft Guidance (DG) Document. These relate to:

1. Details of the condition (DG Section 3.1)
2. Clinical management – allergic asthma (DG Section 3.3)
3. Eligibility criteria for people with allergic asthma (DG Section 3.5)
4. Applicability of trial data to NHS clinical practice (DG Section 3.7)
5. Clinical efficacy estimates (DG Section 3.8 and Section 3.9)
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The EAG provides a critical evaluation of the company's response to the DG where the company has either provided additional evidence, or has made a comment where additional clarification is required from the EAG. The company also presented updated base and scenario analyses following DG, as well revised base-case analyses. The revised base-cases incorporate additional assumptions compared to the updated base-case and represent the company's current set of preferred assumptions. The EAG's critique should be read in conjunction with the company's DG response document and the Evidence Assessment Report (EAR).

One issue which was not raised by the company, but which some stakeholders commented on, was the use of surgical treatments for allergic rhinitis. These comments suggested that surgery was not beneficial and that immunotherapy may avoid the need for surgery. The EAG's clinical adviser thought that surgery was rarely used for allergic rhinitis, since it gives only temporary relief and is therefore unlikely to provide a long-term solution.

2 CRITIQUE OF THE COMPANY'S COMMENTS IN RESPONSE TO THE DRAFT GUIDANCE DOCUMENT

2.1 Comment 3: Eligibility criteria for people with allergic asthma (Section 3.5)

The company re-stated the eligibility criteria for people with allergic asthma to be treated with 12 SQ HDM as "*patients with HDM AA diagnosed by clinical history and a positive test indicating HDM sensitisation (skin prick test or specific immunoglobin E (IgE)). Of these patients, those eligible for treatment with 12 SQ-HDM SLIT are those patients not well controlled by inhaled corticosteroids and associated with mild to severe HDM AR, aligned with the summary of product characteristics (SmPC). This could include patients treated with inhaled corticosteroids alone, or in combination with long-acting beta-agonists. HDM AA patients 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 three months*". However, this did not clarify the issue in section 3.5 of the draft guidance which was how 'asthma not well controlled by inhaled corticosteroids' would be defined or interpreted in clinical practice. The EAG asked their clinical adviser about how she interpreted 'not well controlled'; she thought interpretation of this term was very difficult, though noted that control relates to both frequency of symptoms and to there being no recent asthma exacerbations. This issue is also discussed in 2.2 ii) below.

2.2 Comment 4: Applicability of trial data to NHS clinical practice (Section 3.7)

The company commented on several aspects of the applicability of the trial data to NHS practice. The EAG would like to make a broad point about the key methodological issues raised in the EAR about the randomised controlled trials (RCTs). We consider that most of the methodological issues are a consequence of the trials being designed with a focus on regulatory approval, but with little attention to issues relevant to reimbursement decisions. The so-called "efficacy-effectiveness gap" (which describes the differences in outcomes between patients treated in RCTs and those treated in the real world) therefore may be large for the trials included in this appraisal, particularly the AA+AR trials. The EAG notes that two stakeholders made comments in response to the DG which allude to trial MT-04 being a "proof of principle" study. The EAG reiterates its concerns that the trials' results should not be considered as reliable estimates of the 12 SQ-HDM SLIT treatment effects expected to be seen in the UK NHS clinical practice.

i) *Company survey*: The company reported that an online survey was conducted to validate the conclusions of the MT-04 and MT-06 clinical trials in the context of UK clinical practice. It included responses from 46 UK healthcare professionals and reported that 89% of respondents believed the available clinical trial data supported the use of 12 SQ-HDM SLIT within its licensed indication in

UK clinical practice, and 76% believed that the available data supports improved AA control. However, the EAG notes that the survey did not ask specific questions about the methodological concerns about the trials which were raised in the appraisal, other than one question about outcomes in the pollen season. In addition, for reimbursement decisions, the ***magnitude*** of the effect of 12 SQ-HDM SLIT needs to be reliably estimated and this was not covered by the survey.

ii) *Inclusion criteria of MT-04:* The company stated that trial MT-04 excluded patients with Asthma Control Questionnaire (ACQ) > 1.5 at baseline because severe asthma is a risk factor for adverse reactions to AIT and treatment should not be initiated in this population. The EAG's clinical adviser considered the criterion of having an ACQ of 1.0-1.5 to be narrow and restrictive, with the upper limit not being a particularly good indicator of the presence of severe asthma.

The issue of how the marketing authorisation wording of asthma being 'not well controlled by inhaled corticosteroids' will be interpreted in practice remains. Stakeholders offered different opinions on ACQ thresholds and how they related to level of asthma control. One considered that an ACQ > 1.5 was not well-controlled, with scores of 0.75-1.5 being partially controlled. Another considered that 'uncontrolled asthma' was actively symptomatic ACQ > 1.0 and using SABA at least every week, despite concordance (sic - compliance?) with inhaled corticosteroids. The EAG also notes inconsistency in the company's interpretation: in the phase 2 company-sponsored Mosbech et al 2014 trial,[1] which the company cites in its response in support of the AA treatment benefit of 12 SQ-HDM SLIT, an inclusion criterion was "controlled asthma at enrolment (ACQ score < 1.5)", implying that patients with an ACQ < 1.5 have controlled asthma. Indeed, the Mosbech et al 2014 paper describes trial subjects as having controlled status throughout the trial, with little room for improvement. The EAG's concerns about the applicability of the MT-04 trial population to the NHS setting therefore remain.

The company added that the inclusion criteria of MT-04 were aligned with the SmPC and also with its anticipated place in therapy in the NHS. The EAG disagrees with this statement, noting that there is no mention of ACQ restrictions in the marketing authorisation and that patients with prior electronic diary compliance rates of < 80% in the run-up to randomisation were excluded from MT-04, even though such patients may be eligible for treatment with 12 SQ-HDM SLIT in the NHS setting. Given their lower diary compliance, these patients may be less likely to adhere well to treatment, so their exclusion is an important issue.

iii) *Mandated withdrawal of inhaled corticosteroids in MT-04:* The company accepted that this is not consistent with NHS practice, but stated that ensuring enough events to robustly estimate a statistically significant difference in asthma exacerbations was required from a regulatory perspective.

The EAG notes that given that HDM sensitive AA is not a rare disease, this could have instead been addressed by recruiting more patients e.g., by having less restrictive eligibility criteria – see ii) above. An important problem with the 50% and then 100% mandatory treatment withdrawal approach used in MT-04 is that the reported treatment effect may not have been driven so much by the efficacy of 12 SQ-HDM SLIT but by the lack of efficacy of the restricted routine care provided. The EAG considers that this approach does not provide efficacy data which are reliable enough for use in this appraisal. 12 SQ-HDM-SLIT's license states that reductions in asthma controller medication should be performed gradually and according to asthma management guidelines. The EAG reiterates that two stakeholders made comments which allude to MT-04 being a "proof of principle" study, and maintains that the study does not adequately represent the magnitude of effect that would be expected in NHS practice.

Furthermore, expert clinical advice received by the company suggested that the primary objective of treatment for AA is disease management, with stepping down treatment only considered once control is achieved. In a survey of 46 UK clinicians (including allergy, ENT, or respiratory consultants) where 94% (n=43) of respondents agreed AA control must be achieved before treatment can be stepped down[2] while in an advisory board where 71% (n=5) of respondents agreed that asthma control is the primary objective of AA treatment and that asthma control should be achieved before stepping down symptomatic medications.[3] This further supports the fact that the MT-04 trial design is not reflective of current clinical practice.

The company presented data from the Phase 2 Mosbech et al. trial[1] to "*support the AA treatment benefit of 12 SQ-HDM SLIT in addition to MT-04*". However, the benefits did not relate to exacerbations, but to reductions in ICS dose. The company did not mention the absence of statistically significant differences for the other assessed asthma outcomes: ACQ score, FEV1, peak expiratory flow and Asthma Quality of Life Questionnaire, reported by Mosbech et al.

iv) *Primary efficacy assessment outside of the pollen season:* The company presented one-year TCRS graphs of a post-hoc analysis of the MT-06 cohort split by sensitisation subgroup; no error bars or results of tests of statistical significance were presented, although the treatment benefit appears to be maintained throughout the year. No further data were available for trial MT-04 which was the trial the EAG had most concerns about, given that asthma exacerbations were only evaluated outside of the major pollen season.

v) *Prohibition of concomitant medications in MT-04 and MT-06:* The EAG views the company's stance on this issue as being contradictory. On the one hand the company considers that the prohibited elements of standard of care are not likely to meaningfully impact patient outcomes. On the other hand, the company states that the (prohibition of treatments) approach was taken to improve

standardisation between study arms and reduce potential confounding due to differences in standard of care medication use. The EAG highlights the particularly important prohibition of LABAs in MT-04, given their importance in routine asthma care. The full list of prohibited treatments is listed in Appendix N of the company's submission, with most treatments being excluded "due to possible interference with efficacy".

Reducing trial arm differences in standard of care means that patients will not be receiving standard of care, but less than standard of care. When comparing any active treatment with placebo in a clinical trial it is a reasonable expectation that the use of standard of care treatments may differ over time between study arms, with greater use expected in placebo groups. Attempting to reduce such differences by prohibiting the use of concomitant treatments underestimates how standard of care would be used in practice, which is likely to bias the trial's results in favour of the new intervention (in this case 12 SQ-HDM SLIT); NHS practice would allow use of the many treatments which trial MT-04 prohibited.

vi) *Duration of clinical trials:* The EAG notes some stakeholder comments supporting the use of trial durations of less than 3 years and of outcome measurement only at specific periods of the year. The EAG also notes that the company (ALK-Abelló) has sponsored two tablet immunotherapy trials with better external validity with respect to these issues. Valovirta et al.[4] reported an asthma preventative long-term RCT of SQ grass sublingual immunotherapy in children with grass pollen allergy; it used a 3-year treatment period followed by a 2-year follow-up period and had both Summer and Winter follow up visits. It is unclear why such methods were not also used for trials MT-04 and MT-06. Dahl et al,[5] reported on an RCT in adults receiving 3 years of treatment with grass tablet immunotherapy, followed by 2 years of further follow-up. However, the rhinoconjunctivitis symptom and medication score outcome were restricted to the pollen seasons. The company therefore has conducted long-term trials before, to reflect the treatment duration seen in practice but has also demonstrated variation in its adoption of restrictive outcome assessment periods.

2.3 Comment 3: Clinical efficacy estimates (Section 3.8 and Section 3.9)

The company stated that mean differences in the trials were impacted by the large placebo effects observed in both MT-04 and MT-06, reducing the relative treatment effect of 12 SQ-HDM SLIT in comparison with placebo, stating that "*The placebo effect observed in the clinical trials is believed to be due to participants being re-trained on how to use symptomatic medications during the clinical trial follow-up. Patients also had frequent contact with study clinicians, which would not be expected in routine clinical practice*". The EAG notes that while these effects may be real, they would be expected to be the same in each trial arm, so should not affect the validity of the relative efficacy results.

The company presented more real world evidence in the form of results from the Registry for Immunotherapy (BRIT) – a web-based registry for patients under the care of British Society for Allergy & Clinical Immunology (BSACI) consultants practising in the UK. The primary analysis considered two quality of life questionnaires. One assessed paediatric disease (PADQLQ), so some of the patients assessed –may have been outside of the population remit of this appraisal (the number of patients < 12 years old was not reported). The other assessed rhinoconjunctivitis (RQLQ). The BRIT data included [redacted] patients who initiated treatment with 12 SQ-HDM SLIT, although only [redacted] patients had measurements for either RQLQ or PADQLQ and only [redacted] had at least one subsequent measurement based on the same instrument. The mean age was [redacted] years and [redacted] had pre-existing asthma. The analysis considered only patients with a baseline measurement and at least one subsequent follow up measurement. No details or data were given on why data were missing. Data for RQLQ were available for only [redacted] patients and data for PADQLQ were available for only [redacted] patients. The EAG therefore concludes that these very limited data add little new to the evidence base.

