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

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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:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from** ALK Abello**:**
   a. Full submission summary
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Allergy UK
   b. Anaphylaxis UK
   c. Asthma and Lung UK
   d. Association of Respiratory nurses (ARNS)
   e. British Thoracic Society
   f. Royal college of Physicians (RCP)

4. **Expert Personal perspectives:**
   a. Dr Shuaib Nasser– clinical expert, nominated by AKL ltd
   b. Amena Warner – Patient expert, nominated by Allergy UK

5. **External Assessment Report** prepared by York

6. **External Assessment Report – factual accuracy check**

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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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]

Document B

Company evidence submission

October 2023

File name	Version	Contains confidential information	Date
ALK. 12 SQ-HDM NICE Document B.	**Final**	**No**	**20th October 2023**

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B.1 Decision problem, description of the technology and clinical care pathway

B1.1 Decision problem

This submission covers the full marketing authorisation for 12 SQ-HDM SLIT-tablet (standardised allergen extract from the house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* 12 SQ-HDM* per oral lyophilizate) for the treatment of patients aged 12 to 65 years with a confirmed diagnosis of persistent moderate-to-severe house dust mite (HDM) allergic rhinitis (AR) despite the use of symptom-relieving medication, and patients aged 18 to 65 years with a confirmed diagnosis of HDM allergic asthma (AA) not well-controlled by inhaled corticosteroids (ICS) and associated with mild-to-severe HDM AR.

The decision problem addressed in this submission is presented in Table 1.

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Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged 18 to 65 years with house dust mite sensitisation with persistent moderate-to-severe house dust mite allergic rhinitis despite use of symptom-relieving medication, or allergic asthma not well-controlled by inhaled corticosteroids and associated with mild-to-severe allergic rhinitis. People aged 12 to 17 years with house dust mite sensitisation with persistent moderate-to-severe house dust mite allergic rhinitis despite use of symptom-relieving medication	As per NICE final scope	N/A
Intervention	SQ-HDM SLIT as an add-on to standard therapy	12 SQ-HDM	Intervention aligned with NICE final scope
Comparator(s)	Established clinical management without SQ-HDM SLIT	SOC AA+AR SOC AR	Comparator aligned with NICE final scope. Established clinical management efficacy is represented by the placebo arms of the clinical trials
Outcomes	The outcome measures to be considered include: For house dust mite sensitisation with persistent moderate-to-severe house dust mite allergic rhinitis despite use of symptom-relieving medications: • Severity of rhinitis symptoms • Complications of allergic rhinitis (such as sinusitis or middle ear infections)	As per NICE final scope	N/A

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Rhinitis medication use • Adverse effects of treatment • Health-related quality of life For house dust mite sensitisation with allergic asthma that is not well-controlled by inhaled corticosteroids and associated with mild-to-severe allergic rhinitis: • Use of ICS • Use of rescue medication • Time to first moderate or severe asthma exacerbation after ICS reduction • Reduction of the risk of an asthma exacerbation • Lung function • Severity of rhinitis symptoms • Complications of allergic rhinitis (such as sinusitis or middle ear infections) • Adverse effects of treatment • Health-related quality of life • Overall survival		
Special considerations including issues related to equity or equality	None stated	Considerations related to access to specialist services for allergic respiratory disease patients	Despite the large burden of allergic respiratory disease (ARD) for both patients and the NHS, there is a lack of accessible and well-resourced specialist services for ARD patients. As the first dose of 12 SQ-HDM is administered in

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			secondary care, this may be considered to represent a barrier to some patients for whom allergy services are less accessible
Abbreviations: HDM, house dust mite; AA, allergic asthma; AR, allergic rhinitis; IgE, immunoglobin E; ARD, allergic respiratory disease; SOC, standard of care; SLIT, sublingual immunotherapy; ICS, inhaled corticosteroids.			

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B1.2 Description of the technology being evaluated

Table 2 presents an overview of the technology being appraised (12 SQ-HDM SLIT-tablet, hereby referred to as 12 SQ-HDM). Please see Appendix C for the summary of product characteristics (SmPC) and UK Assessment Report.

Table 2: Summary of the technology being evaluated [1]

UK approved name and brand name	ACARIZAX® 12 SQ-HDM* oral lyophilisate
Mechanism of action	12 SQ-HDM is an allergy immunotherapy containing a high standardised concentration of allergen extract from the house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. 12 SQ-HDM is an aetiological treatment which aims to modify the patient's immune response to HDM allergens. Whilst the exact mechanism of the clinical effect is not fully understood, the modification of the immune response has been demonstrated in both the upper and lower airways through the increase in house dust mite-specific IgG4, and its induction of a systemic antibody response that can compete with immunoglobin E (IgE) in the binding of house dust mite allergens. 12 SQ-HDM works by addressing the cause of house dust mite respiratory allergic disease. The underlying protection provided by 12 SQ-HDM leads to improvement in disease control and improved quality of life, demonstrated through symptom relief, reduced need for other medications, and a reduced risk for exacerbation. The treatment may need to be taken for 8 to 14 weeks before any improvement is noticed.
Marketing authorisation/CE mark status	12 SQ-HDM oral lyophilisate (PL 10085/0058) was approved by the MHRA on 17 May 2021 for the treatment of allergic rhinitis (inflammation of the lining of the nose) in adults and adolescents (12-65 years of age), and related allergic asthma caused by house dust mites in adults (18-65 years of age) [2].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	12 SQ-HDM is indicated in adult patients (18-65 years) diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test and/or specific IgE), who have at least one of the following conditions: • Persistent moderate-to-severe house dust mite allergic rhinitis despite use of symptom-relieving medication • House dust mite allergic asthma not well-controlled by inhaled corticosteroids and associated with mild-to-severe house dust mite allergic rhinitis. Patients' asthma status should be carefully evaluated before the initiation of treatment.

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	12 SQ-HDM is indicated in adolescents (12-17 years) diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test and/or specific IgE) with persistent moderate-to-severe house dust mite allergic rhinitis despite use of symptom-relieving medication.
Method of administration and dosage	12 SQ-HDM treatment should be initiated by physicians with experience in the treatment of allergic diseases. Following this, patients can self-administer at home. 12 SQ-HDM is provided as an oral lyophilizate. Once 12 SQ-HDM is taken, swallowing should be avoided for approximately 1 minute. The recommended dose for adults (18-65 years) and adolescents (12-17 years) is one oral lyophilisate (12 SQ-HDM) daily. The onset of the clinical effect is expected 8-14 weeks after treatment initiation. If no improvement is observed during the first year of treatment with 12 SQ-HDM, there is no indication for continuing treatment. International treatment guidelines and consensus statements refer to a treatment period of 3 years for AIT to achieve disease modification after its cessation [3, 4].
Additional tests or investigations	A diagnosis of AA and/or AR by clinical history and a positive test of house dust mite sensitisation (skin prick test and/or specific IgE) is required before treatment initiation. 12 SQ-HDM treatment should be initiated by physicians with experience in the treatment of allergic diseases. Following this, patients can self-administer at home.
List price and average cost of a course of treatment	£80.12 per pack of 30 tablets of 12 SQ-HDM 12 SQ-HDM (pack sizes are as 30 oral lyophilisates and 60 lyophilisates). The average annual cost of 12 SQ-HDM treatment is £975.46 per patient, assuming once-daily dosing. (NB These prices are still to be agreed with the Department of Health)
Patient access scheme (if applicable)	N/A
*SQ-HDM is the dose unit for ACARIZAX®. SQ is a method for standardisation on biological potency, major allergen content, and complexity of the allergen extract. **Abbreviations:** AA, allergic asthma; AIT, allergen immunotherapy; AR, allergic rhinitis; HDM, house dust mite; IgE, immunoglobin E. IgG4, Immunoglobulin G4; N/A, not applicable	

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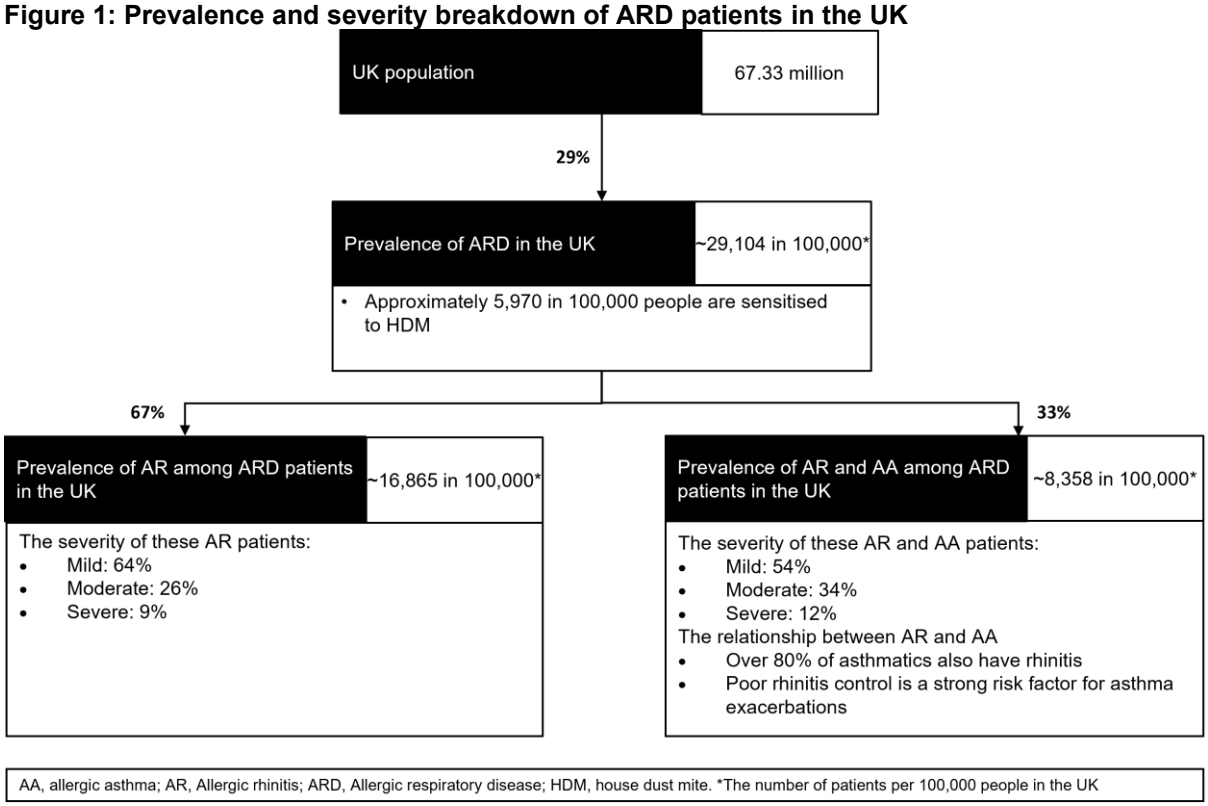
B1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

B1.3.1.1 Disease definition and epidemiology

Allergic respiratory disease (ARD) is an immunological disorder of mucosal inflammation driven by the generation of IgE antibodies to aeroallergens. The term 'ARD' describes a group of respiratory conditions triggered or exacerbated by allergies. In this submission, ARD refers to inflammation manifestations in the upper and lower airways known as AR and AA, respectively [5-7]. It is estimated that ARD affects 19.5 million people in the UK, with approximately 4 million of these being sensitised to HDM [8]. The severity and prevalence breakdown of the ARD condition in the UK population is presented in Figure 1 [8].