2.4 Comment 6: Real-world evidence (Section 3.10)

The company presented preliminary results from RELY, a retrospective study set in Sweden & Denmark, which examined the effect of SQ SLIT tablets (grass and HDM) on symptom-relieving AR medication use in AR patients, with or without asthma. The company stated that the methodology used was aligned with the REACT study, with propensity matching used to identify control patients. The company considered that RELY's results suggest that one-year efficacy estimates derived from MT-04 and MT-06 are likely to underestimate the total benefit of treatment with 12 SQ-HDM SLIT. The EAG disagrees with this interpretation of the RELY study.

The company constructed a control group from the population of AR patients by matching based on the logit of the propensity score. The propensity score was defined as the probability of treatment using a logistic regression model with a subset of the baseline variables. There were discrepancies in the summary document, which made it unclear which variables the company matched on. Additionally, the company did not provide definitions or justify their choice of variables. Patients were matched without replacement using a greedy nearest neighbour search. The company matched the Danish and Swedish cohorts separately. Matching was considered successful if the standardised differences between the case and control variables were less than 10%.

The EAG considers propensity score matching to be an appropriate method to construct the control arm. However, the company did not provide sufficient reasoning for the decisions they made such as their choice of replacement method. The company also did not report the results of the propensity scores. In both the Danish and Swedish patient cohorts the company did not find any imbalances between the case and control groups. The EAG found the groups to be generally well-matched for

both cohorts; however, the number of patients in the final results after propensity matching was substantially lower than the number suggested as necessary in the power calculations.

Whilst the EAG acknowledges that the RELY report submitted by the company is preliminary, several important limitations were noted. Firstly, although 7168 patients were included in the study (3584 cases, 3584 controls) and were recruited retrospectively between 2005-2021, data were reported for only 4014 (56%) patients at year 2 and 1664 (23%) at year 3, raising concerns about treatment persistence (i.e. the proportion of patients who continued to take treatment, year on year). On a related issue, the level of adherence was not adequately reported nor recorded; "exposed" patients (i.e. those taking SQ SLIT-tablets) were identified via at least 2 dispensations of SQ SLIT-tablets within 365 days. This criterion means that patients who received one dispensation of SQ SLIT tablets and then stopped taking them were excluded from the study (so the study population is not sufficiently representative). Given that pack sizes are typically 30 or 90 tablets, the timeframe used for this criterion may also mean that some patients were not adhering adequately to SQ SLIT.

Other limitations noted by the EAG include:

- Results were not split by sub-population i.e. the type of SQ SLIT tablets taken – grass or HDM – and the proportion of patients in each of these subgroups is not reported
- No results were reported for asthma outcomes (they are: number of asthma dispensations in total, step down in treatment step, any asthma exacerbation, and any respiratory infection)
- No results were reported for the subgroups of "persistent" and "non-persistent" users

Although real world studies (such as REACT) have been used to inform long-term effectiveness parameters in this appraisal, the EAG would like to point out that these studies were not identified via a systematic review of the literature, so it was unclear whether all relevant studies had been identified and considered for inclusion in the model. The EAG has recently identified a large RWE study which casts doubt on the applicability of the MT-04 and MT-06 trial treatment adherence rates to real clinical settings. Pfaar et al.[6] conducted a retrospective, database study based on prescription data from statutorily insured German patients. Allergen immunotherapy (AIT) prescriptions were identified and for each prescription treatment durations were estimated using the manufacturer's recommendations. Non-persistence was classed as either: i) complete cessation of the AIT product, ii) a gap between successive AIT prescriptions exceeding 90 days, or iii) a switch to non-index AIT in the same allergen category. Analyses were stratified by allergen category (grass pollen, tree pollen or house dust mites) and mode of AIT: depigmented polymerized allergen extract (dSCIT), other subcutaneous AIT (oSCIT), and sublingual AIT (SLIT). In all allergen categories dSCIT had the highest persistence, followed by oSCIT, with SLIT inferior to both. Median persistence over all three

allergen categories ranged from 389 to 482 days for dSCIT, 258 to 370 days for oSCIT and 110 to 122 days for SLIT.

For HDM-SLIT specifically, the study reported low levels of persistence at one year, and very low levels of persistence at 3 years, as shown in Table 1 below. This is an important issue, given that i) the recommended minimum treatment duration for allergen immunotherapy is 3 years, ii) 12 SQ-HDM SLIT trial follow up durations are typically between 12 and 18 months (i.e. there are no 3 year data) and iii) the large differences in persistence between the available trial data and the real word data (around 80-90% of patients were still adherent at the end of the MT-04 and MT-06 trials). There is therefore uncertainty both about discontinuation rates for 12 SQ-HDM SLIT and the magnitude and persistence of treatment effect in patients who discontinue (See Section 4).

Table 1 Persistence of HDM-SLIT use in the study by Pfaar et al.

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

2.5 Comment 7: Modelling approach for AA+AR (DG Section 3.11)

Treatment stepping

The EAR highlighted that the differences in costs of standard of care between AA+AR model health states rely on a strong and implausible assumption that relative increases in ICS dose between levels of control observed in the MT-04 trial[7, 8] directly translate to a proportional increase in costs across all standard of care asthma medications. Furthermore, the EAG also noted that the approach taken to estimate standard of care treatment costs relies on numerous assumptions that are necessary due to a) the MT-04 trial not being reflective of UK clinical practice, and b) the company's modelling approach not reflecting transitions between health states defined based on treatment steps.

In response to DG, the company acknowledges that treatment stepping is an important part of the management of AA with AR in UK clinical practice, but emphasised that the primary objective of treatment for AA is disease management, with stepping down treatment only considered once control is achieved. The EAG details in Section 2.2, the evidence provided by the company to support these statements. The EAG does not dispute that asthma control is the objective of AA treatment, but rather that the AA+AR model does not appropriately capture AA management and that, for it to do so, the model structure should explicitly account for asthma disease progression over treatment steps, which are conditional on AA control. The AA+AR model structure in the original CS did not allow for patients who are uncontrolled to step up treatment until AA control is achieved or to step down treatment once sustained AA control is achieved. Finally, the MT-04 trial[7, 8] did not allow for

treatment to be delivered in accordance to NHS clinical practice (see Section 2.2), as ICS reductions were protocol driven rather than a function of control and introducing/withdrawing treatments conditional on control in accordance with clinical guidance was not allowed.

In the company's revised AA+AR base-case, the AA treatment cost differences between health states are no longer informed by the relative increase in ICS use between AA levels of control in MT-04 trial.[7, 8] Instead, the distribution of AA treatments is conditioned on AA control levels by imposing an assumed shift of the treatment distribution towards increasingly higher treatment steps when the level of AA control changes from 'well controlled' to 'partially controlled' and 'uncontrolled'. The company's revised base-case analysis assumes that the proportion of patients in treatment steps 1 and 2 are reduced (by 25% and 50% for partly vs. well controlled and uncontrolled vs. well controlled, respectively), and the proportion of patients in steps 3, 4, and 5 are correspondingly increased. The distribution of treatments by health state in the company's revised base-case is illustrated in Table 2, alongside the health state treatment costs in the company's updated and revised base-case.

Table 2 Distribution of treatments across steps and treatment costs in the company's AA+AR model

Treatment	Proportion of patients by treatment step in the company's revised base-case					
	12 SQ-HDM			Standard of care AA+AR		
	Uncontrolled	Partly controlled	Well controlled	Uncontrolled	Partly controlled	Well controlled
Step 1	15.48%	23.22%	30.96%	15.48%	23.22%	30.96%
Step 2	7.11%	10.67%	14.23%	7.11%	10.67%	14.23%
Step 3	62.34%	53.24%	44.14%	62.34%	53.24%	44.14%
Step 4	14.61%	12.48%	10.35%	14.48%	12.36%	10.25%
Step 5	0.46%	0.39%	0.32%	0.59%	0.50%	0.42%
Treatment costs in company's base-case						
Updated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The company justified their updated modelling approach for the AA treatment costs based on 80% [redacted] of the advisory board respondents agreeing that asthma control level would determine the distribution of patients across treatment steps. It is also important to note that the clinicians consulted on the advisory board [redacted].[3]

While the direction of shift in the treatment distribution across AA control may have clinical plausibility, the magnitude of this shift remains uncertain. The company's revised base-case merely replaces their original base-case assumption that the shift in treatment costs across AA control level can be informed by the relative increases in ICS dose between levels of control observed in the MT-04 trial by another assumption. The assumption introduced in the company's revised base-case is not supported by any additional empirical evidence.

Inclusion of AR management costs in the AA+AR model

When critiquing the AA+AR model structure, the EAR highlighted that this model did not explicitly model AR (cost and health) outcomes (Section 4.2), as the health states were defined strictly around AA control level. The DG stated that "*the model for people with allergic asthma with allergic rhinitis should also include the costs and benefits on allergic rhinitis in both treatment arms*". In the response to DG, the company has attempted to address this issue by revising the AA+AR model to include treatment arm specific AR treatment costs (also referred to as AR management costs) in the AR with AA patient population, assuming AR severity distributions within each AA control health state would be consistent with the baseline AR severity in MT-06.[7, 8]

It is unclear to the EAG why the company took this approach to address the committee's concerns. In the original version of the model the AR severity distribution informed by the company's Delphi panel[9] (rather than the MT-06 baseline AR severity[10, 11]) was used to derive a weighted average of AR treatment cost for the AA+AR. The AR severity distributions and weighted costs derived from alternative sources are show in Table 3, alongside the AR costs applied in the company's models. The company's new approach to incorporate AR treatment costs within the AA+AR model was implemented in addition to the AR costs already considered in the original CS and reported in the EAR. Thus, the EAG considers that this model update does not address the committee's concerns about the AA+AR model structure not explicitly modelling AR outcomes. Importantly, it introduces double counting of AR treatment costs. Furthermore, it is unclear to the EAG if the company considers either of the two AR severity distribution used to weight the AR treatment costs is more reflective of distribution of AR severity in the AA+AR population, as both these distributions are used to inform the company's revised base-case.

Table 3 Alternative AR severity distributions and AR costs in the AA+AR model

AR severity	Delphi panel		MT-06 baseline	
Mild	64.25%		0.00%	
Moderate	26.47%		58.68%	
Severe	9.28%		41.32%	
Treatment	**12 SQ-HDM**	**SoC**	**12 SQ-HDM**	**SoC**
Weighted cost of AR	[redacted]	[redacted]	[redacted]	[redacted]
AR costs applied by treatment	**12 SQ-HDM**		**SoC**	
Company updated base-case	[redacted]		[redacted]	
Company revised base-case	[redacted]		[redacted]	

Abbreviations: SoC, standard of care.

Modelling asthma exacerbations conditional on AA control

The key issue around the company's modelling approach for AA exacerbations in the AA+AR model, pertained to the use of evidence from the MT-04 trial[7, 8] to inform the AA exacerbations clinical effectiveness parameters. The EAG remains concerned that the MT-04 trial is not reflective of clinical practice as the pharmacotherapy delivered in both trial arms was not adjusted by stepping treatment up or down according to the level of asthma control, and because the protocol driven reduction of ICS for all patients in period 3 of the MT-04 trial would not be expected in the NHS. In the DG, the committee states a preference for an AA+AR model structure that is more reflective of the stepping up and stepping down of treatments and disease progression. Furthermore, the EAR noted that the company's assumptions on the risk of an exacerbation being independent of AA control level and that exacerbations do not affect subsequent health state membership were not clinically plausible, a concern that was incorporated into the DG.