Figure 1: Prevalence and severity breakdown of ARD patients in the UK



AA, allergic asthma; AR, Allergic rhinitis; ARD, Allergic respiratory disease; HDM, house dust mite. *The number of patients per 100,000 people in the UK

Source: Data on file (modified Delphi) [8], Bousquet et al. (2008) [3], Scadding et al. (2017) [9]

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B1.3.1.2 Pathophysiology

Both AR and AA are the result of mucosal inflammation, driven by an IgE-mediated inflammatory response to harmless allergens. In HDM-sensitised patients, an allergic immune response occurs on exposure to HDM-derived (Dermatophagoides pteronyssinus and Dermatophagoides farinae) allergens.

Airborne, aerosolised HDM allergens infiltrate the respiratory system of the sensitised individual. Upon invading the respiratory tract, allergen particles are hydrated and discharge their allergenic contents onto the mucosal barrier. These allergens are engulfed and phagocytosed by dendritic cells residing within the mucosal tissue, before subsequently being presented on the surface as antigens, which induces the activation and differentiation of naïve CD4 T cells into T Helper Cell Type 2 (TH2). These TH2 cells secrete several cytokines, including IL-4 and IL-13. IL-4 instructs B cells to transition from producing the immunoglobin M (IgM) antibody to producing the IgE antibody. IgE antibodies then bind to, and activate basophils and mast cells, triggering the release of various mediators such as histamine, leukotrienes, and prostaglandins. This cascade of events triggers the clinical manifestations associated with the allergic reactions [5-7].

In AR, the mucosal inflammation occurs in the paranasal sinuses and lower airways, triggering excess mucus production and causing the airways to narrow. The upper airways can also become inflamed, resulting in AR symptoms such as sneezing and congestion.

Similarly, in AA, mucosal inflammation triggers excess mucus production and causes the airways to narrow. It can also cause inflammation in the lower airways, which affects airflow in the lungs and results in asthma symptoms such as breathlessness, a tight chest, and coughing [5-7].

B1.3.1.3 Clinical presentation

The clinical manifestations of ARD are influenced by factors such as the airborne allergen in question, sensitisation profiles, and the site of inflammation within the airways.

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ARD has a heterogeneous presentation, including nasal (congestion, itchy and/or runny nose), respiratory (coughing, dyspnoea, chest tightness, wheezing), and ocular symptoms (eye redness, itchy and/or watery eyes) [5-7, 10]. Approximately two-thirds of ARD patients present with AR symptoms only and one-third present with symptoms of both AR and AA [8].

AR can be classified as mild, moderate, or severe, and is defined on the basis of the presence or absence of impairment in any of the four health-related quality of life (HRQoL) items: sleep, daily activities/sport, work/school, and troublesome symptoms [11]. Patients with mild AR have no affected items, patients with moderate AR have 1 to 3 affected items, and patients with severe AR have all four affected items.

- **Troublesome symptoms:** ARD patients can experience sinusitis (67-82% of ARD patients); conjunctivitis (75.6% of AR patients), which can result in visual impairment; oral allergy syndrome (22% of AR patients), which can lead to anaphylaxis upon eating fruits, vegetables, and nuts; and repeat respiratory infections (11.6% of AA patients). Approximately, 1,541 patients die of acute respiratory failure each year [12-16].

- **Sleep disturbance:** 57% of AR patients experience difficulty falling asleep and 44.9% of AA patients experience frequent nocturnal awakenings which impacts the quality of their sleep [17, 18].

- **Impairment of school or work:** Productivity at work is reduced by an average of 21% for ARD patients vs. the general population [19]. This reduced performance also extends to adolescents, increasing their likelihood to perform poorly in exams by 1.1-1.8 times when compared to the general population [20, 21]. Patients with ARD also have an increased number of absences from work due to their condition, with an average of 4.1 days absent per AR patient per year [22].

- **Impairment of daily activities, leisure and/or sport:** 32.8% of AR patients report that their condition impacts their ability to take part in outdoor activities [23].

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Consequently, AR patients with persistent moderate-to-severe disease have reduced quality of life (QoL) and often experience problems with their mental health [17, 23-25].

Of the patients with ARD, 39-47% experience anxiety/depression. There is also an association that individuals with anxiety and/or depression are more likely to have poorly controlled asthma [24, 25].

B1.3.1.4 Impact on the NHS

ARD has a significant impact on the NHS. Patients with more severe disease tend to have a higher number of visits to both primary and secondary care services. For AR, the number of visits to primary care per year is estimated to be approximately 8.5 million, costing the NHS an approximately £355 million [8, 26]. For patients with both AR and AA, the number of visits to primary care per year is estimated at 11.7 million, costing the NHS approximately £492 million [8, 26]. The estimated number of visits to secondary care is slightly lower, with 4.9 million visits to secondary care for AR patients, and 4.2 million visits for AR and AA patients, costing the NHS approximately £1.1 billion and £972 million, respectively [8, 27] (see Appendix R).

B.1.3.2 Clinical pathway

B1.3.2.1 ARD diagnosis

The ARD treatment pathway in the UK initially consists of self-care or pharmacy treatments, followed by patients visiting primary care services. Patients are mostly diagnosed with ARD in primary care using clinical history: 50% of AR and 79% of AR and AA patient diagnoses are made in primary care. If a patient's clinical history is unclear, further testing may be carried out. This most commonly takes the form of skin prick testing, although some centres offer radioallergosorbent (RAST) or FeNO testing. Diagnostic guidelines are rarely used by experienced GPs; NICE and local guidelines are the most relevant for these patients [8].

Currently, a more advanced ARD diagnosis, including the specific allergen sensitisation and type of asthma/rhinitis, is made in secondary care, using clinical history, FeNO testing, skin prick tests, and/or blood test (IgE). Although rarely used

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directly in the specialist setting, clinicians follow the British Society for Allergy and Clinical Immunology (BSACI) guidelines [8].

B1.3.2.2 ARD patient management

ARD patients whose symptoms cannot be self-managed are typically managed within the primary care setting (5,593 patients per 100,000 people in the UK) [8]. Patients with the most severe disease, which is characterised by AA complications, or a lack of response to prior treatment, require onward referral to secondary care (866 patients per 100,000 people in the UK) [8].

The NICE Clinical Knowledge Summary on AR [28] incorporates recommendations from the BSACI [9] and the Allergic Rhinitis and its impact on Asthma (ARIA) international guidelines (2016 revision) [29] for the diagnosis and management of patients with AR. The overall treatment pathway is based on the BSACI rhinitis treatment algorithm [9], summarised in Figure 2.

ARD patients are typically treated in UK clinical practice with a range of symptomatic therapies, in line with NICE or Global Initiative for Asthma (GINA) guidelines in primary care and BSACI and ARIA guidelines in secondary care.

If a person has a diagnosis of AR, advice on allergen avoidance is usually recommended [28]. However, in the context of HDM sensitisation, allergen avoidance is very difficult as the allergen is in the home and tends to be present all year round [9, 29]. For patients with mild-to-moderate, intermittent, or mild persistent symptoms, oral or intranasal antihistamines are the first line of therapy [9, 28] . For patients with moderate-to-severe persistent symptoms, or those for whom initial treatment is ineffective, intranasal corticosteroids are recommended [9, 28] . If symptoms continue to persist despite these treatments, combination therapies can be explored, including combinations of oral antihistamines and intranasal corticosteroids, or combined preparations of intranasal corticosteroids and intranasal antihistamines [9, 28].

If these treatments are ineffective, despite compliance and proper technique, clinicians can consider add-on therapies, depending on the persistent/refractory symptoms. These are summarised in Table 3 [9, 28].

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Table 3: Add-on AR therapies

Persistent/refractory symptoms	Treatment
Watery rhinorrhoea	Intranasal anticholinergics e.g., ipratropium bromide
Itching/sneezing	Regular non-sedating oral H1-antihistamines
Nasal congestion	Intranasal decongestants e.g., xylometazoline
Persistent symptoms with history of asthma	LTRA e.g., montelukast alongside oral, or intranasal antihistamines
Abbreviations: LTRA, leukotriene receptor antagonist.	

Use of systemic corticosteroids is rarely indicated in the management of AR, except as short-term rescue medication to treat severe nasal obstruction [9].

Notably, the BSACI guidelines recommend allergy immunotherapy (AIT) for perennial allergic rhinoconjunctivitis (ARC) in patients with an allergy to HDM who respond inadequately to anti-allergic drugs, and where the allergen is not easily avoided (see Figure 2 [9]).

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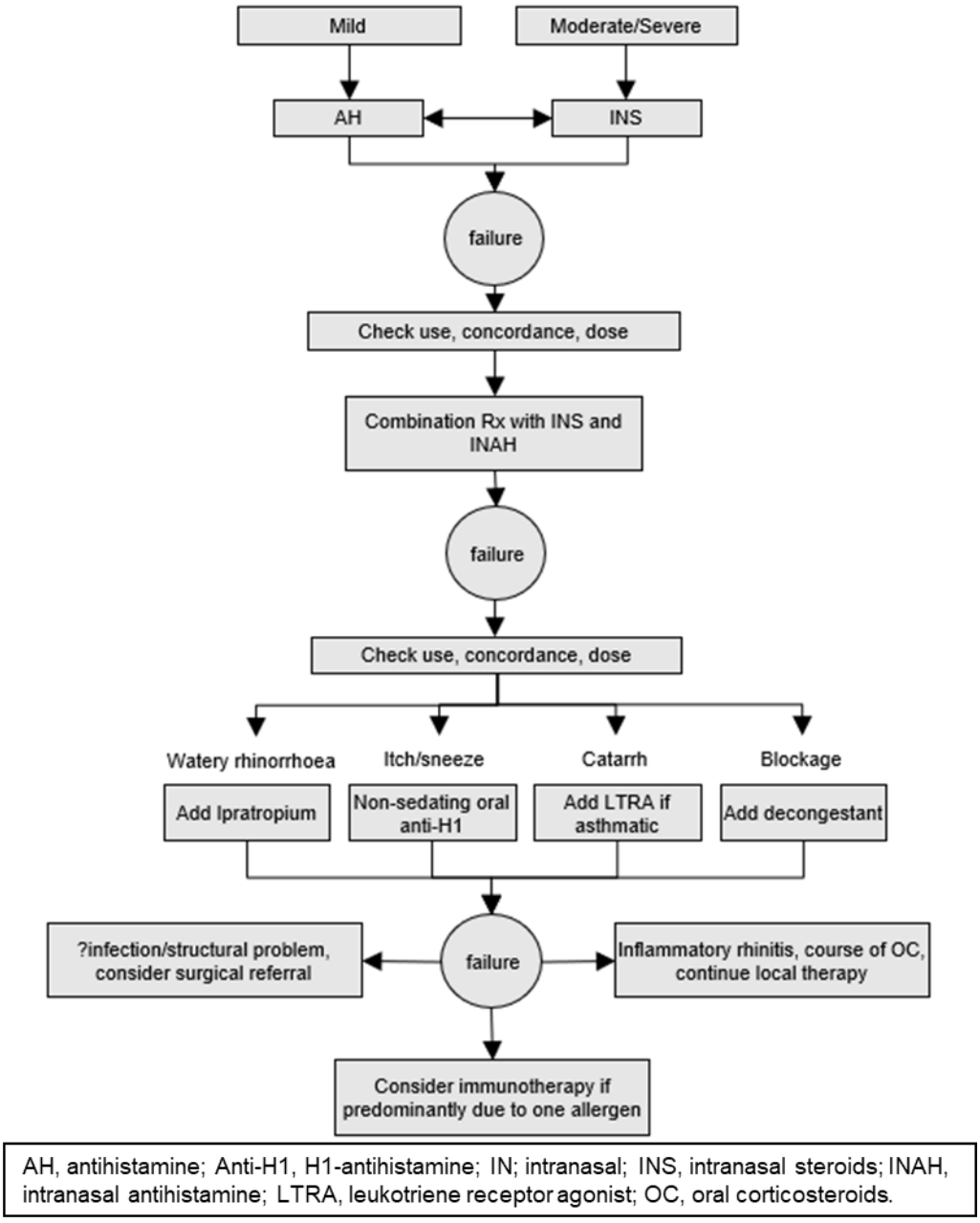
Figure 2: BSACI rhinitis treatment algorithm



The current ARIA guidelines recommend the consideration of AIT for patients with AR/conjunctivitis and/or AA caused predominantly by allergen exposure, with poor symptom reduction despite adequate pharmacotherapy during the allergy season and/or change in natural allergy history [30].