The company's revised model has been updated so that the incidence of exacerbations can be conditioned based on a patient's current AA control level. The company did not identify data relating asthma control level to exacerbation risk in patients with HDM AA, or AA more generally. They did, however, highlight one study in patients with moderate to severe atopic asthma, which suggested that for each 1-point increase in ACQ score, patients risk of exacerbation in the following two weeks increased by 50% (hazard ratio, 1.50; 95% confidence interval, 1.03-2.20).[12] The company implemented this update by assuming that the incidence of exacerbations from MT-04 (ICS reduction phase) reflects patients with partly controlled AA, and that patients with controlled and uncontrolled AA experience 50% less, and more, exacerbations, respectively. The annual probabilities of exacerbation in the company's revised base-case are shown in Table 4.

Table 4 Annual probability of an exacerbation in the company's revised base-case

	12 SQ-HDM SLIT			Standard of Care		
	Well controlled	**Partly Controlled**	**Uncontrolled**	**Well controlled**	**Partly Controlled**	**Uncontrolled**
Moderate	18.01%	36.02%	54.04%	22.33%	44.66%	66.99%
Severe	4.01%	8.01%	12.02%	6.85%	13.70%	20.55%

The EAG's main concern regarding the company's approach is that the treatment specific baseline risk for AA exacerbations in the 'partially controlled' health state is still informed by the MT-04 trial[7, 8] ICS reduction phase, which is not representative of clinical practice (and is expected to be an overestimation – see Section 2.2).

The EAG considers that it would have been more consistent with the company's preferred model structure to estimate the probability of AA exacerbations conditional on level of control (rather than by treatment received) based on empirical evidence, and to let differences in the frequency of the exacerbations between treatments be driven by the treatment specific health state membership over time. The company's current approach potentially implies a treatment effect on exacerbations over and above, what was observed in the MT-04 trial.[7, 8] However, this would not resolve the issues raised by the EAG in terms of the appropriateness of the MT-04 trial data to inform clinical effectiveness in the AA+AR model (see Section 2.2).

Modelling asthma control based on GINA classification

In the EAR (section 4.2.6.), the EAG highlighted that the company mapped ACQ scores to GINA criteria[13] rather than directly using ACQ scores collected from patients in the MT-04 trial, to classify patients in terms of their asthma control, as per BTS/SIGN guidelines[14] and as implemented in the economic models of previous NICE TAs on asthma (e.g. TA565[15] and TA880[16]). In response to DG, which emphasised this aspect, the company acknowledged the EAG and the committee's preference for modelling asthma control level based on ACQ score rather than the GINA classification.[13] The company stated that the mapped GINA health-state classification, which was anchored on the GINA 2010 criteria,[13] was based upon the ACQ scores collected in MT-04. Furthermore, the company highlighted that the GINA classification used in the model is anticipated to be consistent with estimates directly obtained from ACQ measurements.

As no new evidence was put forward by the company on this matter in response to the DG, the EAG reiterates its concerns:

a) The company did not provided any rationale for the use of the GINA guidance, or the disregarding of other relevant guidelines (NICE[17] and BTS/SIGN[14]). Given that all these guidelines are commonly used in clinical practice in the UK, the EAG is concerned that the fundamental differences between them could imply different health-state classification in terms of asthma control;
b) The company's classification of patients in terms of their asthma control is not aligned with the classification implemented in economic models from previous NICE TAs on asthma (e.g. TA565[15] and TA880[16]);
c) One of the eligibility criteria of the MT-04 trial[7, 8] was that individuals would need to have ACQ scores of between 1.0 and 1.5 at randomisation. Thus, if the company were to follow the approach of previous TAs, all recruited patients in MT-04 would have been considered as having controlled asthma, while, according to the classification performed via GINA mapping of ACQ scores, 0% of patients in either arm of MT-04 were classified as having controlled asthma. Thus, in contrast to what the company states, the EAG believes that direct ACQ classification of patients is unlikely to be consistent with the GINA classification implemented by the company. Please see a discussion of ACQ classification in section 2.2.ii).

The EAG emphasises again that, at the core of EAGs concerns, is the use of the MT-04 trial[7, 8] evidence to inform the current decision problem, which, in the EAGs view is of limited use for decision making (as highlighted throughout the EAR, for which a summary can be found in the concluding section for the cost-effectiveness analysis, section 6.6., and here reiterated on section 2.2).

2.6 Comment 8: Adolescent allergic rhinitis population (DG Section 3.12)

The EAG noted that the company did not include any adolescent related evidence in the AR model, in the original CS, thus implicitly assuming that the evidence collected for the adult subpopulation in the MT-06 trial[10, 11] was directly generalisable to the full population in the AR model (see Section 4.2.3., EAR). At the clarification stage, the company provided evidence from P001[18, 19] and TO-203-32 trials[20, 21] which included adolescent patients, but indicated that it would be impossible to incorporate any point estimates from the P001 trial in the cost-effectiveness model for AR. However, the company did provide and incorporate data for adolescents aged 12-17 years from the P001 trial[18, 19] in the AR treatment specific health-related quality of life (HRQoL), which suggests greater benefits for this subpopulation compared with adults. The DG noted that the cost-effectiveness of 12 SQ-HDM SLIT in the adolescent subpopulation remained an area of uncertainty that would need to be resolved by additional evidence on health-related quality of life for this subpopulation.

In response to the DG, the company provided a scenario analysis over their revised base-case, assuming a starting age of 12, and the difference in health-related quality of life collected in the

P001[18, 19] adolescent subgroup rather than MT-06.[10, 11] The company notes in their response to DG that, based on the reduction in TCRS in comparison with placebo in the P001 study in the adult and adolescent subpopulations (19.2% and 22.4%, respectively), the assumption of generalisability across subpopulations is conservative. Furthermore, the company provided the results of a survey of UK clinicians,[2] which suggested that *"only 2% of respondents believed that a similar or equivalent response to 12 SQ-HDM SLIT would not be observed between adult and adolescent patients"*. All clinicians in the company's advisory board, believed that 12 SQ-HDM SLIT would perform equivalently in adolescent and adult patients.

The EAG considers that this scenario analysis does not necessarily overcome the absence of treatment effectiveness evidence for the adolescent subpopulation in the AR model, as the source of treatment effectiveness remains the MT-06 trial which included only adults (18-65 years of age).[10, 11] Even if the (short and long-term) effectiveness can be assumed equivalent for the adolescent and adult subpopulation, the issues affecting the effectiveness data from MT-06[10, 11] (see Section 4.2.6., EAR) and the uncertainties introduced by this still remain. The EAG also notes that the trial utilities for the adolescent subpopulation from trial P001[18, 19] in the company's scenario analyses are treatment specific, and that corresponding health state specific utilities were not made available by the company. This means that the EAG cannot formally explore the impact use of alternative approaches to HRQoL on cost-effectiveness (see Section 1.5, issue 9, EAR), for the adolescent subpopulation.

2.7 Comment 9: Long-term effectiveness and retreatment (DG Section 3.13)

Another key aspect raised by the EAG relates to the assumptions introduced by the company for both AA+AR and AR models on the medium to long-term effectiveness of 12 SQ-HDM SLIT. The EAG considered the assumed improvements in health for 12 SQ-HDM SLIT from 2 to 10 years not to be supported by published evidence. The EAG considered also that any long-term effectiveness assumptions beyond 9 years were subjective and very uncertain, and that no evidence existed to support any assumptions beyond 20 years.

In response to the DG document, the company justifies their medium to long-term effectiveness assumptions by: i) highlighting the findings of the REACT study,[22] stating that, over a maximum of nine-years of follow-up, there was no indication of waning or loss of treatment effect for patients treated with AIT, caveating that the pooled analysis is based on AIT (mostly SCIT) and for a variety of allergens; ii) presenting results of the RELY RWE study with up to five years of follow-up, where it is claimed that the effect of treatment with 12 SQ-HDM SLIT increases beyond one year, and that the long-term outcomes associated with SCIT are likely to be generalisable to SLIT (see Section 2.4); iii) considering that the immediate loss of treatment effect after 10 years, as per the EAG's base-case,

is implausible, conservative and incompatible with available evidence; and iv) highlighting the findings of the Delphi panel as described in the original submission.

The EAG notes that:

a) as highlighted in the EAR (section 4.2.6.2), the EAG considers the opinion of the Delphi clinical experts' panel to be aligned with the findings of the REACT study[22] (conditional on the limitations of this study as described in section 3.2.3 of the EAR), in that the effectiveness of 12 SQ-HDM SLIT is likely to be maintained for at least 10 years. Figure 1, reproduced from the REACT study,[22] shows constant change in AR prescriptions in the SLIT-tablet subgroup from year 1 to year 9. There is no clear evidence to support an increment in the effect of treatment over time. The company's assumptions of improvements in health for 12 SQ-HDM SLIT from 2-5 and 5-10 years are therefore not justified. The EAG considers the annual rates of change used by the company, and reflecting an increment of the effect of 12 SQ-HDM SLIT from 2-10 years, to be arbitrary and not aligned with the available evidence.

b) The RELY RWE study preliminary findings seem to indicate that, over a 5-year period and for AR patients with or without asthma, reductions in AR prescriptions generally increased over time, with the AIT group experiencing greater prescription reductions in comparison with the matched controls. The EAG notes that the study population included not only patients with the HDM allergen but also grass allergen, and that no subgroup analysis results have been presented for HDM-related AA+AR and AR allergies. Thus, the EAG considers the RELY study preliminary findings to be of limited value for the current appraisal. Please see section 2.4 for further details.

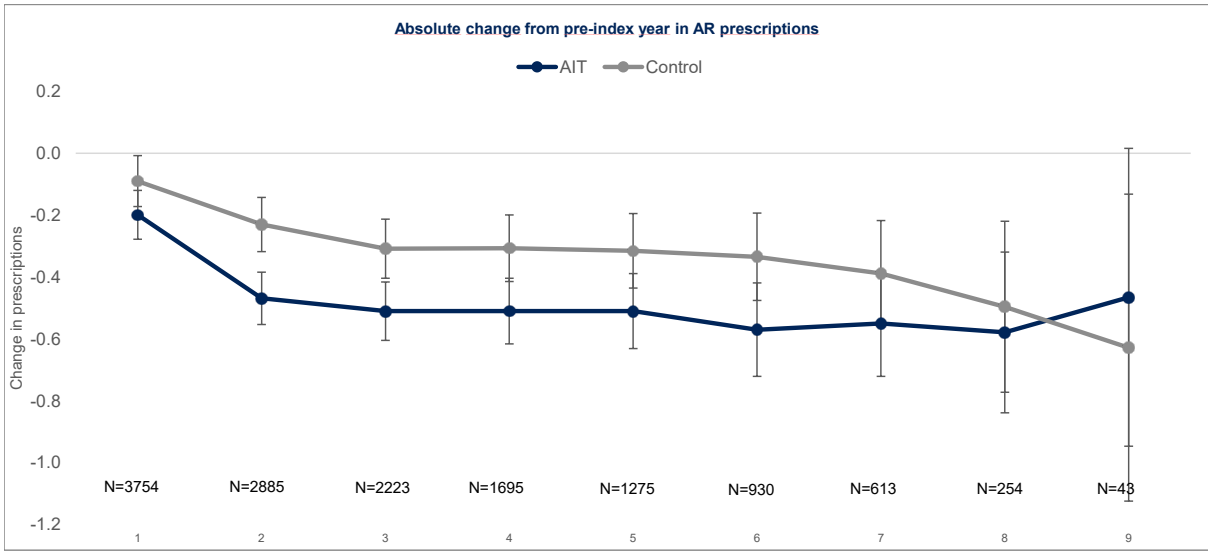
c) As for the 10-20 years period, no new evidence has been presented by the company in response to the DG and, thus, the EAG reiterates that the only available evidence is from clinical experts in the advisory boards, which mentioned that a potential waning effect over the 10-20 years period was unlikely to completely disappear. The EAG considers the company's assumption of 12 SQ-HDM SLIT treatment waning initiation in year 15 of the model to be arbitrary, as is the assumption of 80% of the patients in the 12 SQ-HDM SLIT arm matching the distribution of patients in the standard of care arm by year 20. Thus, the EAG believes that any long-term effectiveness assumption beyond 9 years is subjective and very uncertain, with no evidence beyond 20 years. Recognising this uncertainty and the conclusions of the advisory boards on this matter, the EAG carried out a number of further scenario analyses over the EAG's preferred base-case analysis, considering different waning assumptions. Results of these analyses can be found in the EAR, section 6.5.