The GINA guidelines, which are used for the diagnosis and management of AA, are based on the concept of control-based management [31]. According to the guidelines, asthma management involves a continual cycle involving assessment, adjustment of

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treatment, and review. First, patients should be assessed based on their symptom control, future risk of exacerbations, decline in lung function, medication adverse effects including inhaler compliance and technique, and any comorbidities. Treatment strategies are adjusted based on this assessment, including treatment of comorbidities, non-pharmacologic strategies, and adjustment of asthma medication. The long-term goals of asthma management are to achieve good symptom control and maintain normal activity levels, as well as to minimise future risk of exacerbations, persistent airflow limitation, and treatment side effects. Pharmacotherapies for asthma are classified into three main categories, summarised in Table 4 [31].

Table 4: Asthma medications

Category	Use	Medication
Controller medication	For control of symptoms (dose and frequency of use depends on disease severity)	• ICS • ICS-LABA (ICS-formoterol is preferred)
Reliever/rescue medication	For quick relief of asthma symptoms (as needed)	• ICS-formoterol • SABA • ICS-SABA
Add-on therapies	For difficult-to-treat and severe asthma	• LAMA • LTRA • Biologics
Abbreviations: ICS, Inhaled corticosteroid; LABA, Long-acting beta agonist; SABA, short-acting β 2-agonist; LAMA, Long-acting muscarinic antagonist; LTRA, Leukotriene receptor antagonist		

Asthma medication is adjusted in a stepwise approach based on the extent of the patients' asthma control over the previous 2-3 months. The GINA guidelines describe five treatment steps in which patients' treatment dosage is increased or decreased and/or other treatments are added or removed [31].

Notably, the GINA guidelines recommend considering SLIT in Step 2-4 as an optional reliever for adult patients with AR and sensitisation to HDM who have sub-optimally controlled AA despite low to high dose ICS, provided FEV_1 is >70% predicted [31] (Figure 3).

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Figure 3: Other controller options in the GINA guidelines [31]

STEP 2	STEP 3	STEP 4
Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT*	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*

Abbreviations: ICS, Integrated care system; SABA, Short-acting β2-agonist; LTRA, leukotriene receptor antagonists; HDM, House dust mite; SLIT, Sublingual immunotherapy; LAMA, Long-acting muscarinic antagonists.

B1.3.2.3 Therapeutic need

Despite appropriate administration and compliance with existing treatments, a subset of moderate-to-severe ARD patients have uncontrolled disease (36% moderate and 45% severe AR; 24% moderate and 44% severe AR+AA), and as such, their treatment satisfaction is low [8]. 59-66% of ARD patients are unsatisfied with their symptom control despite maximum use of pharmacotherapy [32]. This displays a clear unmet need for a better treatment option for these patients.

Uncontrolled disease is associated with persistent symptoms and exacerbations. The GINA guidelines illustrate the way in which uncontrolled disease can affect several aspects of a patient's QoL: they define a patient as having uncontrolled disease when, in the past 4 weeks, they have had 3 or 4 of the following symptom control issues [31]:

- Daytime asthma symptoms more than twice a week
- Asthma symptoms that cause a patient to wake up during the night
- SABA reliever required more than twice per week to manage symptoms
- Activity limited due to asthma

Introduction to 12 SQ-HDM

12 SQ-HDM is a new generation of allergen immunotherapy (AIT) in the form of a sublingual immunotherapy (SLIT) lyophilisate tablet. 12 SQ-HDM provides an alternative treatment option for patients whose symptoms are inadequately controlled despite compliant use of existing treatments [3, 33].

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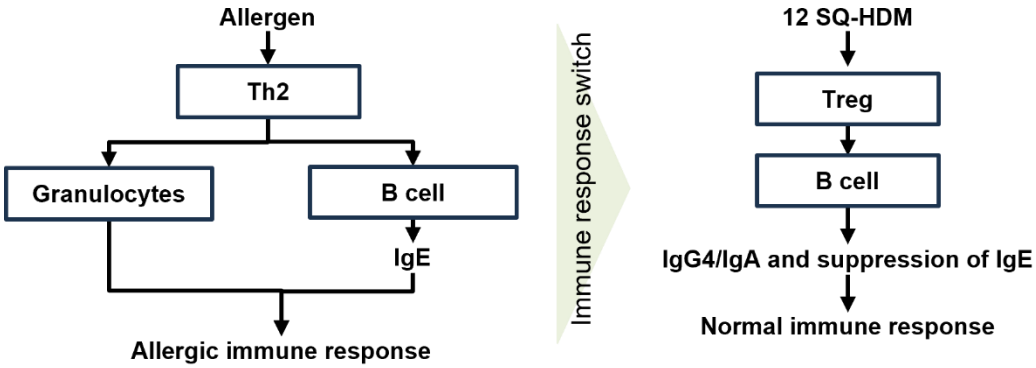
12 SQ-HDM contains a highly standardised allergen extract from the house dust mites Dermatophagoides pteronyssinus and Dermatophagoides farina. It is indicated for the treatment of adults and adolescents with HDM AR and adults with HDM AA+AR [1]. The efficacy and safety of 12 SQ-HDM has been demonstrated in multiple Phase 3 clinical trials (see Section B.2). 12 SQ-HDM is palatable, has a favourable safety profile, and is suitable for home treatment (following advised, but not mandatory, initiation in secondary care) [34-36].

The complete and exact mechanism of action regarding the clinical effect of AIT is not fully understood, however, 12 SQ-HDM works via the repeated administration of allergens to allergic individuals with the purpose of inducing a switch from an allergic response to a tolerance-building immune response. In contrast to current pharmacotherapy, 12 SQ-HDM is an aetiological treatment, addressing the underlying mechanism of HDM AR, aiming to modify the patient's immunologic response to HDM allergens. This averts the allergic symptoms by preventing the 'inflammatory cascade': T and B cell activation, cytokine secretion, and the induction of IgE production, which leads to the binding of mast cells and basophils and the release of histamine and leukotrienes. Treatment with 12 SQ-HDM has been demonstrated to induce an increase in house dust mite-specific IgG4 and to induce a systemic antibody response which can compete with IgE in the binding of house dust mite allergens (see Figure 4[33]). Onset of the clinical effect is to be expected 8-14 weeks after initiation of treatment [1].

Figure 4: The mechanism of action for 12 SQ-HDM (figure adapted from [33])



Abbreviations: TH2, T helper cell type 2; IgA, Immunoglobulin A; IgE, Immunoglobulin E; IgG4, Immunoglobulin G4; SQ, Standardised quality; HDM, house dust mite

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Aim/outlined place in therapy for 12 SQ-HDM

12 SQ-HDM is licensed for the treatment of patients aged 12 to 65 years (adolescents and adults) with a confirmed diagnosis of persistent moderate-to-severe HDM AR despite the use of symptom-relieving medication, and patients aged 18 to 65 years (adults) with a confirmed diagnosis of HDM AA not well-controlled by ICS and associated with mild-to-severe HDM AR. 12 SQ-HDM is intended to be an addition to the formulary, rather than a replacement for an existing drug in the treatment pathway. Based on responses from a modified Delphi panel with UK allergy specialists (see Appendix M1 for the report containing anonymised and consolidated feedback), an average of 43 per 100,000 patients in the UK would be treated with 12 SQ-HDM, assuming patients had optimal access to the appropriate allergy services [8].

The BSACI [9], ARIA [30] and GINA [31] guidelines recommend the use of AIT, including SLIT-tablets, in ARD patients with uncontrolled disease exposed to relevant allergens. Wider access to AIT, especially SLIT, has been demonstrated to provide long-term symptom control, reduce the need for symptomatic treatments, and provide a treatment option for ARD patients, especially for those with moderate-to-severe disease who have uncontrolled disease despite compliant use of current treatments, or those who have tolerability issues [1]. The potential disease-modifying effect of immunotherapy may reduce the progression of disease and therefore reduce the comorbidities associated with the condition, as mentioned in Section B.2.6 [34-36].

B.1.3.3 12 SQ-HDM reimbursement in other countries

12 SQ-HDM is nationally reimbursed in the following countries: Austria, Belgium, Czechia, Canada, Denmark, France, Finland, Germany, Israel, Japan, Luxembourg, Netherlands, Norway, Poland, Switzerland, Spain, Sweden, Slovenia, and Slovakia.

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B1.4 Equality considerations

There are no known equality issues relating to the use of 12 SQ-HDM for treatment of HDM-induced AR in patients 12-65 years of age and HDM-induced AA in patients aged 18-65 years of age.

Despite the large burden of ARD for both patients and the NHS, there is a lack of accessible and well-resourced specialist services for ARD patients. Treatment is currently dependent on the patient's postcode: the local secondary care service's capacity in terms of workforce, as well as the availability of SLIT treatment in the service, fluctuates regionally [8]. Results from a Hospital Episode Statistics (HES) data analysis found that across England, only 14% of patients referred to secondary care with an aero-allergen diagnosis, were seen at an allergy specialist centre (see Appendices R1 and R2). The fact the first dose of 12 SQ-HDM is administered in secondary care may be considered to represent a barrier to some patients for whom allergy services are less accessible.