d) Findings from the REACT study[22] indicate that differences exist with respect to observed changes in AR prescriptions over time between AIT (SCIT+SLIT) and SLIT only subpopulation. While in the

AIT group reductions in AR prescriptions generally increased over time, for the SLIT subpopulation reductions in AR prescriptions did not increase over time – see Figure 1. The EAG considers the RELY RWE study preliminary findings to somewhat contradict the findings of the REACT study, where reductions in AR prescriptions generally increased over time for SQ HDM SLIT. Thus, the EAG considers that no clear evidence exists to support the claim that long-term outcomes associated with SCIT are generalisable to SLIT, and, thus, that this remains an area of uncertainty.

e) Finally, as stated in the EAR, the EAG's clinical expert considered that the medium to long-term benefit of treatment with 12-SQ HDM SLIR is predicated on the assumption of a 3-year treatment duration. Treatment durations lower than 3 years would imply shorter or no medium to long-term benefit, and these may lead to the need for retreatment. The EAG agrees with the company's assumption that retreatment with 12 SQ-HDM SLIT is likely to be infrequent, although the fact that its likelihood is clearly conditional on initial treatment duration, has also been highlighted by the EAG's clinical expert. The EAG does not consider retreatment with 12 SQ-HDM SLIT to be a key aspect of this appraisal or a key driver of the economic analysis results.

Figure 1 REACT study[22] - Change from pre-index year in AR prescriptions in SLIT-tablet subgroup.



2.8 Comment 10: Primary and secondary resource use (DG Section 3.14)

The EAR highlighted the uncertainties associated with the company's approach to modelling the impact of 12 SQ-HDM SLIT in primary and secondary care use compared to standard of care in both the AA+AR and AR models (see Section 1.5, issue 10, EAR). The EAG's base-case used alternative data sources to inform the reduction in primary and secondary care resource use (see Table 6 and Table 7) with 12 SQ-HDM SLIT compared to SoC. The rationale for preferring these data sources is detailed in EAR (see Section 4.2.8.6). In the DG, the committee noted concerns that savings in primary and secondary care costs associated with 12 SQ-HDM SLIT might be overestimated and that

additional evidence to support the company's modelling assumptions for the extent of any reduction in primary or secondary care visits associated with 12 SQ-HDM SLIT, would be needed. The committee also stated that if data from people having subcutaneous house dust mite SCIT was used to estimate the relative reduction in secondary care for 12 SQ-HDM SLIT, justification that reduced secondary care visits for subcutaneous immunotherapy could be generalised to sublingual immunotherapy would be needed.

In the company's response to DG, the company states that there is consistent evidence from both RCTs and real-world data that AIT treatment reduces healthcare resource utilisation, which applies to both primary and secondary care visits in both the AR+AA with AR patient populations. The evidence presented to support this statement includes studies which were included in the original CS, and therefore, the EAG does not consider it necessary to critique this evidence again (see Section 4.2.8.6, EAR). The new evidence presented in response to DG consists of:

1 Unpublished real-world data collected by the company
   The RELY study (see Section 2.4 for the EAG's critique) statistically significant reductions in AR prescriptions for patients treated with SQ HDM SLIT in comparison with matched controls in the context of clinical practice in Denmark and Sweden, across a 5-year time horizon.
2 Clinical opinion collected by the company in
   2.1 An online survey of UK clinicians[2]
   The survey found that [redacted] Furthermore, the large majority (43 (93.5%) anticipated a reduction in symptomatic medication use with treatment with 12 SQ-HDM SLIT).
   2.2 An advisory board of UK clinicians[3]
   All 9 respondents agreed "[redacted]

The company also reports, a scenario analysis performed over the company's revised base-case and assuming the lowest reduction in secondary care visits identified in the literature (odds ratio 0.72 for AIT vs. control in all hospitalisation [including outpatient and inpatient admissions] reported in the REACT study for the pre-existing asthma cohort, corresponding to a 28% risk reduction[22]) for both the AA+AR and AR models. The EAG highlights that REACT is based on AIT (mostly SCIT) and for a variety of allergens, and that estimates of effect on hospitalisation compared to control are not presented separately for i) SCIT and SLIT or ii) by allergen, so the EAG cannot comment on the generalisability of the results to 12 SQ-HDM SLIT. In addition, the company stated that a threshold

analyses was run to identify the reduction in secondary care visits that would result in 12 SQ-HDM SLIT being cost neutral under the revised base-case assumptions; the reduction was of 20.15% and 37.18% in the AA and AR, and AR models, respectively. The updated model does not have functionality to run any of the analyses referred in this paragraph, but the EAG was able to reproduce the company's results. The results of these scenario analyses performed over the company's revised base-case were not reported in full in the company's submission and, thus, they are not discussed in Section 3.

The EAG notes that these reductions in primary and secondary care visits are incorporated into both the company's and EAG base-cases for the AA+AR and AR models. The key uncertainty is around the magnitude of effect of treatment on health care resource use; an uncertainty that is recognised by the company as part of their submission their response to DG.[23] The evidence presented by the company does not provided an alternative set of treatment effect estimates on the primary and secondary care use of 12 SQ-HDM SLIT compared to standard of care that the EAG considers preferable to the sources used in the EAG base-case.

2.9 Comment 11: Modelling health-related quality-of-life (DG Section 3.15)

One of the key aspects raised by the EAG around modelling HRQoL was that the treatment-specific approach considered by the company in their base-case does not align with the model structures developed for AA+AR and for AR, respectively. In response to the DG document, the company justifies the use of treatment-specific utilities as base-case by stating that: i) it believes it will consider the totality of the benefit associated with 12 SQ-HDM SLIT to patients; ii) it captures the totality of the disease burden as utility estimates were derived from generic health-related quality-of-life instruments collected as part of the MT-06[10, 11] and MT-04[7, 8] clinical trials, using EQ-5D and SF-36 instruments, respectively; and iii) aligns with the explicit preferences stated by NICE in the methods guide, stating that generic measures collected directly from clinical trial data are preferred over mapped utility values.

The EAG maintains its preference for the use of health state specific utilities. The EAG notes that:

a) NICE Decision Support Unit Technical Support Document 12,[24] which provides guidance on the use of utility data in economic models, clearly states that "*Ideally each individual health state in the model would be populated using health-state utility values derived from patients whose health condition(s) reflect the health state definitions used in the model.*" Furthermore, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force Report on the estimation of health-state utilities for economic models[25] reinforces this by stating that: "*When clinical trials are used to collect health-state utility data, it is often the case that the approach to the analysis is strongly influenced by the standard, between-arm*

comparisons that are used for regulatory submissions. However, if reimbursement submissions are to be made using an economic model, then it is more appropriate that the health-utility data in a clinical trial be analyzed to inform that model, rather than be analyzed by treatment arm.". This ISPOR report provides also an example where a traditional by-arm comparison failed to show significant utility differences identified when considering relevant clinical events;

b) Furthermore, the EAG considers the use of treatment specific utilities, which are assumed constant across asthma control levels and rhinitis severity, not to have clinical validity. That is, the EAG believes that attributing the same utility estimate to an uncontrolled, a partially controlled and a controlled asthma health state, not to appropriately represent individuals' HRQoL in each of these mutually exclusive health states. Similar critique can be done over the use of treatment specific utilities for the different AR severity health states.
c) The NICE manual on health technology evaluations, on section 4.3.9 and figure 4.1, states that "*When EQ-5D data is not available, this data can be estimated by mapping other health-related quality-of-life measures or health-related benefits seen in the relevant clinical trials to EQ-5D.*", and also that only if evidence shows that EQ-5D is not appropriate, then the use of other generic preference-based measures may be considered.[26]
d) For the AA+AR model, the EAG is in agreement with the company's view that the Asthma Quality of Life Questionnaire (AQLQ) assessment responses collected in MT-04,[7, 8] and mapped to EQ-5D, will not capture the impact of AR on patient outcomes, as the AQLQ questionnaire is only sensitive to changes in AA symptoms;
e) The SF-36 instrument can be used to generate preference-based index values via the SF-6D.[27] However, SF-6D index values have been found to substantially differ from EQ-5D index values for a number of patient/population groups, including chronic obstructive airways disease.[28] A validated and broadly used mapping algorithm is available to map SF-36 onto EQ-5D index values.[29]

Thus, for both AA+AR and AR models, the EAG considers that the appropriate approach to the modelling of HRQoL is to consider health-states utility values. For the AA+AR model, the EAG considers that, using the SF-36 instrument, the company could have derived health-state specific utilities by: a) directly generating preference-based index values via the SF-6D, but estimating utilities for each health state, according to patients classification into controlled, partially controlled or uncontrolled asthma; or b) generating EQ-5D index values by mapping SF-36 responses using the Rowen et al.[29] mapping algorithm, and subsequently estimating utilities for each health state, according to patients classification into controlled, partially controlled or uncontrolled asthma. The latter is the EAG's preferred approach as it aligns with the requirements and hierarchy of evidence, as set out in the NICE manual on health technology evaluations.[26] It aligns also with the relevant

literature around the use of SF-36 responses to derive utility index values.[28] The EAG is unable to carry out either a) or b) analyses as we do not have access to the relevant data, but the company could perform these analyses.

2.10 Comment 12: Cost-effectiveness estimates (DG Section 3.15)

The company claims to have made significant revisions to the economic model to better reflect the preferences of the committee, with all the changes nominally improving the cost-effectiveness of 12 SQ-HDM SLIT compared to the standard of care, and that only residual (decision) uncertainty remains.

The EAG highlighted throughout these report that the evidence provided by the company, including the economic model updates, do not address the key issues raised in the EAR and the committee discussion at ACM1. In Section 3, the EAG critiques the company's additional cost-effectiveness results.

3 CRITIQUE OF THE COMPANY'S ADDITIONAL COST-EFFECTIVENESS ANALYSES

3.1 Summary of the company's additional analyses

The company submitted in response to the DG an updated version of the economic model for the AA+AR and AR populations, alongside a separate document summarising the modelling updates and analyses.[23] In this document, the company reports the results of "corrected" base-case analyses for the AA+AR and AR population (see Table 1 and 3 of the company's document).[23] The EAG refers to the company's "corrected" base-case as the company's updated base-case to avoid confusion with further analyses conducted by the EAG in Section 4. The company also presents results for the revised base-case analyses which incorporate additional assumptions compared to the updated base-case and represent the company's current set of preferred assumptions (see Table7 of the company's document);[23] these assumptions are detailed in Table 6. In addition, the company presents a revised base-case for the adolescent AR subpopulation assuming a starting age of 12, and the treatment specific difference in HRQoL collected in the P001 adolescent subgroup[18, 19] rather than MT-06[10, 11] (Table 4, in the company's document).[23] All of the company's analyses results are deterministic.

The company's does not describe the corrections that have been implemented into the updated base-case analyses, and does not justify their inclusion. Through examination of the economic version of the model, the EAG established that the company did not fully incorporate into their model the corrections performed by the EAG to the company's original base-case analyses (see Section 6.1,

EAR). Table 6 describes the EAG corrections and illustrates which ones were included by the company in their updated model.

Table 5 Corrections to the company's updated base-case model

Parameter	Correction implemented by the EAG (Section 6.1, EAR)	Included by the company in the updated model
Proportion of AA+AR patients to discontinue	Corrected the proportion of patients receiving 12 SQ-HDM who discontinue for other non-exacerbation related reasons (corrected proportion of 8.87%, instead of 8.49%)	Yes
Unit costs of salbutamol, ciclesonide, desloratadine and Sodium cromoglicate	Revised to reflect the costs in the latest version of eMIT. Where information of the setting (primary or secondary care) of where the drug is used was not obtained, the EAG assumed 50% use in each setting.	No
Management costs – annual cost of GP visits for standard of care in the AR population	Corrected the estimate for the costs of annual GP visits for standard of care which were mistakenly multiplied by the proportion of patients in mild, moderate or severe severity levels, respectively.	No
Management costs – relative reduction associated with 12 SQ-HDM for the AA+AR population	Corrected the relative reduction in GP/specialist visits to exclude the randomisation period in MT-04 and consider visit 4 to 13 (corrected relative reduction estimate of 31.19%, instead of 25.76%). This correction was proposed by the company in their reply to points for clarification (B21), but, although mentioned as being part of the company's base-case, it was not updated in the electronic version of the AA+AR model.	Yes
Standard errors of exacerbation disutilities for the different observation periods	The SEs of the disutility related moderate and severe exacerbations for the different observation periods (7, 14, 21 and 28 days), sourced from Briggs et al.[30], were negative and not accounted for in the probabilistic modelling. The EAG assumed the absolute value of the SE of the disutilities provided and linked these to the probabilistic modelling.	Yes

Abbreviations: AA: allergic asthma, AR: allergic rhinitis, HDM: house dust mite, eMIT: electronic market information tool, GP: general practitioner, EAG: expert advisory group, SE: standard error

The company conducted a number of scenario analyses, which are described and reported in the document summarising the modelling updates and analyses(see Tables 1 to 6 of the company's document).[23] None of the scenario analyses had a sizeable impact on the estimates of cost-effectiveness.

For the AA+AR population, the company's revised base-case analysis is broadly similar to their original base-case; the company's revised base-case assumptions differ from the original's (and from the updated base-case) in terms of:

- Distribution of AA treatment across steps conditional on AA control;
- Inclusion of AR management costs in the AA+AR model;
- Risk of asthma exacerbations conditional on AA control.

Table 6 illustrates the differences between the company's original base-case and their revised base-case in response to the DG consultation, alongside the EAG base-case (which has remained unchanged from the EAR) for the AA+AR population. For the AR model, both the company's and the

EAG's base-case assumptions remain unchanged from those presented at ACM1. The EAG contrasts the differences between the company's base-case assumptions and the EAG's for the AR model in Table 7.

Table 6 Comparison of EAG and company's base-case assumptions: AA+AR model

Assumption	EAG base-case	Company's original base-case	Company's revised base-case in response to DG
Evidence source to inform short-term effectiveness	MT-04 maintenance period[7, 8]	MT-04[7, 8] ICS reduction period[7, 8]	No change from the company's original base case
Medium to long term effectiveness	Patients in the 12 SQ-HDM SLIT treatment arm match the distribution of patients in the standard of care arm post-10 years. No treatment waning.	Patients in the 12 SQ-HDM SLIT treatment arm match the distribution of patients in the standard of care arm post-20 years. Treatment waning initiation in year 15 of the model and waning end in year 20, 80% of the patients in the 12 SQ-HDM SLIT arm matching the distribution of patients in the standard of care arm by year 20	
Model utilities	Health state specific utilities and informed by Briggs et al.[30] using AQLQ data from MT-04 mapped to EQ-5D-3L	Treatment specific utilities informed by SF-36 data from MT-04 mapped to SF-6D	
Distribution of biologic treatments for patients at Step 5 of GINA guideline	33% omalizumab and 33% tezepelumab.	17% omalizumab, 17% tezepelumab, 17% mepolizumab and 17% dupilumab	
Evidence source to inform reduction in primary and secondary care appointments	MT-04 maintenance period[7, 8]	MT-04[7, 8] ICS reduction period[7, 8]	
AA treatment costs	Same distribution of AA treatments (CARIOCA study) across levels of AA control and AA treatment costs differences between health states are informed by the relative increase in ICS use between AA levels of control in MT-04 trial[7, 8]	Same as EAG base-case	Different distribution of treatments across levels of AA control informed by the assumption that occupancy in step 1 & 2 is reduced by the same proportion that it is increased in step 3-5, with the following proportions: . 25% for 'partly' vs. 'well controlled'; . 50% for 'uncontrolled' vs. 'well controlled'. The baseline distribution of treatments by step, i.e., the 'well controlled' state distribution is informed by the CARIOCA study.
Inclusions of AR treatment costs in the AA and AR model	AA+AR health state treatment costs incorporate treatment specific AR health state costs by adding to each AA health state treatment cost:	Same as EAG base-case	AA+AR health state treatment costs incorporate treatment specific AR health state costs by adding to each AA health state treatment cost:

	. the AR health state treatment costs weighted by the distribution of AR severity as informed by the company's Delphi panel.		. the AR health state treatment costs weighted by the distribution of AR severity as informed by the company's Delphi panel, and; . the AR health state treatment costs weighted by the distribution of AR severity as informed by the baseline distribution in MT-06.[10, 11]
Risk of AA exacerbations	Independent of level of AA control, informed by the MT-04ICS reduction period[7, 8]	Same as EAG base-case	Dependent of level of AA control. Assumes treatment specific probabilities of AA exacerbation derived from the MT-04ICS reduction period[7, 8] apply to 'partially controlled' health state and applies assumed RR to derive probabilities in the health states: . 'Well controlled': RR=0.5 . 'Uncontrolled': RR=1.5

AA, allergic asthma; AQLQ ,asthma quality of life questionnaire; AR, allergic rhinitis,; ICS, intranasal corticosteroids; RR, relative risk.

Table 7 Comparison of EAG and company's revised base-case assumptions: AR model

Assumption	EAG base-case	Company's revised base-case in response to DG
Medium to long term effectiveness	Patients in the 12 SQ-HDM SLIT treatment arm match the distribution of patients in the standard of care arm post-10 years. No treatment waning.	Patients in the 12 SQ-HDM SLIT treatment arm match the distribution of patients in the standard of care arm post-20 years. Treatment waning initiation in year 15 of the model and waning end in year 20, 80% of the patients in the 12 SQ-HDM SLIT arm matching the distribution of patients in the standard of care arm by year 20
Model utilities	Health state specific utilities informed by EQ-5D-3L from MT-06[10, 11]	Treatment specific utilities informed by EQ-5D-3L from MT-06[10, 11]
Evidence source to inform reduction in secondary care appointments	MT-06 (4.92% relative reduction)[10, 11]	El-Qutob et al. (73.53% relative reduction)[31]

3.2 Critique of the company's additional analyses

The EAG has a number of concerns about the assumptions incorporated in the company's revised base-case, which have been highlighted in Section 2.5. In brief the EAG is concerned that:

- While it seems clinically plausible that the AA treatment costs are conditional on AA, the size of this shift is uncertain and not driven by empirical evidence but by assumptions (similarly to the approach in the company's original base-case). Importantly, The EAG does not consider that this model update addresses the issues raised in the EAR (Section 1.5, key issue 10).
- The inclusion of AR management costs in the AA+AR model was not necessary as the original model already incorporated these costs and it introduces double counting of AR costs;
- The assumptions introduced to condition the asthma exacerbation risk on AA control, introduce an additional treatment effect 12 SQ-HDM SLIT compared to the standard of care, the magnitude of which has not been validated by the company. The EAG considers that it would have been more consistent with the company's preferred model structure to estimate the probability of AA exacerbations conditional on level of control (rather than by treatment received) based on empirical evidence, and to let differences in the frequency of the exacerbations between treatments to be driven by the treatment specific health state membership over time. This alternative approach would not, however, resolve the issues raised by the EAG in terms of the appropriateness of the MT-04 trial data[7, 8] to inform clinical effectiveness in the AA+AR model (see also Sections 2.2 and 2.3).

Importantly, the EAG considers that the economic evidence presented by the company does not change the conclusions of the cost-effectiveness section (Section 6.5, EAR). To illustrate this, the EAG conducts further cost-effectiveness analyses in Section 4.

4 EAG ADDITIONAL ANALYSES

The EAG corrected the company's revised base-case by:

- Implementing the full set of EAG model corrections described in Table 5 as the company's partial implementation of these corrections was not justified (see Section 2.5);
- Removing the additional inclusion of AR management costs in the AA+AR model, as this potentially double counting of these costs (see Section 2.5).

The company's revised base-case following is henceforth referred to as the company's corrected base-case.

The EAG also performed additional analyses over the company's corrected base-case to examine the individual impact of the EAG preferred assumptions (see Table 6 and Table 7) for:

- Medium to long-term effectiveness;
- Model utilities;
- Reduction in secondary care use with 12 SQ-HDM SLIT

The results of the company's corrected base-case for the AA+AR population and EAG scenarios performed over this are reported in Table 8, alongside the EAG base-case analysis (which remains unchanged from the EAR). The corresponding set of analyses for the AR population are presented in Table 9.

Table 8 Deterministic cost-effectiveness results for the EAG's additional scenarios over the company's base-case assumptions – AA+AR population

	Total Costs	Total QALYs	Incr. Costs	Incr. QALYs	ICER (£/QALY gain)
EAG base-case					
Standard of care	£26,780	18.47			
12 SQ-HDM	£28,676	18.48	£1,895	0.02	£123,269
Company corrected base-case					
Standard of care	£ 26,728	15.73			
12 SQ-HDM	£ 24,474	16.11	-£2,254	0.37	12 SQ-HDM dominant
Sc.1 Company corrected base-case + evidence based medium to long-term effectiveness assumptions*					
Standard of care	£26,728	15.73			
12 SQ-HDM	£26,682	15.94	-£45	0.21	12 SQ-HDM dominant
Sc.2 Company corrected base-case + health state specific utilities sourced from Briggs et al.[3]					
Standard of care	£26,728	18.57			
12 SQ-HDM	£24,474	18.64	-£2,254	0.07	12 SQ-HDM dominant

Sc.3 Company corrected base-case + 7.35% relative reduction for 12 SQ-HDM SLIT on secondary care visits**					
Standard of care	£26,728	15.73			
12 SQ-HDM	£27,681	16.11	£953	0.37	£2,547

*considering a sustained effect from 12 SQ-HDM from 2 to 10 years and where the distribution of patients in the 12 SQ-HDM SLIT treatment arm matches the distribution of patients in the standard of care arm post-10 years

**assumed the same as for the primary care relative reduction in MT-04 maintenance period

Abbreviations: HDM, house dust mite; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Sc., scenario.