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B.2 Clinical effectiveness

B2.1 Identification and selection of relevant studies

Two systematic literature reviews (SLRs) were conducted to identify and summarise the results of published randomised control trials (RCTs) examining the efficacy of 12 SQ-HDM SLIT-tablets and other HDM AIT formulations (subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT)-drops) for HDM AR and HDM AA. The original SLR was produced in 2015; an updated SLR was conducted in 2023 to identify any additional data published between 2015 and 2023. The first SLR in 2015 assessed the feasibility of conducting indirect comparisons between 12 SQ-HDM and SCIT or SLIT-drops. As alternative AIT treatments are unlicensed and not regularly used in routine clinical practice in the NHS, and consequently were not identified by NICE as relevant comparators, this analysis was not included in the updated SLR and has not been presented in this submission. See Appendix D for full details of the process and methods used to identify and select clinical evidence relevant to the technology being evaluated.

The original and updated SLRs identified a total of 13 clinical studies that investigated the efficacy and safety of 12 SQ-HDM, of which five pivotal Phase 3 clinical trials have been identified as providing relevant clinical effectiveness evidence for this submission. Table 5 provides a summary of the 13 clinical studies identified in the clinical SLR.

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Table 5: Summary of clinical studies investigating the efficacy and safety of 12 SQ-HDM

Trial name	Study design	Disease area	Dosing (SQ-HDM)	Participants (N)	Included in model	Rationale for use/non-use in model
Pivotal trials						
MT-04 (MITRA) Virchow et al., 2016 [36]	Phase 3	HDM AA and AR	6,12	834	Yes	Key study evidencing efficacy and safety of 12 SQ-HDM in the AA+AR population Outcomes from the MT-04 trial are relevant to the decision problem and have been used in the model.
MT-06 (MERIT) Demoly et al., 2015 [34]	Phase 3	HDM AR with or without AA/ARC	6,12	992	Yes	Key study evidencing efficacy and safety of 12 SQ-HDM in the AR population Outcomes from the MT-06 trial are relevant to the decision problem and have been used in the model.
P001 Nolte et al., 2016 [35]	Phase 3	HDM AR with or without AA/ARC	12	1482	No	Key studies evidencing efficacy and safety of 12 SQ-HDM in the AA and/or AR population in adolescents and adults Outcomes from these studies are not transferable to the cost-effectiveness model. Further detail on the rationale from their exclusion from the model is provided in Section B.3.
TO-203-31 Tanaka et al., 2020 [37]	Phase 2/3	HDM AA with or without AR	6,12	826	No	
TO-203-32 Okubo et al., 2016 [38]	Phase 2/3	HDM AR	6,12	900	No	
Other supportive trials						
Gunawardana et al., 2017 [39]	Phase 1	HDM AR	12	23	No	Phase 1 study design not appropriate for further consideration within this analysis.
Bozek et al., 2021 [40]	NR	HDM AR and AA	NR	32	No	This study has been excluded given the assessment of low-quality evidence, with high risk of bias due to small patient population.

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Hoshino et al., 2020 [41]	NR	HDM AA and AR	6	112	No	This study has been conducted in a small Japanese only patient population. Outcomes from this study are not transferable to the cost-effectiveness model.
P003 Nolte et al., 2015 Zieglmayer et al., 2016 [42, 43]	Phase 2b	HDM AR with or without AA/ARC	6,12	124	No	Phase 2 trials were not considered as key studies given the availability of more relevant data from Phase 3 trials. Outcomes from this study are not transferable to the cost-effectiveness model.
MT-02 Mosbech et al., 2015 Mosbech et al., 2014* [44, 45]	Phase 2/3	HDM AR and AA	1,3,6	604	No	The trial results are not relevant for this analysis as treatment dosages are lower than the licensed dose (12 SQ-HDM).
Masuyama et al., 2018 [46]	Phase 3	HDM AR	6	458	No	This study has been excluded as the trial population considers only children and adolescents with 6 SQ-HDM.
MT-11	Phase 3	HDM AA	12	533	No	This study has been excluded as the trial population considers children and adolescents with AA. The licensed indication for HDM AA is adults only. Data from the MT-11 study are not relevant for this decision problem and not part of the current indication.

Abbreviations: AR, allergic rhinitis; AA, allergic asthma; ARC, allergic rhinoconjunctivitis; HDM, house dust mite; SQ, standardised quality.
*A study identified outside of the clinical SLR as the study was originally marked as a duplicate.

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Two Phase 2 clinical studies (P003 and MT-02) that are part of the SQ-HDM SLIT clinical trial programme were identified in the clinical SLR. Data from the Phase 2 clinical trials found that a dose response was seen for all areas of HDM ARD, including efficacy, immunology, and safety. The observed safety profile in MT-02 (evaluating doses of 1, 3, and 6 SQ-HDM in patients with mild-to-moderate HDM-induced AA) gave reason to believe that investigation of a dose higher than 6 SQ-HDM would be well-tolerated and potentially lead to better efficacy [44]. The overall results of MT-02 showed that ICS use could be reduced while maintaining asthma control when patients were treated with 6 SQ-HDM. Subgroup analyses further showed that patients with more severe AA had increased treatment effects compared to those with milder disease (MT-02) [44, 45]. The P003 environmental exposure chamber trial demonstrated that the statistically significant improvements in efficacy could be observed as early as 8 weeks following initiation of 12 SQ-HDM [42, 43]. There were no safety observations that gave rise to concern. Following the positive results of the Phase 2 studies, the 6 and 12 SQ-HDM doses were assessed in the Phase 3 clinical trials.

The five key Phase 3 clinical studies providing evidence on the efficacy of 12 SQ-HDM are discussed in detail through Section 2.2. to 2.12. The efficacy of 12 SQ-HDM is demonstrated in adult AA patients in the Phase 3 MT-04 trial [36] and Phase 2/3 TO-203-31 [37], in adult AR patients in the Phase 3 MT-06 trial [34], and in adult and adolescent AR patients in the Phase 3 P001 trial [35], and Phase 2/3 TO-203-32 trial [38].

The MT-04, MT-06, and TO-203 trials also explored the 6 SQ-HDM dose. However, only results for the indicated dose, 12 SQ-HDM, are detailed in this submission.

B2.2 List of relevant clinical effectiveness evidence

B.2.2.1 Pivotal Phase 3 randomised controlled trials

The key clinical studies evidencing the efficacy and safety of 12 SQ-HDM as a treatment for AA and AR, and AR alone are detailed in Table 6 to Table 10.

Table 6: Summary of MT-04 [47]

Study	MT-04 (The MITRA trial)

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Study design	Phase 3, randomised, parallel-group, double-blind, placebo-controlled, and multi-national trial.
Population	Adults (≥18 years) with HDM AA and AR. Subjects had to have clinically relevant history consistent with HDM-induced asthma not well-controlled by ICS, for at least 1 year before trial entry.
Intervention(s)	Drug: 6 SQ-HDM and 12 SQ-HDM
Comparator(s)	Drug: placebo
Indicate if study supports application for marketing authorisation	Yes

Reported outcomes specified in the decision problem	• Asthma symptoms and exacerbations
	  ○ Time to first moderate or severe asthma exacerbation after ICS reduction
	  ○ Total number of asthma exacerbations
	  ○ ACQ score
	• Use of ICS and the use of rescue medication
	  ○ Health care resource use and rate of hospitalisation
	• Lung function
	  ○ PEF
	  ○ FEV_1
	• AEs of treatment
	  ○ AEs
	  ○ SAEs
	  ○ AE-related discontinuations
	• HRQoL
	  ○ AQLQ(S) and SF-36

All other reported outcomes	All reported outcomes are listed in Appendix N .
Abbreviations: ACQ, Asthma control questionnaire; AQLQ, Asthma quality of life questionnaire; AE, adverse event; HDM, house dust mite; ICS, Inhaled corticosteroids; PEF, peak expiratory flow; SAE, serious adverse event.	

Table 7: Summary of MT-06 [48]

Study	MT-06
Study design	Phase 3, randomised, parallel-group, double-blind, placebo-controlled, multi-national trial.
Population	Adults (18-65 years of age), with HDM AR. The clinical history had to be consistent with moderate-to-severe persistent HDM AR with or without asthma, with AR symptoms of at least 1 year before trial entry despite having received symptomatic treatment. Furthermore, the symptoms had to be troublesome and interfere with usual activities or sleep.
Intervention(s)	Drug: 6 SQ-HDM and 12 SQ-HDM
Comparator(s)	Drug: placebo
Indicate if study supports application for marketing authorisation	Yes

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Reported outcomes specified in the decision problem	• Severity of rhinitis symptoms and medication use
	  ○ TCRS
	  ○ DMS and DSS
	  ○ TCS
	• AEs of treatment and complications of AR
	  ○ AEs
	  ○ AE-related discontinuations
	  ○ SAEs
	• HRQoL
	  ○ RQLQ and EQ-5D

All other reported outcomes	All reported outcomes are listed in Appendix N
Abbreviations: TCRS; total combined rhinitis score; DMS, daily medications score; DSS, daily symptom score; EQ-5D, EuroQoL 5 dimension; TCS, total combined rhinoconjunctivitis score; AE, adverse event; SAE, serious adverse event; RQLQ, Rhinitis quality of life questionnaire; AR, allergic rhinitis; HDM, house dust mite;	

Table 8: Summary of P001 [49]

Study	P001
Study design	Parallel assignment, placebo-controlled, randomised, double-blind, multicentre Phase 3 study assessing the efficacy and safety of 12 SQ-HDM.
Population	Adolescents and adults (12 years of age and older) with moderate-to-severe HDM AR/ARC of 1-year duration or more, with or without asthma
Intervention(s)	Drug: 12 SQ-HDM Please note during the trial the active treatment for the P001 trial was referred to as MK-8237. MK-8237 is referred to throughout this document as 12 SQ-HDM.
Comparator(s)	Drug: placebo
Indicate if study supports application for marketing authorisation	Yes

Reported outcomes specified in the decision problem	• Severity of rhinitis symptoms and medication use
	  ○ TCRS
	  ○ DSS and DMS
	  ○ TCS
	  ○ Average AR/ARC symptoms assessed by VAS
	• AEs of treatment and complications of AR
	  ○ AEs
	  ○ AE-related discontinuations
	  ○ SAEs
	• HRQoL
	  ○ RQLQ (S) and EQ-5D-5L

All other reported outcomes	All reported outcomes are listed in Appendix N
Abbreviations: TCRS; total combined rhinitis score; DMS, daily medications score; DSS, daily symptom score; TCS, total combined rhinoconjunctivitis score; AE, adverse event; SAE, serious adverse event; RQLQ, Rhinitis quality of life questionnaire; AR, allergic rhinitis; HDM, house dust mite; VAS, visual analogue scale.	

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Table 9: Summary of TO-203-31 [50]

Study	TO-203-31
Study design	Phase 3, randomised, double-blind, placebo-controlled, multicentre trial.
Population	Adults (18-64 years of age), with HDM AA not well-controlled by ICS, with more than 6 months treatment with ICS.
Intervention(s)	Drug: 6 SQ-HDM and 12 SQ-HDM
Comparator(s)	Drug: placebo
Indicate if study supports application for marketing authorisation	No

Reported outcomes specified in the decision problem	• Asthma symptoms and exacerbations
	  ○ Time to first moderate or severe asthma exacerbation after ICS reduction
	  ○ Total number of asthma exacerbations
	  ○ ACQ score
	• Use of ICS and the use of rescue medication
	  ○ Health care resource use and rate of hospitalisation
	• Lung function
	  ○ PEF
	  ○ FEV_1
	• AEs of treatment
	  ○ AEs
	  ○ SAEs
	  ○ AE-related discontinuations
	• HRQoL
	  ○ AHQ-JAPAN

All other reported outcomes	All reported outcomes are listed in Appendix N

Abbreviations: ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; AE, adverse events; AHQ, asthma health questionnaire; HDM, house dust mite; ICS, Inhaled corticosteroids; PEF, peak expiratory flow; FEV, forced expiratory flow.