Table 9 Deterministic cost-effectiveness results for the EAG's additional scenarios over the company's base-case assumptions – AR population

	Total Costs	Total QALYs	Incr. Costs	Incr. QALYs	ICER (£/QALY gain)
EAG base-case analyses					
Standard of care	£15,580	18.68			
12 SQ-HDM	£18,116	18.73	£2,536	0.05	£50,479
Company corrected base-case					
Standard of care	£ 15,580	19.03			
12 SQ-HDM	£ 12,681	19.29	-£2,899	0.26	12 SQ-HDM dominant
Sc.1 Company corrected base-case + evidence based medium to long-term effectiveness assumptions*					
Standard of care	£15,580	19.03			
12 SQ-HDM	£15,366	19.17	-£214	0.14	12 SQ-HDM dominant
Sc.2 Company corrected base-case + health state specific utilities from MT-06					
Standard of care	£15,580	18.68			
12 SQ-HDM	£12,681	18.80	-£2,899	0.12	£8,550
Sc.3 Company corrected base-case + 4.92% relative reduction for 12 SQ-HDM SLIT on secondary care visits**					
Standard of care	£15,580	19.03			
12 SQ-HDM	£17,836	19.29	£2,256	0.26	£8,550

*considering a sustained effect from 12 SQ-HDM from 2 to 10 years and where the distribution of patients in the 12 SQ-HDM SLIT treatment arm matches the distribution of patients in the standard of care arm post-10 years

**from MT-06

Abbreviations: HDM, house dust mite; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Sc., scenario.

The EAG additional analyses suggest that the key cost-effectiveness drivers for both populations remain the same as those identified in the EAR (see Section 6.4).

The EAG noted in Section 2.4, that there is uncertainty surrounding the discontinuation rates for 12 SQ-HDM SLIT over time in clinical practice and the impact of discontinuation on the persistence of treatment effect. To explore how this uncertainty may impact on the estimates of cost-effectiveness the EAG conducted additional analyses where the discontinuation rates for 12 SQ-HDM SLIT are varied to extreme values (0% and 100%), as well as applying estimates derived from Pfaar et al.[6] (Table 1, 18 years + age class). These analyses also apply a range of estimates for the persistence of treatment effect for 12 SQ-HDM SLIT for those who discontinue treatment (0%, 50% and 100%). The results of these analyses are presented in Table 10 and Table 11 for the AA+AR population and in Table 12 and Table 13 for the AR population.

Overall, for both AA+AR and AR EAG base-case models, results show that the increase in the proportion of patients who discontinue with 12 SQ-HDM SLIT implies a decrease in the total costs for 12 SQ-HDM. This is mainly driven by fewer patients receiving 12 SQ-HDM SLIT and, thus, by a reduction in the treatment and administration related costs. If the increase in the proportion of patients who discontinue is paired with a reduction of discontinued patients who benefit from treatment, a reduction of the estimated total QALYs for 12 SQ-HDM SLIT is observed.

For the company's corrected base case, the same phenomena occur, although, given the substantially higher relative reduction of secondary care use associated with 12 SQ-HDM SLIT (e.g., for the AA+AR company's model 54.58% vs 7.35% in the EAG model), the reduction in treatment and administration related costs do not outweigh the increase in secondary costs. Thus, an increase in the total costs of 12 SQ-HDM SLIT is observed, except in the extreme scenario where 100% of patients discontinue in Year 1 to Year 3 and all of these patients receive the benefit from 12 SQ-HDM SLIT.

Table 10 Deterministic cost-effectiveness results for the discontinuation scenarios over the EAG's base-case assumptions – AA+AR population

	Total Costs	Total QALYs	Incr. Costs	Incr. QALYs	ICER (£/QALY gain)
EAG base-case					
Standard of care	£26,780	18.47			
12 SQ-HDM	£28,676	18.48	£1,895	0.01	£123,269
Sc. 1.1 - EAG base-case + 0% patient discontinuation Year 1 to Year 3					
Standard of care	£26,780	18.47			
12 SQ-HDM	£28,804	18.49	£2,023	0.02	£122,544
Sc. 1.2 - EAG base-case + 100% patient discontinuation Year 1 to Year 3 + 50% with 12 SQ HDM benefit for those who discontinue					
Standard of care	£26,780	18.47			
12 SQ-HDM	£27,529	18.48	£749	0.01	£87,971
Sc. 1.3 - EAG base-case + patient discontinuation Year 1 to Year 3 according to Pfaar et al. + 50% with 12 SQ HDM benefit for those who discontinue					
Standard of care	£26,780	18.47			
12 SQ-HDM	£27,779	18.48	£998	0.01	£100,991
Sc. 2.1 - EAG base-case + 100% patient discontinuation Year 1 to Year 3 + 0% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£26,780	18.47			
12 SQ-HDM	£27,940	18.47	£1,160	0.001	£2,278,946
Sc. 2.2 - EAG base-case + patient discontinuation Year 1 to Year 3 according to Pfaar et al. + 0% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£26,780	18.47			
12 SQ-HDM	£28,173	18.47	£1,392	0.003	£426,652
Sc. 3.1 - EAG base-case + 100% patient discontinuation Year 1 to Year 3 + 100% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£26,780	18.47			
12 SQ-HDM	£27,117	18.49	£337	0.02	£20,400
Sc. 3.2 - EAG base-case + patient discontinuation Year 1 to Year 3 according to Pfaar et al.+ 100% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£26,780	18.47			
12 SQ-HDM	£27,384	18.49	£604	0.02	£36,587

Abbreviations: HDM, house dust mite; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Sc., scenario.

Table 11 Deterministic cost-effectiveness results for the discontinuation scenarios over the company's base-case assumptions – AA+AR population

	Total Costs	Total QALYs	Incr. Costs	Incr. QALYs	ICER (£/QALY gain)
Company corrected base-case					
Standard of care	£26,728	15.73			
12 SQ-HDM	£24,474	16.11	-£2,254	0.37	12 SQ-HDM dominant
Sc. 1.1 - Company corrected base-case + 0% patient discontinuation Year 1 to Year 3					
Standard of care	£26,728	15.73			
12 SQ-HDM	£24,091	16.15	-£2,637	0.42	12 SQ-HDM dominant
Sc. 1.2 - Company corrected base-case + 100% patient discontinuation Year 1 to Year 3 + 50% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£26,728	15.73			
12 SQ-HDM	£25,057	15.95	-£1,671	0.22	12 SQ-HDM dominant
Sc. 1.3 - Company corrected base-case + patient discontinuation Year 1 to Year 3 according to Pfaar et al 2023 + 50% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£26,728	15.73			
12 SQ-HDM	£25,250	15.96	-£1,477	0.22	12 SQ-HDM dominant
Sc. 2.1 - Company corrected base-case + 100% patient discontinuation Year 1 to Year 3 + 0% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£26,728	15.73			
12 SQ-HDM	£27,293	15.76	£565	0.03	£19,501
Sc. 2.2 - Company corrected base-case + patient discontinuation Year 1 to Year 3 according to Pfaar et al 2023 + 0% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£26,728	15.73			
12 SQ-HDM	£27,422	15.77	£695	0.04	£17,699
Sc. 3.1 - Company corrected base-case + 100% patient discontinuation Year 1 to Year 3 + 100% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£26,728	15.73			
12 SQ-HDM	£22,815	16.14	-£3,913	0.41	12 SQ-HDM dominant
Sc. 3.2 - Company corrected base-case + patient discontinuation Year 1 to Year 3 according to Pfaar et al 2023 + 100% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£26,728	15.73			
12 SQ-HDM	£23,072	16.14	-£3,656	0.41	12 SQ-HDM dominant

Abbreviations: HDM, house dust mite; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Sc., scenario.

Table 12 Deterministic cost-effectiveness results for the discontinuation scenarios over the EAG's base-case assumptions – AR population

	Total Costs	Total QALYs	Incr. Costs	Incr. QALYs	ICER (£/QALY gain)
EAG base-case					
Standard of care	£15,580	18.68			
12 SQ-HDM	£18,116	18.73	£2,536	0.05	£50,479
Sc. 1.1 - EAG base-case + 0% patient discontinuation Year 1 to Year 3					

Standard of care	£15,580	18.68			
12 SQ-HDM	£18,228	18.73	£2,648	0.05	£51,385
Sc. 1.2 - EAG base-case + 100% patient discontinuation Year 1 to Year 3 + 50% with 12-SQ HDM benefit for those who discontinue					
Standard of care	£15,580	18.68			
12 SQ-HDM	£16,621	18.71	£1,040	0.03	£40,372
Sc. 1.3 - EAG base-case + patient discontinuation Year 1 to Year 3 according to Pfaar et al. + 50% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£15,580	18.68			
12 SQ-HDM	£16,888	18.71	£1,308	0.03	£40,056
Sc. 2.1 - EAG base-case + 100% patient discontinuation Year 1 to Year 3 + 0% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£15,580	18.68			
12 SQ-HDM	£16,788	18.68	£1,208	0.00	No difference in effectiveness
Sc. 2.2 - EAG base-case + patient discontinuation Year 1 to Year 3 according to Pfaar et al. + 0% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£15,580	18.68			
12 SQ-HDM	£17,042	18.69	£1,461	0.01	£106,193
Sc. 3.1 - EAG base-case + 100% patient discontinuation Year 1 to Year 3 + 100% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£15,580	18.68			
12 SQ-HDM	£16,454	18.73	£873	0.05	£16,946
Sc. 3.2 - EAG base-case + patient discontinuation Year 1 to Year 3 according to Pfaar et al. + 100% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£15,580	18.68			
12 SQ-HDM	£16,735	18.73	£1,155	0.05	£22,404

Abbreviations: HDM, house dust mite; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Sc., scenario.

Table 13 Deterministic cost-effectiveness results for the discontinuation scenarios over the company's base-case assumptions – AR population

	Total Costs	Total QALYs	Incr. Costs	Incr. QALYs	ICER (£/QALY gain)
Company corrected base-case					
Standard of care	£15,580	19.03			
12 SQ-HDM	£12,681	19.29	-£2,899	0.26	12 SQ-HDM dominant
Sc. 1.1 - Company corrected base-case + 0% patient discontinuation Year 1 to Year 3					
Standard of care	£15,580	19.03			
12 SQ-HDM	£12,413	19.31	-£3,167	0.28	12 SQ-HDM dominant
Sc. 1.2 - Company corrected base-case + 100% patient discontinuation Year 1 to Year 3 + 50% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£15,580	19.03			
12 SQ-HDM	£13,630	19.18	-£1,950	0.15	12 SQ-HDM dominant
Sc. 1.3 - Company corrected base-case + patient discontinuation Year 1 to Year 3 according to Pfaar et al. + 50% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£15,580	19.03			
12 SQ-HDM	£13,824	19.18	-£1,756	0.15	12 SQ-HDM dominant
Sc. 2.1 - Company corrected base-case + 100% patient discontinuation Year 1 to Year 3 + 0% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£15,580	19.03			

12 SQ-HDM	£16,595	19.04	£1,014	0.01	£98,840
Sc. 2.2 - Company corrected base-case + patient discontinuation Year 1 to Year 3 according to Pfaar et al. + 0% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£15,580	19.03			
12 SQ-HDM	£16,701	19.05	£1,120	0.02	£65,454
Sc. 3.1 - Company corrected base-case + 100% patient discontinuation Year 1 to Year 3 + 100% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£15,580	19.03			
12 SQ-HDM	£10,638	19.31	-£4,942	0.28	12 SQ-HDM dominant
Sc. 3.2 - Company corrected base-case + patient discontinuation Year 1 to Year 3 according to Pfaar et al. + 100% with 12 SQ-HDM benefit for those who discontinue					
Standard of care	£15,580	19.03			
12 SQ-HDM	£10,920	19.31	-£4,661	0.28	12 SQ-HDM dominant

Abbreviations: HDM, house dust mite; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; Sc., scenario.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

SQ HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites (review of TA834) [6280]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Asthma + Lung UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	At Asthma + Lung UK (A+LUK) we are fighting for everyone's right to breathe. We're the nation's lung charity and we're here for everyone who's living with a lung condition, regardless of what that condition may be. Asthma + Lung UK is a registered charity registered with the Fundraising Regulator.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]
If so, please state the name of the company, amount, and purpose of funding.
	• AstraZeneca (benralizumab, tezepelumab) –
	  ○ 2023 donation for Taskforce for Lung Health Industries Forum Membership - £50,000
	  ○ 2024 donation for Taskforce for Lung Health Industries Forum Membership - £55,000
	  ○ AstraZeneca provided funding for A+LUK's new Asthma Action Plans - £67,000
	• GlaxoSmithKline (mepolizumab)
	  ○ 2023 donation for Taskforce for Lung Health Industries Forum Membership - £50,000
	  ○ 2024 donation for Taskforce for Lung Health Industries Forum Membership - £55,000
	• Novartis (omalizumab)
	  ○ None
	• Sanofi (dupilumab)
	  ○ 2023 donation for Taskforce for Lung Health Industries Forum Membership - £25,000
	  ○ 2024 donation for Taskforce for Lung Health Industries Forum Membership - £55,000
	• Teva (reslizumab)
	  ○ None

4c. Do you have any direct or indirect links	No.

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information included in the submission was gathered from secondary sources including Asthma + Lung UK publications. Unpublished research of patient experience of both allergic asthma and allergic rhinitis is also included. All information included in the submission fully cited.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Perennial allergic asthma is a very common long-term condition caused by exposure house dust mites and their faeces which are present in beds and sofas in all UK homes. This results in symptoms that can include persistent breathlessness, a tight chest, sputum production and cough, all of which can cause potentially life-threatening asthma attacks. Allergic asthma is commonly accompanied by perennial allergic rhinitis – sneezing, and a blocked or runny nose – which significantly impairs quality of life. People with allergic rhinitis highlighted similar concerns to those listed above: that their conditions can be difficult to manage in some environments and that reducing the risk of dust requires additional time and effort. Patients have highlighting concerns linked to their sleep; that sleeping in a room that's dusty can stop them sleeping, having knock on effects for their wellbeing and life.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Current care for allergic asthma and allergic rhinitis focuses on symptom alleviation. Patients highlighted that this can be difficult to manage because allergy activation can be unpredictable depending on their environment.
8. Is there an unmet need for patients with this condition?	Patients whose symptoms are not well controlled by inhaled and/or intranasal corticosteroids or whose perennial allergic rhinitis symptoms are not alleviated by antihistamines would benefit from allergen immunotherapy. For these patients, current treatment is often not sufficient to control symptoms or to improve quality of life.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patient concern regarding perennial allergic asthma and perennial allergic rhinitis relates to the conditions' impact upon quality of life. Asthma + Lung UK cites unpublished qualitative study of several patients in our submission, highlighting the impact of the conditions' unpredictability of being triggered, especially in new environments that may be more dusty. One patient explained that they feel "slightly paranoid" because of this, further demonstrating the conditions' impacts upon patients' quality of life, and that this impact goes beyond exacerbation risk. Because exposure to house dust mites 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. HDM SLIT has been shown to have long lasting impact after 3 years treatment, potentially meaning a significant reduction in the need for treatment in subsequent years. Feedback from patients has revealed this to be an attractive advantage. From unpublished qualitative study, Asthma + Lung UK understands that patients would be supportive of an immunotherapy option that reduces their symptoms, such as SQ HDM SLIT, for either condition or both. Multiple studies have shown SQ HDM SLIT to b effective and well tolerated (Demoly P, Leroyer C, Serrano E, Le Maux A, Magnier G, Chartier A. The SQ HDM SLIT-Tablet is safe and well tolerated in patients with House Dust Mite allergic rhinitis with or without asthma: A "real-life" French study. Clin Transl Allergy. 2022 Mar;12(3):e12129. doi: 10.1002/clt2.12129. PMID: 35344293; PMCID: PMC8967264.; SQ HDM SLIT-tablet is effective in patients not well-controlled in GINA treatment steps 2-4 Johann Christian Virchow, Victoria Cardona, Hanne Villesen, Christian Ljørring, Bente Riis, Frederic de Blay European Respiratory Journal Sep 2016, 48 (suppl 60) PA4108; DOI: 10.1183/13993003.congress-2016.PA4108)

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patient concerns regarding the perceived disadvantages of allergen immunotherapy, including SQ HDM SLIT, are predominant with patients that have well-controlled symptoms of either condition or both, and who have minimal impact from their condition(s) upon their quality of life. Disadvantages include reliance on a daily medication as opposed to ad hoc symptom relief.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	N/A

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Perennial allergic asthma and perennial allergic rhinitis are very common long term conditions affecting millions of people in the UK. • Asthma is a serious condition that kills 3 people in the UK every day. Asthma attacks, including those triggered by allergy to dust mites, are a serious threat to patient health. • The quality of life of people with these conditions is impacted by their condition, and this can be significant depending on condition severity. • Treatment of these conditions through symptom management often works well but can be difficult to manage when allergy triggers are unexpected.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

SQ HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites (review of TA834) [6280]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Society of Allergy and Clinical Immunology (BSACI)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** A specialist in the treatment of people with this condition? **Yes** A specialist in the clinical evidence base for this condition or technology? **Yes** Other (please specify):
5a. Brief description of the organisation (including who funds it).	The BSACI is the UK's professional and academic society which represents the specialty of allergy at all levels. Its aim is to improve the management of allergies and related diseases of the immune system in the United Kingdom, through education, training and research.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	ALK – Supplied data from BSACI Immunotherapy Registry £2,500 ALK - Sponsorship of Immunotherapy Registry £20,000 ALK - Annual Conference Sponsorship £34,625 ALK - Advertising in BSACI Publication £ 7,500 ALK – Grant for Abstracts Awards £1,000 ALK – Sponsorship of National Allergy Strategy £10,000 Novartis – Sponsorship of a leaflet £6,000 Novartis – Sponsorship of Immunotherapy Registry £15,000 Astra Zeneca - Conference Sponsorship £17,545 Astra Zeneca – Advertising in BSACI Publication £11,000 Astra Zeneca – Sponsorship of Webinar on Asthma and Allergies £2,000

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	1. To alleviate symptoms of moderate-severe allergic rhinoconjunctivits caused by house dust mite allergy and 2. To control symptoms of asthma/bronchospasm caused by house dust mite allergy In addition, the treatment may, in common with other forms of allergen immunotherapy, induce long-lasting allergen tolerance and disease modification, including prevention of allergic asthma, especially when used early in childhood (Hamelmann E et al. Allergy 2024;79:1018-1027).
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	For patients with HDM-induced allergic rhinitis: **In clinical trials**, a 15% or greater difference between active and placebo arms in combined symptom-medication scores for allergic rhinoconjunctivits when used in addition to standard pharmacotherapy (oral antihistamine and intranasal corticosteroid). This is in line with FDA guidance given when considering efficacy of two grass pollen SLIT products, where they set a threshold of 15% decrease in combined symptom and medication scores (US FDA Allergenic Products Advisory Committee meeting, December 11, 2013. Allergenic Products Advisory Committee > 2013 Meeting Materials, Allergenic Products Advisory Committee (archive-it.org) – transcript available on request). In fact, a 15% threshold is almost certainly harder to achieve for a perennial allergen such as house dust mite, given the difficulty in ensuring additional factors (e.g. other allergen exposure, non-allergic rhinitis, rhinosinusitis) are uniform and the allergic sensitisation causative, than for seasonal allergens, where symptoms are very clearly attributable to specific allergen exposure. **In routine clinical practice**, an improvement in RQLQ of 0.5 or greater. For patients with HDM-induced asthma and allergic rhinitis, when given for asthma indication: A reduction in asthma-exacerbations requiring GP visit, oral prednisolone and/or a step-up in regular treatment (annual exacerbation rate reduction of 30% or more); or an improvement in ACQ by 0.5 or greater; or a reduction in inhaled corticosteroid dose by 40% or more.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Absolutely. A large proportion of patients with allergic rhinitis are uncontrolled and/or unsatisfied with currently available treatments – a recent study in Belgium found 60% of sufferers have suboptimal control (Scheire et al. Journal of Allergy and Clinical Immunology In Practice 2024;12:1865-1876), the situation is very likely to be the same in the UK. Moreover, use of medications with adverse impacts such as systemic corticosteroids and over-use of nasal and systemic decongestants was high – a picture we see reflected in clinical practice in the UK. Patients suffer symptoms which greatly affect quality of life, impair sleep and adversely affect work and academic achievement. House dust mite allergy is the second most common cause of severe allergic rhinitis in the UK, behind grass pollen. These patients deserve access to all the available treatment options, including allergen immunotherapy, used once standard treatment has proved insufficiently effective. A number of these patients will also suffer with HDM-induced allergic asthma. 12 SQ-HDM SLIT has the capacity to treat and improve both diseases, and to provide long-lasting allergen tolerance, with disease modification and sustained benefit over many years (Fritzsching et al. Lancet Regional Health- Europe 2022:13:10027).

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Allergic rhinitis: oral antihistamines and intranasal corticosteroids are the mainstay of treatment; some patients will see further benefit from combined intranasal steroid plus intranasal antihistamine, where available. Other treatments – LTRAs, nasal ipratropium bromide spray, intranasal decongestants – are merely adjunctive treatments with either minimal effect or appropriate for short term use only. Pharmacotherapy can be combined with allergen avoidance measures but reducing exposure to house dust mite in the home is difficult, expensive and of limited proven value. Allergic asthma: inhaled corticosteroids (ICS) and inhaled beta agonists are the mainstay of treatment, as per GINA or BTS-SIGN guidelines. Treatment step-up and step-down occurs according to symptoms, spirometry/PEFR, blood/exhaled biomarkers and exacerbation frequency. Exacerbations not responding to increased ICS and beta agonist use are treated with systemic corticosteroids. Frequent exacerbations (at least 3 per year) requiring systemic steroids would be cause for consideration of monoclonal antibody/biologic drugs.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Allergic rhinitis: Scadding GK et al. BSACI rhinitis guidelines. Clin Exp Allergy 2017;47:856-889 Roberts G et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy 2018;73:4:756-798

	Hellings PW et al. EUFOREA treatment algorithm for allergic rhinitis. Rhinology 2020; 58;6:618 – 622 Asthma: GINA guidelines 2023, BTS-SIGN guidelines 2019
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	For rhinitis, the pathway of care would typically be GP to allergist/immunologist or GP to ENT surgeon. There are considerable regional differences across the UK, given the relatively low numbers of allergy/immunology specialist clinics. For asthma, typically GP to respiratory physician, but, where available, and if the patient is suffering from allergic rhinitis and asthma, GP to allergist/immunologist may also take place (affected by the same regional variation).
9c. What impact would the technology have on the current pathway of care?	It is possible that availability of 12 SQ-HDM SLIT would encourage GPs to refer to allergy/immunology instead of ENT, or to allergy/immunology instead of respiratory physicians, but this is very likely to be limited by clinic availability and unlikely to lead to large changes in referral numbers.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes. We use Acarizax (12 SQ-HDM SLIT) for a small number of patients with HDM-induced allergic rhinitis, with or without allergic asthma, who fail to be controlled (or who cannot tolerate) optimum standard pharmacotherapy. We use it for house dust mite induced allergic asthma where there is also house dust mite induced allergic rhinitis and standard treatments (inhaled steroids and beta agonists) are not adequately controlling the disease but there are insufficient exacerbations to consider a biologic and lung function is well-maintained (FEV1 greater than 70% predicted).
10a. How does healthcare resource use differ between the technology and current care?	Acarizax (12 SQ-HDM SLIT) is initially given under supervision, typically in a nurse-led allergy/immunology clinic, with the patient observed for one hour afterwards. After that initial dose, further doses can be taken at home with remote monitoring (telephone/video clinics) over the next 3 years (typically after 3 months initially, extending to 6 monthly contact). Current care consists of either standard pharmacotherapy – intranasal steroids etc. – or, in specialist clinics, subcutaneous immunotherapy (SCIT). Compared to subcutaneous treatment, 12 SQ-HDM SLIT involves far fewer resources – subcutaneous treatment requires 12-40 clinic visits over 3 years, depending on the product used – and is far safer, with severe allergic reactions being exceedingly rare, in contrast to subcutaneous treatment which carries a risk of systemic allergic reaction in approximately 1 in every 100-1,000 injections. There is no evidence of any difference in efficacy between the two modes of treatment. Sublingual treatment is more environmentally friendly and more efficient of patient time (Cardel L-O et al. Scientific Reports