Table 10: Summary of TO-203-32 [51]

Study	TO-203-32
Study design	Phase 3, randomised, parallel-group, double-blind, placebo-controlled, multicentre trial.
Population	Adults and adolescents (12-64 years) with moderate-to-severe HDM-induced AR and a positive specific IgE level against D pteronyssinus, D farinae, or both with at least a 1-year medication history of AR.
Intervention(s)	Drug: 6 SQ-HDM and 12 SQ-HDM
Comparator(s)	Drug: placebo
Indicate if study supports application	Yes (adolescent subgroup)

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for marketing authorisation	

Reported outcomes specified in the decision problem	• Severity of rhinitis symptoms and medication use
	  ○ TCRS
	  ○ DSS and DMS
	  ○ TCS
	• AEs of treatment and complications of AR
	  ○ AEs
	  ○ AE-related discontinuations
	  ○ SAEs
	• HRQoL
	  ○ JRQLQ

All other reported outcomes	All reported outcomes are listed in Appendix N
Abbreviations: TCRS, total combined rhinitis score; DMS, daily medications score; DSS, daily symptom score; TCS, total combined rhinoconjunctivitis score; AE, adverse event; SAE, serious adverse event; RQLQ, Rhinitis quality of life questionnaire; AR, allergic rhinitis; HDM, house dust mite; JRQLQ, Japanese Allergic Rhinitis Standard QoL Questionnaire	

B.2.2.2 Non-interventional studies

A non-systematic review of evidence was conducted by the company to identify and summarise the results of published real-world evidence studies reporting long-term efficacy data for 12 SQ-HDM and other company non-HDM AIT products. 7 non-interventional studies were identified as including an assessment of 12 SQ-HDM, of which 3 were considered not relevant to this submission (2 were conducted in child population and 1 evaluated sleep disorders associated with HDM ARD). 4 studies were ultimately considered relevant to this submission: The CARIOCA study [52], Reiber et al., 2021 [53], Sidenius et al., 2021 [54], and the REACT study [55].

This section provides an overview of the 4 non-interventional studies included as supportive evidence in this submission. An overview of these studies is provided in

Table 11. Section B.3. provides more detail on the inclusion of these studies in the cost-effectiveness analysis of 12 SQ-HDM.

Table 11: Overview of the non-interventional studies reporting long-term efficacy data for AIT

	CARIOCA [52]	**Reiber et al., 2021** [53]	**Sidenius et al., 2021** [54]	**REACT** [55]
N	1,483 (SAF)	1,525	198 (ITT)	92,048
Region	France (Europe)	Germany (Europe)	Sweden and Denmark (Europe)	Germany (Europe)

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	CARIOCA [52]	Reiber et al., 2021 [53]	Sidenius et al., 2021 [54]	REACT [55]
Population	HDM AR with/without AA	HDM AR and/or AA	HDM AR with/without AA	AR with/without asthma
Age groups	18-65	18-65	18-65	No age inclusion criteria
Trial design	'Real-life', non-interventional, multicentre, non-comparative, longitudinal, prospective, and descriptive study	Non-interventional, open-label, and observational study	Non-interventional, multicentre, observational study	Retrospective, observational, propensity score matched (PSM) cohort study
Primary objective	To add evidence on the safety of the SQ-HDM SLIT-tablet in patients with AR, alone or with AA, under real-life conditions in France	To characterise the benefit, safety, and tolerability of the HDM SLIT-tablet, in a real-life setting using data from German from 2016 to 2018	To investigate the safety profile, tolerability, and outcome of ACARIZAX after 1 year of treatment in clinical practice in Sweden and Denmark	To demonstrate longer-term and sustained effectiveness of AIT in the real-world using claims data from German from 2007 to 2017

Abbreviations: SAF, safety population; ITT, intention-to-treat population; HDM, house dust mite; AR, allergic rhinitis; AA, allergic asthma; PSM, propensity score-matched.

The CARIOCA study [52]

The CARIOCA study is a non-interventional, descriptive, multicentre, prospective and longitudinal (one-year) French study. The study's objective was to investigate the safety and tolerability of SQ-HDM SLIT-tablet in adult patients with HDM AR with or without asthma. The average duration of treatment was 380 days (±57). In this study, AR and AA symptoms of HDM respiratory allergy patients treated with 12 SQ-HDM were described and were collected at inclusion before the first intake. Patients' symptom evolution was assessed with patients' symptoms, which were also collected throughout the study.

Between May 2018 and May 2019, 1,526 patients were enrolled and 1,494 were included in the full analysis set (FAS) population. Of the FAS population, 20 patients did not meet the selection criteria, and 11 patients did not receive 12 SQ-HDM. As a result, 1,483 were eligible for analysis and included in the safety population. Overall,

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858 patients completed the study. The mean age of patients was 34 years; 59% were female, 64% were poly-sensitised, and 16% had reporting having already taken HDM AIT but not in the 12 months before inclusion.

Rhinitis and asthma symptom control were evaluated by the AR control test (ARCT) and asthma control test (ACT), respectively. The distribution of asthma control at inclusion was 54% well, 28% partially, and 18% uncontrolled. The study's findings revealed an improvement in asthma control at the end of the study for 12 SQ-HDM patients, with 81% of AA patients well-controlled, 14% partially controlled, and 5% uncontrolled. ACT improved by 3.0 points on average from the start to the end of the trial. Schatz et al., 2009 [56] report that data from four independent samples of adult asthmatic patients support a minimally important difference (MID) for the ACT of 3 points). ARCT data for 641 out of 852 AR patients were available. Of the 446 AR patients who had uncontrolled AR at inclusion (69.8%), 380 (85%) were controlled by the end of the study.

Overall, the CARIOCA study found that in real-life settings, there was an improvement of both AR and asthma control after treatment with 12 SQ-HDM. Furthermore, the results indicate a good safety profile for 12 SQ-HDM, regardless of asthma control.

Reiber et al., 2021 [53]

A non-interventional, open-label, observational study was conducted by Reiber et al., in Germany. The study aimed to characterise the benefit, safety, and tolerability of the HDM SLIT-tablet, in a real-life setting. The trial was conducted in 356 allergists' offices from January 2016 to April 2018. The study analysed a total of 1,525 patients, of which 1,096 patients had AR (without AA) and 429 patients had AA (AR and AA: 424; and AA: 5). Patients' AA symptom control was assessed between 1-3 months after treatment initiation, followed by subsequent follow-up visits approximately every 3 months for a total observation period of up to one year, and a median treatment duration of 301 days.

The patients received medication according to the GINA guidelines. Patients classified as Step 1 comprised 30.6%, Step 2 37.2%, Step 3 19.9%, Step 4 1.9%,

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and Step 5 0.2% (10.2% had no medication). The level of asthma control at baseline was assessed as well-controlled in 36.9% of patients, partially controlled in 41.2%, and uncontrolled in 22.0%.

Allergy symptoms were found to improve with 12 SQ-HDM treatment, and the use of symptomatic treatment decreased at the last visit of the study compared to baseline assessments. The proportion of patients with AA (AA plus AR or AA; n=369 patients) who were assessed as well-controlled increased from 36.9% at baseline to 78.3% in their level of allergic asthma symptom control at the last visit [53]. These results demonstrate the effectiveness of 12 SQ-HDM treatment in real life and support the results of the MT-04 trial [36].

Of the 1,525 patients, 32.1% experienced an AE, of which 27.9% were possibly related to treatment (treatment-related adverse events; TRAEs). Treatment was discontinued owing to TRAEs in 10.8% of patients with AR and in 17.7% of patients with AA plus AR. The severity of TRAEs was assessed as mild-to-moderate in 24.7% of patients and severe in 3.0%. The most frequent TRAEs (7.6% to 3.1%) observed during the entire observation period were oral pruritus, throat irritation, mouth swelling, swollen tongue, lip swelling, dyspnoea, and oral paraesthesia, which is consistent with the safety profile obtained from the pivotal MT-04 and MT-06 RCTs [34, 36, 53].

Sidenius et al., 2021 [54]

This non-interventional multicentre, observational study aimed to investigate the safety profile, tolerability, and outcomes of 12 SQ-HDM after one year of treatment in clinical practice among 198 adult patients with HDM AR with or without AA (four patients were excluded from the FAS). Patients were followed at three visits for one year, where asthma control (according to the GINA guidelines) and AR and AA medication use were recorded.

The mean age of subjects was 38 years. Of the 198 analysed patients, 58% had AR only, and 42% had both AR and AA. Overall, 84% of patients completed the study and had data available at visit three.

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21 (32%) patients obtained an improvement in asthma control of at least one step between the first and third visits (p=0.013). AR and AA patients also experienced a significant reduction in daytime asthma symptoms and fewer nighttime awakenings due to asthma. Over time, asthma medication was also reduced in the AA with AR subgroup – specifically, ICS and SABA were reduced by 20% and 23%, respectively, between the first and third visits.

Overall, 80% of patients experienced an AE between the first and third visits. Of these, 75% were mild, 21% moderate, and 2% severe. 4 SAEs were recorded but considered to be not treatment-related. One SAE of dyspnoea was considered possibly treatment-related but was reported to potentially be related to the patient's pre-existing grass pollen allergy. Regarding discontinuations, 84% of patients completed the study and had data available at Visit 3. No anaphylactic reactions occurred during the study, and no adrenaline was administered.

The REACT study [55]

The REACT (Real-world effectiveness in allergy immunotherapy) study was a retrospective observational, propensity score-matched (PSM) cohort study using claims data between 2007 and 2017 from a German health insurance fund database (Betriebkrankenkasse [BKK]). The study aimed to assess the long-term effectiveness of AIT modalities for the treatment of AR and asthma in a real-world setting.

The study included subjects with AR with or without AA. The study included patients who were treated with AIT for an average of 549 (standard deviation (SD): 284) days during the study; a control group not treated with AIT was also included in the study population. 46,024 AIT-treated subjects were matched 1:1 with control subjects. 14,614 AIT-treated patients were included in the pre-existing asthma cohort alongside an identical number of matched controls.

During the study period, 115,098 patients out of the 5,983,511 available patients in the database had at least one AIT prescription, of which 46,024 were eligible for inclusion. AIT-treated subjects had an average age of 29.5 years and 53% were male. AIT was administered as SCIT in 36,927 patients, SLIT-drops in 4,816 patients, and SLIT-tablets in 3,754 patients. In total, 7,774 patients were on HDM

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AIT. Outcomes were analysed as within-group (pre- vs post-AIT) and between-group (AIT vs. control) differences over 9 years of follow-up. Pre-existing asthma patients in the AIT group received on average 2.5 asthma prescriptions (SD: 3.3). Diagnosis codes for asthma and use of controller medications mimicking the GINA steps were used to assess changes in asthma treatments. At baseline, which considered the year prior to starting AIT treatment, at least 16% of patients in the analysis had at least one severe asthma exacerbation. At 9 years of follow-up, the subpopulations consisted of 3,692 patients in the main cohort and 1,142 patients in the pre-existing asthma cohort.

Compared to the pre-index year, AIT was consistently associated with greater reductions compared to control subjects in asthma prescriptions and in AR prescriptions, which was sustained for 9 years. Additionally, the AIT group had a significantly greater likelihood of stepping down asthma treatment in comparison with the control group in Year 3 (OR: 1.15, p<0.0001), in Year 5 (OR: 1.27, p<0.0001), and in Year 9 (OR: 1.30 p=0.032).

The study demonstrated sustained, long-term reductions in the number of severe asthma exacerbations (Year 9, 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. In addition, the number of anaphylaxis cases around treatment initiation were low.

B2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 MT-04

B2.3.1.1 Trial design

MT-04 was a randomised, parallel-group, double-blind, placebo-controlled, multi-national, multicentre trial conducted in Europe that included patients with HDM AA not well-controlled by ICS. The overall trial design is presented in Figure 5 [36, 47].

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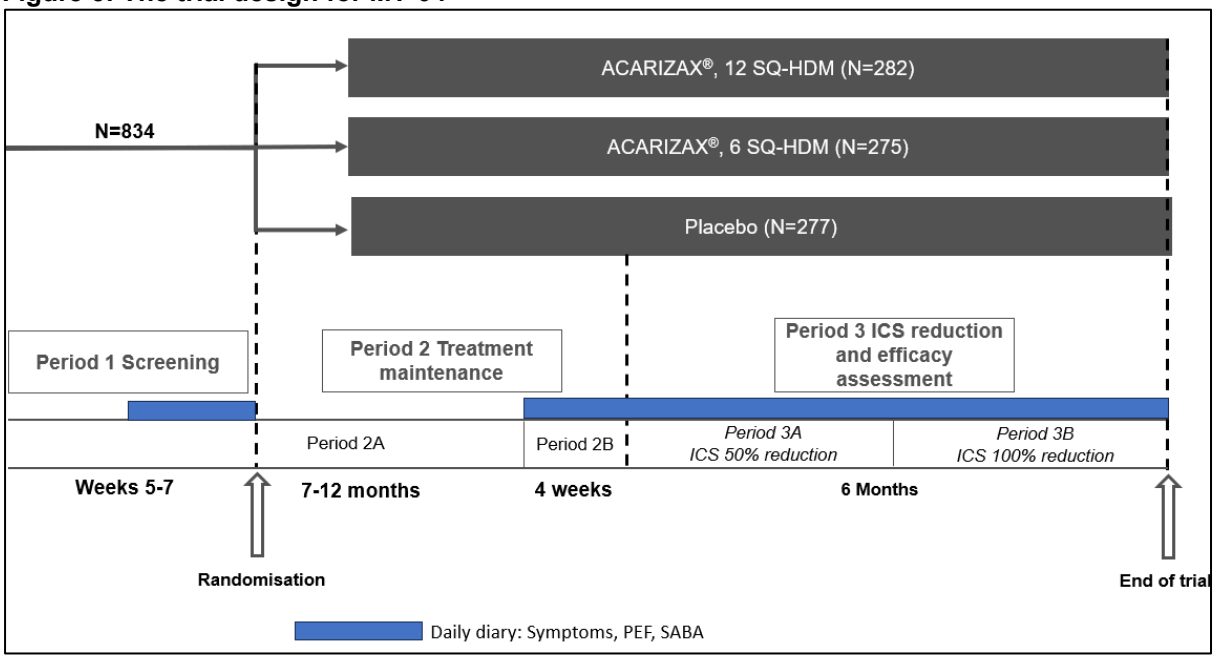
Figure 5: The trial design for MT-04 [36, 47]



During Period 1 (the screening period), eligible patients were switched from their regular asthma controller medication (including combination products) to equivalent doses of ICS (budesonide) and SABA as needed. The recordings of patient's lung function (PEF scores), asthma symptoms and SABA use during the last 2 weeks of Period 1 (screening Period) served as each subject's baseline and were used for the generation of asthma exacerbation alerts in Period 3 (ICS reduction/withdrawal period).

From randomisation (Visit 3) and throughout Period 2 (Visit 4-8), participants received 6 SQ-HDM, 12 SQ-HDM, or placebo in addition to ICS and SABA. During the approximately final 4 weeks of Period 2 (Period 2B), participants completed electronic diaries twice daily recording asthma symptoms, medication use, and lung function.

Period 3 was considered as the efficacy assessment period, during which patients had their daily ICS dose reduced by 50% in the first 3 months (Period 3A), then subsequently completely withdrawn for an additional 3 months (Period 3B), although the latter change was only for participants who did not experience an asthma exacerbation during Period 3A. If participants experienced an asthma exacerbation during Period 3B, when they did not use any ICS, the patient was discontinued from

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the trial. Throughout Period 3, participants measured lung function (PEF), and reported asthma symptoms and SABA use twice daily.

B2.3.1.2 Eligibility criteria

Table 12: Summary of the inclusion and exclusion criteria of the MT-04 trial [47]

Inclusion criteria	Exclusion criteria
≥18 years of age	A clinical history of persistent AA or AR caused by an allergen to which the subject was regularly exposed and sensitised (except HDM)
Clinical history consistent with HDM-induced asthma of at least 1 year prior to trial entry	A clinical history of intermittent (seasonal) AA or AR if the seasonal allergen was causing symptoms in the period of the year corresponding the ICS reduction period (Period 3)
Use of an appropriate amount of ICS (incl. combination products) in accordance with the GINA Guideline Step 2-4 for the control of the asthma symptoms for a period of at least 6 months within the past year	Previous treatment with immunotherapy with HDM allergen for more than 1 month within the last 5 years
Documented reversible airway obstruction	A clinical history of chronic sinusitis (>3 months)
ACQ score ≥1.0 at screening	Hospitalisation for more than 12 hours due to asthma exacerbation within the last 3 months prior to screening visit
1.0≤ACQ≤1.5 at Visit 3 (randomisation)	Symptoms of or treatment for upper respiratory tract infection, or other relevant infectious process at randomisation
FEV1≥70% of the predicted value	Inflammatory conditions in the oral cavity with severe symptoms, such as oral lichen planus with ulcerations or severe oral mycosis, at randomisation
A positive skin prick test response to Dermatophagoides pteronyssinus and/or Dermatophagoides farinae	Immunosuppressive treatment (ATC code L04 or L01) within 3 months prior to the screening visit (except steroids for allergy and asthma symptoms)
Positive specific IgE levels (>0.70kU/L) against Dermatophagoides pteronyssinus and/or Dermatophagoides farinae	

Abbreviations: AA, allergic asthma; AR, allergic rhinitis; ICS, inhaled corticosteroid; HDM, house dust mite.

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B2.3.1.3 Settings and locations

MT-04 was conducted at 109 trial sites across the following 13 countries: Austria, Germany, Denmark, Spain, France, United Kingdom, Croatia, Lithuania, Latvia, Netherlands, Poland, Serbia, Slovakia.

B2.3.1.4 Trials drugs

Eligible patients were treated with 6 SQ-HDM, 12 SQ-HDM, or placebo. Subjects received daily treatment for 13-18 months.

B2.3.1.5 Permitted and disallowed concomitant medications

Permitted concomitant medication:

Concomitant medications were defined as medications continued by a subject upon entry into the trial (Visit 1), and all medications used in addition to the investigational medicinal product (IMP; either 12 SQ-HDM, 6 SQ-HDM, or placebo) and symptomatic medications provided during the trial.

Concomitant medications were to be kept to a minimum during the trial. However, if considered necessary for the subject's well-being and unlikely to interfere with the IMP, concomitant medications were allowed to be prescribed at the discretion of the investigator according to the local SOC[47].

Any use and changes in concomitant treatment (e.g., new treatment, discontinuation of treatment, or change in dosage/routine) during the trial were recorded.

Symptomatic medication (non-investigational products)

As patients during the trial were expected to experience asthma symptoms which would require additional treatment. Symptomatic medications were provided to participants as predefined, open-labelled medication.

Symptomatic medications were allowed to be used as needed in addition to the IMP to which the patients had been randomised. ICS was provided as budesonide powder for inhalation in strengths of 100 or 200 µg per dose, and were used as daily controller treatment of asthma until Period 3B (ICS complete withdrawal) or throughout the trial for patients having an asthma exacerbation in Period 3A (ICS

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50% reduction) and continuing the trial. Switching of asthma controller medication to ICS (i.e., budesonide) was performed in accordance with the GINA 2008 estimation of equipotent inhaled glucocorticosteroids (see Appendix N). For a subject to be eligible for treatment, dosing of ICS after switching at randomisation had to be within the range of 400-1200 µg budesonide.

Throughout the trial, SABA was provided as salbutamol for inhalation in a strength of 200 µg/dose, for use as-needed to control asthma symptoms. Oral steroids were provided as prednisone or prednisolone tablets in strength of 5, 10 or 20 mg/tablet depending on the availability in each country. Oral steroids were used in accordance with the individual asthma action plan: only to treat acute severe asthma symptoms, acute deterioration of asthma symptoms, or acute deterioration in lung function in cases where the subject could not get in contact with the investigator [47].

Prohibited concomitant medication:

Concomitant medications prohibited during the trial are listed in Appendix N.

B2.3.1.6 Outcomes used in the economic model or specified in the scope

The key outcomes from MT-04 relevant to this appraisal are presented in Table 13.

Table 13: Outcomes from MT-04 relevant to this appraisal [47]

Primary outcomes
• Time to first moderate or severe asthma exacerbation during Period 3 (ICS reduction/ withdrawal)
Key secondary outcomes
• Time to first asthma exacerbation with deterioration in asthma symptoms • Proportion of patients with a MID change in ACQ controlled for change in ICS • Proportion of patients with a MID change in AQLQ(S) controlled for change in ICS • Immunology measured as change from baseline to end of trial in terms of specific IgG_4 against HDM allergens
Safety outcomes
• AEs • AE discontinuations • SAEs • Vital signs • Safety laboratory assessments • FEV1 • Physical examinations
Abbreviations: ICS, inhaled corticosteroid; ACQ, asthma control questionnaire; AQLQ asthma quality of life questionnaire; IgG4, immunoglobulin G4; HDM, house dust mite; AE, adverse event; SAE, serious adverse event; FEV, forced expiratory volume.

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Primary and secondary efficacy endpoints included assessments of asthma exacerbations, asthma symptoms, nocturnal awakenings, lung function (PEF or FEV1), use of asthma symptomatic medications as well as unscheduled visits to the trial sites, visits to emergency rooms, or hospitalisations.