	2024;14:1575). In clinics where the alternative option is subcutaneous immunotherapy, the technology will reduce healthcare resource use; in other circumstances, the increase will be modest and offset by the likely reduction in GP and hospital visits given improved disease control.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist allergy/immunology clinics in secondary care; or specialist ENT or respiratory clinics, if the treating consultant has knowledge and experience in use of allergen immunotherapy.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	If restricted to the above specialist clinics, none.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. In well-selected patients, inadequately controlled or unable to tolerate optimum standard care, I anticipate a clear improvement in symptoms and quality of life (Blaiss et al. The Journal of Allergy and Clinical Immunology: In Practice (2024), doi: https:// doi.org/10.1016/j.jaip.2024.01.038).
11a. Do you expect the technology to increase length of life more than current care?	No
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. In patients failing to respond to optimum pharmacotherapy, I expect to see an increase in HRQoL with 12 SQ-HDM SLIT used alongside standard pharmacotherapy (Blaiss et al. The Journal of Allergy and Clinical Immunology: In Practice (2024), doi: https:// doi.org/10.1016/j.jaip.2024.01.038).
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The treatment will only be effective in individuals with allergic sensitisation to house dust mite.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The only equivalent comparator is subcutaneous house dust mite allergen immunotherapy which is given to patients on a named-patient basis at specialist allergy/immunology clinics by regular injection. All injections are given in clinic, typically with a one-hour observation period afterwards. 12 SQ-HDM SLIT treatment will be easier than this for both patients and healthcare professionals as only the first dose of treatment need be taken in clinic, under supervision. Thereafter, daily doses can be taken at home. This is more convenient for patients and a reduced workload for healthcare professionals (not to mention being safer). This aside, compared to standard treatment for allergic rhinitis with intranasal steroids and asthma with inhaled steroids and inhaled beta agonists, the treatment is simple to take, so, whilst it is an additional treatment, the addition is not burdensome. There are no interactions with other medicines. A proportion of patients will suffer local allergic side effects (itching, swelling beneath the tongue etc.), and a few (<5%) will find these intolerable and stop treatment.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	All patients must be tested for evidence of house dust mite IgE sensitisation prior to starting treatment. This is usually a standard test in patients referred to specialist allergy/immunology clinics for allergic rhinitis and/or asthma and is also often tested for in ENT and respiratory clinics treating rhinitis and asthma, respectively. Patients must: have shown good compliance with, or had intolerable side effects from, or other reason not to take, standard therapies; been counselled on how to take sublingual immunotherapy and possible side effects and reasons to withhold treatment; have an FEV1 of at least 70% predicted if suffering with asthma. Treatment would be stopped in the event of intolerable side

	effects (e.g. severe oral itching not responding to antihistamines and not declining over time) or a failure to derive meaningful benefit after 6 months treatment.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	There is evidence that use of allergen immunotherapy in patients with allergic rhinitis can reduce the risk of them developing asthma. The data is predominantly derived from studies in children and adolescents (see Valovirta et al J Allergy Clin Immunol. 2018;141(2):529-538 as an example). I suspect this prevention of asthma development would not be picked up in the QALY calculations.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Allergen immunotherapy is the only disease modifying treatment for allergic rhinitis and asthma, able to induce true allergen tolerance, with persistent effect after discontinuation. Evidence of use in children also suggests asthma prevention and prevention of development of additional allergic sensitisations.
16a. Is the technology a 'step-change' in the management of the condition?	Yes. Allergen immunotherapy access is patchwork and divided by postcode. It is provided by only a limited number of specialist allergy/immunology clinics on a named patient basis, with funding provided by departmental budgets, meaning limited numbers of patients can access treatment. More widespread access to this technology would democratise access to treatment.
16b. Does the use of the technology address any	There is a huge unmet need in Allergy due to the limited clinic resources/specialists in the UK. Patients with house dust mite induced allergic rhinitis +/- asthma have very little access to allergen

particular unmet need of the patient population?	immunotherapy, in contrast with similar patients in Europe and North America. This technology will improve access to specific treatment with long lasting benefits.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The technology is very safe – no fatalities or life-threatening adverse reactions have been reported, to my knowledge, including in our own service. Conversely, local side effects are common, affecting at least 20% of patients. These can be bothersome, affecting quality of life, but are generally short lived, resolving within 2-4 weeks of initiating the treatment. A small proportion of patients will find these symptoms intolerable and discontinue treatment (after which, symptoms resolve in a matter of a few days at most, with no lasting side effects).

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	For allergic rhinitis, to a large extent, yes. Intranasal steroids and oral antihistamines are the mainstay of treatment and will be prescribed to the vast majority of sufferers by their GP and/or specialist. The only notable difference from current practice is the use of combined intranasal steroid and antihistamine sprays, though it should be noted that these are not universally available (some CCGs will not prescribe them). Other treatments (see my points above) are of very little added value. For asthma, the MT-04 trial is proof of principle, rather than a reflection of standard practice. Whilst inhaled corticosteroid dose in asthma may be reduced (and even withdrawn) if symptoms are controlled and objective markers (spirometry, exhaled nitric oxide) are normal/improved, these drugs would not be routinely reduced across the board. The study demonstrates the potential of house dust mite sublingual

	immunotherapy to maintain asthma control despite lowering and withdrawal of corticosteroids. A second study (Mosbech H et al. J Allergy Clin Immunol. 2014;134(3):568-575) demonstrated that this treatment allows a reduction in inhaled corticosteroids whilst maintaining asthma control versus placebo.
18a. If not, how could the results be extrapolated to the UK setting?	I believe the allergic rhinitis/MT-06 data does reflect UK practice and does not require extrapolation. My only observation would be that the treatment would generally only be used after patients had also tried a combined intranasal steroid plus intranasal antihistamine, rather than just being on an intranasal steroid +/- oral antihistamine. The MT-04 data is proof of principle of a steroid-sparing effect of sublingual house dust mite immunotherapy. The data is very clear that the treatment reduces the risk of asthma exacerbation versus placebo. This can be extrapolated to infer that being on treatment is highly likely to reduce the risk of exacerbations in a population with incompletely controlled asthma where no across-the-board reduction in treatment is made, rather the variability of asthma and tendency of exacerbations plays out over time – i.e. as in the real world.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	For rhinitis, the combined symptom medication score is by far the most important outcome in allergen immunotherapy trials, and as was recorded in MT-06. This allows consistency and comparison between clinical trials. RQLQ is also helpful from a patient perspective, but seldom used as a primary outcome in rhinitis trials.

	For asthma, exacerbation frequency – particularly severe exacerbations – is the most troublesome outcome for patients, so measuring this, as in MT-04, is the most important outcome. Other outcomes which are of secondary importance include the ACQ and objective parameters (though less directly important to the patient) such as FEV1, PEFR and exhaled nitric oxide.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No surrogate outcomes were used. Evidence suggests three years treatment is required for long-term efficacy. Other studies of sublingual immunotherapy often reach peak impact/patient benefit in the second year of treatment, so further benefits beyond those seen here may be expected.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of. No long-term adverse effects of allergen immunotherapy have come to light after over 100 years of use!
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	This depends on whether a systematic review would only include phase 3 studies or whether phase 2 studies and real-world evidence would also be considered. I would suggest also reviewing the environmental exposure chamber study (Nolte HN et al J Allergy Clin Immunol 2015; 135(6): 1494-501) that was undertaken. This was unaffected by the large placebo affect seen in all phase 3 allergen immunotherapy studies in allergic rhinitis. It showed a nearly 50% improvement in symptom scores in active versus placebo-treated participants.

20. How do data on real-world experience compare with the trial data?	Real-world evidence suggests allergen immunotherapy in general reduces use of standard medication for rhinitis and asthma and also reduces asthma exacerbations and hospitalisation. (See the REACT study).

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	I believe that NICE approval for this technology would have a positive effect on equality of access to allergen immunotherapy. As it currently stands, with allergen immunotherapy being available only in specialist centres on a named patient basis, patients with knowledge of how to navigate the system and how to push for treatment tend to end up getting access to allergen immunotherapy, whereas those with less knowledge and savvy lose out. A clear NICE appraisal could help democratise access.
21b. Consider whether these issues are different from issues with current care and why.	As above.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Allergic rhinitis, with or without allergic asthma, is a major cause of reduced quality of life and productivity; house dust mite allergy is a major cause of allergic rhinitis and allergic asthma. • House dust mite allergen immunotherapy has the potential to improve quality of life (rhinitis) and stabilise disease (asthma) in sufferers failing to respond to standard treatments. • Allergen immunotherapy over three years leads to long-term clinical and immunological tolerance and is associated with reduced risk of asthma exacerbations and new-onset asthma. • House dust mite sublingual allergen immunotherapy is an extremely safe treatment, without long-term, cumulative side effects, in contrast in corticosteroid treatments. •

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Single Technology Appraisal

SQ HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites (review of TA834) [6280]

Professional organisation submission

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	ENT UK
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	ENT UK is a Membership Specialist Surgical Association
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Better symptom control for Allergic Rhinitis
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Recustion in symptoms related top allergic rhinitis
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a cohort of patients with nasal allergy that are not controlled well by standard medication

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Topical steroid nasal sprays / oral or nasal topical antihistamines / short courses of systemic steroid if severe / subcutaneous or sublingual immunotherapy desensitization
9a. Are any clinical guidelines used in the	Yes BSACI Allergy Guidelines and NICE recommendations

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes
9c. What impact would the technology have on the current pathway of care?	It would add an additional alternative
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Similar to existing immunotherapy
10a. How does healthcare resource use differ between the technology and current care?	Different action and oral/sublingual so no injections involved
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care until firmly established
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Minimal / training for specialist nurses

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	yes
11a. Do you expect the technology to increase length of life more than current care?	no
11b. Do you expect the technology to increase health-related quality of life more than current care?	yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Those with significant symptoms of allergic rhinitis that do not respond well to standard medication

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	No

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes – stop treatmewnt if allergic symptoms increase
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Perhaps but to early to say without evidence
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Easy to take and administer.
16a. Is the technology a 'step-change' in the management of the condition?	Yes as an alternative to existing immunotherapy regimes, especially where injections are required

16b. Does the use of the technology address any particular unmet need of the patient population?	Yes. Ease of use in very symptomatic allergic rhinitis
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Stop the medication if allergic symptoms worsen

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	No
18a. If not, how could the results be extrapolated to the UK setting?	Better design of trials. Keep Allergic rhinitis separate from asthma tirals
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Symptom scores for rhinitis
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No
18d. Are there any adverse effects that were not apparent in clinical	No

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	No able to comment as I do not have specific clinical experience of immunotherapy

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	No

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• The ease of use of sublingual immunotherapy as a means of desensitization makes Acarix an attractive proposition • The tiral data is confusing and whilst effective in Allergic Rhinitis, the benefit di not reach the baseline of 20% change. • Including Asthma within the trials as well as Allergic Rhintis seems to have confused things to the detriment of Allergic Rhinitis management and assessment • The advantage of sublingual therapy would be very advantageous over existing injection therapy •

Thank you for your time.

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