The primary endpoint for the MT-04 trial was the time to first moderate or severe asthma exacerbation during Period 3 (the ICS reduction/withdrawal phase). An asthma exacerbation event was considered to have occurred if one or more of the criteria listed in Table 14 were met, and it led to a change in treatment. The primary analysis was based on a multiple imputation method (FAS-MI dataset). All subjects who discontinued from the trial during Period 2 (treatment maintenance) were included in the primary analysis as if they were following the same distribution as the observed placebo group during efficacy assessment (i.e. during Period 3; ICS reduction/withdrawal) with respect to time to first asthma exacerbation.[47]

Table 14: MT-04 trial definition of moderate and severe exacerbation[47]

Criterion	Definition
Moderate exacerbation	
A	Nocturnal awakening(s) due to asthma requiring SABA use for at least 2 consecutive nights, or an increase of a minimum 0.75 in DSS from the baseline value on at least 2 consecutive days
B	Increase from the baseline value in occasions of SABA use on at least 2 consecutive days (a minimum increase of 4 puffs per day)
C	≥20% decrease in PEF from baseline value on at least 2 consecutive mornings or evenings, or a ≥20% decrease in FEV1 from baseline value
D	Visit to the emergency room or unscheduled visit to the trial centre for asthma treatment not requiring systemic corticosteroids
Severe exacerbation	
E	Need for systemic corticosteroids for the treatment of asthma symptoms for at least 3 days
F	Emergency room visit because of asthma, requiring systemic corticosteroids, or hospitalisation for more than 12 hours because of asthma

Abbreviations: SABA, Short-acting β2-agonist; PEF, Peak expiratory flow; FEV, forced expiratory flow.

Asthma symptoms were assessed by participants in the morning and evening. The asthma DSS ranges from 0 to 12 points and reflects 4 symptoms (cough, wheeze,

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shortness of breath, or chest tightness), each of which were measured on a 4-point scale from 0 (no symptoms) to 3 (severe symptoms). Participants also recorded their use of SABA to control asthma symptoms throughout the trial.

An analysis of the odds for improvement in MID change in ACQ and AQLQ(S) controlled for ICS use was performed, with change measured from baseline to the end of trial.

Asthma control covering the past week was assessed by participants by the ACQ at all visits except Visit 2. The ACQ consists of 7 questions referring to the previous week. 5 questions are related to symptoms (nocturnal wakening, morning symptoms, activity limitation, short of breath, wheeze), 1 question is about the frequency of SABA use, and 1 question is about lung function (percentage of predicted FEV1). Each question is scored on a 7-point scale from 0 to 6, with higher scores indicating poorer responses. The overall ACQ score is the average of the 7 scores of the individual questions. The range of the overall ACQ score is 0 to 6. A score of 0-0.75 is classified as well-controlled asthma; 0.75–1.5 is partially controlled; and a score >1.5 is poorly controlled asthma. The minimum clinically important difference for the ACQ is a change of 0.5 [47].

Asthma QoL was assessed by participants by the AQLQ(S) at Visits 3, 6, 8-13, and all unscheduled visits prompted by asthma exacerbations. The AQLQ contains 32 questions organised into four domains: symptoms, activity limitation, emotional function, and environmental stimuli. Each question is scored on a 7-point scale, with higher scores indicating better QoL and lower scores indicating a more negative impact of asthma on daily functioning and well-being. An improvement of 0.5 to 0.7 points in the AQLQ score is considered clinically meaningful for patients with asthma.

Participants also completed the SF-36 questionnaire at Visits 3, 6, and 9-13. The SF-36 is a generic, multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional health, and mental health) as well as psychometrically-based physical and mental health summary measures.

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Lung function was assessed by means of PEF and FEV1 during Period 2B and the first asthma exacerbation-free period during Period 3.

To assess the immunological response to the treatment, blood samples were drawn to determine HDM-specific IgE and IgG_4 at Visit 1 (screening), Visit 4 (treatment maintenance), Visit 6 (treatment maintenance), Visit 9 (ICS reduction), and Visit 13 (end of trial).

B2.3.1.7 Subject baseline characteristics

Baseline and disease characteristics were generally similar in the 12 SQ-HDM and placebo groups in MT-04: see Table 15 and Table 16.

Table 15: MT-04 baseline patient demographics [47]

Treatment group	Placebo n=277	12 SQ-HDM n=282	Overall N=834
Gender, n (%)			
Male	151 (55%)	147 (52%)	431 (52%)
Female	126 (45%)	135 (48%)	403 (48%)
Ethnic origin, n (%)			
Caucasian	273 (99%)	277 (98%)	822 (99%)
Asian	1 (<1%)	2 (<1%)	4 (<1%)
African	1 (<1%)	2 (<1%)	4 (<1%)
Hispanic	2 (<1%)	1 (<1%)	3 (<1%)
Other	0	0	1 (<1%)
Smoking history, n (%)			
Non-smoker	214 (77%)	214 (76%)	626 (75%)
Previous smoker	36 (13%)	38 (13%)	124 (15%)
Smoker	27 (10%)	30 (11%)	84 (10%)
Age, mean (SD)			
Age (years)	33.0 (12.2)	33.7 (11.6)	33.4 (11.7)
Weight, height, and body mass index (BMI), mean (SD)			
Weight (kg)	76.3 (16.7)	75.9 (16.3)	76.2 (16.4)
Height (cm)	172.8 (10.5)	171.6 (9.4)	171.9 (9.8)
BMI (kg/m^2)	25.5 (5.0)	25.7 (4.7)	25.7 (4.8)

Abbreviations: SQ, standardised quality; HDM, house dust mite; BMI, body mass index; SD, standard deviation.

Approximately half of the subjects were male and almost all subjects were Caucasians, with no major differences between groups. The mean age of the population was 33.4 years old, and the median was 31 years old. No upper age limit was included in the trial inclusion criteria. The maximum age was 83 years old (in the

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placebo group) and 5% of the population was above 55 years old. Participant demographic characteristics were consistent between treatment groups.

The countries recruiting most subjects for the trial were Poland, Spain, Serbia, and France with 38%, 9%, 7%, and 6% of the trial population, respectively, enrolled in these countries[47].

Table 16: MT-04 baseline disease characteristics [47]

Treatment group	Placebo n=277	12 SQ-HDM n=282	Overall N=834
Sensitisation status, n (%)			
Mono-sensitised	102 (37%)	91 (32%)	282 (34%)
Poly-sensitised	175 (63%)	191 (68%)	551 (66%)
GINA asthma control level, mean (SD)			
Partly controlled	200 (72%)	200 (71%)	602 (72%)
Uncontrolled	77 (28%)	82 (29%)	232 (28%)
Lung function, mean (SD)			
Morning PEF (L/min)	456 (132)	443 (125)	444 (127)
Diurnal variability in PEF (L/min)	8.50 (4.70)	8.29 (5.19)	8.61 (5.30)
FEVI (% of predicted value)	94.34 (13.79)	91.39 (12.91)	92.67 (13.17)
HRQoL, mean (SD)			
ACQ score at randomisation	1.22 (0.18)	1.23 (0.17)	1.23 (0.17)
AQLQ(S) score at randomisation	5.54 (0.78)	5.49 (0.78)	5.50 (0.81)
Symptom score, mean (SD)			
Total asthma daytime symptom score	2.63 (2.05)	2.58 (1.92)	2.64 (1.98)
Asthma nocturnal symptom score	0.61 (0.56)	0.57 (0.50)	0.61 (0.53)
Nocturnal awakening requiring SABA intake	0.12 (0.26)	0.11 (0.23)	0.12 (0.24)
Medication use, mean (SD)			
ICS at randomisation (µg budesonide)	580 (246)	602 (264)	588 (252)
24-hour SABA intake (number of 200-pg puffs)	1.30 (1.53)	1.23 (1.47)	1.32 (1.63)
HDM IgG4, mean (SD)			
Dermatophagoides pteronyssinus	0.5 (0.5)	0.4 (0.6)	0.4 (0.5)
Dermatophagoides farinae	0.4 (0.5)	0.5 (0.9)	0.4 (0.6)
Years with HDM AR/AA, mean (SD)			
Asthma	13.3 (10.6)	12.9 (11.5)	12.9 (11.2)
Rhinitis	14.1 (10.8)	12.8 (10.8)	13.3 (10.9)

Abbreviations: SABA, Short-acting β2-agonist; SD, standard deviation; IgG4, immunoglobulin G4; SQ, standardised quality; HDM, house dust mite; ICS, inhaled corticosteroids; AA, allergic asthma; AR, allergic rhinitis; PEF, peak expiratory flow; FEV, forced expiratory flow; GINA, global initiative for asthma; AQLQ, asthma quality of life questionnaire.

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The average asthma daytime symptom score and the average asthma nocturnal symptom score over the baseline did also not reveal any major differences between groups. The overall asthma daytime symptom score over the baseline period was 2.64 (on a 0-12 scale) and the asthma nocturnal symptom score 0.61 (on a 0-3 scale).

The average SABA intake during the baseline period corresponded to 1.32 units per 24-hour. There were no major differences between groups.

An estimate of 'GINA asthma control level' at randomisation showed that even though ACQ <1.5 was required for inclusion in the trial, 28% of subjects were uncontrolled at randomisation according to GINA definition of asthma control. This was equally distributed between treatment groups. The mean duration of HDM AA was 12.9 years, with no major differences between groups.

B.2.3.2 MT-06

B2.3.2.1 Trial design

MT-06 was a one-year, randomised, parallel-group, double-blind, placebo-controlled, multi-national, multi-site trial in Europe. The trial design for MT-06 is shown in Figure 6.

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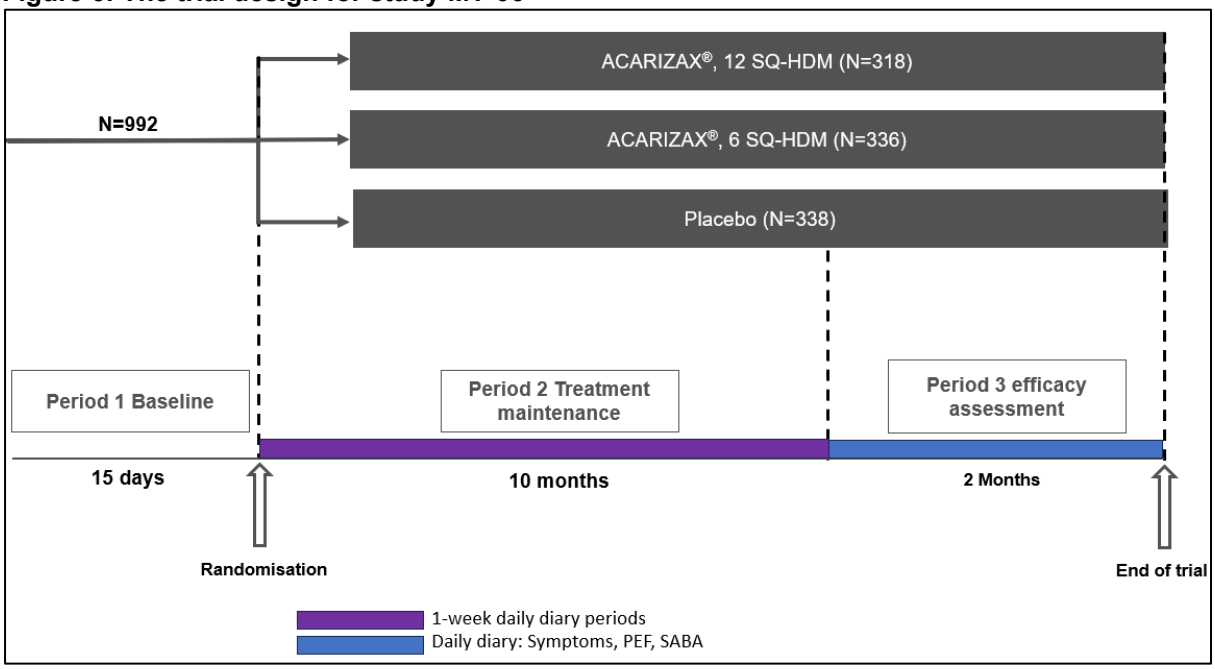
Figure 6: The trial design for study MT-06 [34, 48]



The trial was initiated in October 2011, when the major pollen seasons in Europe (birch and grass) had ended. Between screening and randomisation (Period 1), participants were asked to fill in an electronic diary daily for 15 days, to capture information on rhinitis symptoms, use of symptomatic medications, and impact of rhinitis on daily life.

At randomisation and throughout Period 2 and Period 3, participants received 6 SQ-HDM, 12 SQ-HDM, or placebo. They were also provided with symptomatic medications, namely nasal steroids, oral antihistamines, and antihistamine eye drops, to be used as needed.

Throughout the trial, participants were asked about rhinitis symptoms and HRQoL, and filled in an electronic diary for 1 week following each visit in Period 2 (Visits 3 to 6), and daily during the last 8 weeks of treatment (Period 3, between Visit 7 and Visit 8) [34, 48].

B2.3.2.2 Eligibility criteria

Table 17: Summary of the inclusion and exclusion criteria of the MT-06 trial [48]

Inclusion criteria	Exclusion criteria
18-65 years of age	A clinically relevant history of symptomatic seasonal allergic ARC and/or asthma

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	caused by an allergen to which the subject is regularly exposed and overlapping with the 8-week efficacy assessment period
Clinical history consistent with moderate-to-severe persistent HDM AR (with or without asthma) for at least one year prior to trial entry, with AR symptoms despite having received symptomatic treatment	A clinically relevant history of symptomatic allergic ARC caused by mould or animal hair and dander to which the subject is regularly exposed
Moderate-to-severe HDM AR symptoms during the baseline period, defined as a daily total rhinitis symptom score of at least 6 or a score of at least 5 with one symptom being severe, during at least 8 days of the 15-day baseline period	Reduced lung function (defined as FEV1 <70% of predicted value after adequate pharmacologic treatment)
Use of symptomatic medication for treatment of HDM AR during at least 8 days of the 15-day baseline period	A clinical history of uncontrolled asthma within 3 months prior to screening
Presence of one or more of the following ARIA quality of life items due to HDM AR during the baseline period: • Sleep disturbance • Impairment of daily activities, leisure, and/or sport • Impairment of school or work	Symptoms of or treatment for upper respiratory tract infection, acute sinusitis, acute otitis media, or other relevant infectious process at randomisation
If the subject has asthma, daily use of ICS should be ≤400mcg budesonide or equivalent (i.e. corresponding to GINA treatment steps 1 or 2)	Any nasal condition that could confound the efficacy or safety assessments (e.g., nasal polyposis)
Positive skin prick test response (wheal diameter ≥3 mm) to Dermatophagoides pteronyssinus and/or Dermatophagoides farinae	Inflammatory conditions in the oral cavity with severe symptoms, such as oral lichen planus with ulcerations or severe oral mycosis, at randomisation
Positive specific IgE against Dermatophagoides pteronyssinus and/or Dermatophagoides farinae (defined as ≥IgE Class 2; i.e. ≥0.70 kU/L)	Previous treatment with immunotherapy with HDM allergen or a cross-reacting allergen for more than 1 month within the last 5 years
	Ongoing treatment with any allergy immunotherapy

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	Immunosuppressive treatment within 3 months prior to the screening visit (except steroids for AR and asthma)
	Current treatment with tricyclic antidepressants; catechol-O-methyl transferase inhibitors and mono amine oxidase inhibitors
Abbreviations: ARC, allergic rhinoconjunctivitis; FEV, forced expiratory volume; AR, allergic rhinitis; IgE, immunoglobulin E; ICS, inhaled corticosteroid; GINA, global initiate for asthma; HDM, house dust mite.	

B2.3.2.3 Settings and locations

MT-06 was conducted at 100 trial sites across the following 12 countries: Austria, Bosnia and Herzegovina, Croatia, Czech, Denmark, France, Germany, Latvia, Poland, Romania, Serbia, and Ukraine [48].

B2.3.2.4 Trial drugs

Eligible patients were treated with 6 SQ-HDM, 12 SQ-HDM, or with placebo. Subjects received daily treatment for approximately 12 months.

B2.3.2.5 Permitted and disallowed concomitant medications

Permitted concomitant medications:

Concomitant medications were defined as all medications being continued by a subject on entry into the trial (Visit 1) and all medications used in addition to the IMP (either 12 SQ-HDM, 6 SQ-HDM, or placebo) and symptomatic medications provided during the trial. Concomitant treatments and medications were kept to a minimum during the trial. However, if considered necessary for the subject's well-being and unlikely to interfere with the trial medication, they could be provided according to the local SOC.

Symptomatic medications:

Symptomatic medications were permitted in the trial and provided at randomisations as predefined, open-labelled medication used in addition to the IMP.

For the rhinitis symptoms, participants were provided with:

- Oral antihistamine tablets (desloratadine tablets, 5mg)

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- Nasal corticosteroid spray (budesonide 64 µg/dose)

For the conjunctivitis symptoms, participants were provided with:

- Antihistamine eye drops (azelastine 0.05% or lodoxamide tromethamine 0.1% (in Croatia only)). In Serbia, oral antihistamine tablets were provided instead of eye drops for conjunctivitis symptoms.

Prohibited concomitant medications:

The prohibited concomitant medications in MT-06 are listed in Appendix N.

B2.3.2.6 Outcomes used in the economic model or specified in the scope

The key outcomes of MT-06 that are relevant to this appraisal are presented in Table 18.

Table 18: Outcomes from MT-06 that are relevant to this appraisal [48]

Primary outcomes
• Average TCRS during the efficacy evaluation period
Key secondary outcomes
• Average total AR DSS during the efficacy evaluation period • Average total AR DMS during the efficacy evaluation period • Average overall RQLQ score during the efficacy evaluation period • Average total combined allergic ARC score during the efficacy evaluation period
Safety outcomes
• AEs • AE discontinuations • SAEs • Vital signs • Safety laboratory assessments • FEV1 • Physical examinations
Abbreviations: FEV, forced expiratory volume; AR, allergic rhinitis; AE, adverse event; SAE, serious adverse event; DSS, daily symptom score; DMS, daily medications score; RQLQ, rhinoconjunctivitis quality of life questionnaire; ARC, allergic rhinoconjunctivitis; TCRS, total combined rhinitis score.

The primary endpoint for the MT-06 trial was the average TCRS during the primary efficacy evaluation period (Period 3, between Visit 7 and Visit 8), which took place between 1st October and 15th March to avoid overlapping symptoms caused by pollen allergy.

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The TCRS is calculated as the sum of rhinitis symptom and medication score [range, 0-24]. The total AR DSS was the total of 4 rhinitis symptom scores (runny nose, blocked nose, sneezing, and itchy nose), which were measured on a 4-point scale from 0 (no symptoms) to 3 (severe symptoms) and ranged from 0-12. The total AR DMS was the sum of the total daily scores for all rhinitis medication, and ranged from 0-12. For the medication score, subjects reported their use of specific pharmacotherapy. To transform the amount of symptomatic medications used into medication scores, the scoring principles detailed in Table 19 were applied.

Additionally, total allergic conjunctivitis DSS and DMS were collected; 2 conjunctivitis symptoms (gritty feeling/red/itchy eyes and watery eyes) were measured on a 4-point scale from 0 (no symptoms) to 3 (severe symptoms), as well as total daily scores for all conjunctivitis medication[48].

Table 19: MT-06 trial scoring of symptomatic medication use [48]

Symptomatic medication	Score/dose unit*	Maximum daily dose	Maximum daily score
Rhinitis medication score			
Desloratadine tablets#, 5 mg	4 per tablet	1 tablet	4
Budesonide nasal spray, 64 µg/dose	2 per puff	2 puffs per nostril	8
Maximum daily rhinitis medication score†			12
Conjunctivitis medication score**			
Desloratadine tablets#, 5 mg	2 per tablet	1 tablet	2
Azelastine eye drops, 0.05%	1.5 per drop	2 drops per eye	6
Maximum daily conjunctivitis medication score†			8

*: Scoring scales were not seen by the subjects. #: Desloratadine counted 4 in the rhinitis score and 2 in the conjunctivitis score, based on assumed equal efficacy of antihistamine on the 4 nasal symptoms and 2 eye symptoms (Salmun & Lorber 2002). †: If any subject exceeded the recommended daily dose of symptomatic medication, the actual score was used. **: There was no scoring of the amount of eye drops used in Serbia and Croatia.

QoL was assessed by participants by the RQLQ(S) during baseline (between Visit 1 and 2), weekly at Visits 3-6, and during the efficacy evaluation period (between Visit 7 and 8). The RQLQ(S) consists of 28 questions each on a 7-point (0-6) scale, divided into 7 domains (activities, sleep, non-nose/eye symptoms, practical

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problems, nasal symptoms, eye symptoms, and emotional). All items within each domain are weighted equally. The weekly domain scores were calculated as the average of all items scores for each domain. The weekly overall RQLQ score was the average of all 28 item scores, with higher scores indicating worse rhinoconjunctivitis HRQoL. Participants also completed the EQ-5D questionnaire to collect data on their HRQoL, at Visits 2, 3, 4, 5, 6, 7, and 8.

To assess the immunological response to the treatment, blood samples were collected at Visits 1, 3, 4, 5 and 8 for determination of HDM-specific IgE and IgG_4 in a small subset of subjects (only subjects from German sites who had given consent) [48].

B2.3.2.7 Subject baseline characteristics

Participant baseline demographic and disease characteristics were consistent in the 12 SQ-HDM and placebo groups in MT-06: see Table 20 and Table 21.

Table 20: MT-06 baseline patient demographics [48]

Treatment group	Placebo n=338	12 SQ-HDM n=318	Overall N=992
Gender, n (%)			
Male	166 (49%)	163 (51 %)	494 (50%)
Female	172 (51%)	155 (49%)	498 (50%)
Age, mean (SD)			
Age (years)	32.2 (10.9)	32.1 (10.6)	32.3 (10.9)
Ethnic origin, n (%)			
Caucasian	331 (98%)	314 (99%)	975 (98%)
Asian	1 (<1%)	1 (<1%)	3 (<1%)
African	1 (<1%)	0	2 (<1%)
Hispanic	1 (<1%)	1 (<1%)	2 (<1%)
Other	4 (1%)	2 (<1 %)	10 (<1%)
Smoking status, n (%)			
Non-smoker	272 (80%)	261 (82%)	808 (81%)
Previous smoker	30 (9%)	26 (8%)	85 (9%)
Smoker	36 (11%)	31 (10%)	99 (10%)
Weight, height, and BMI, mean (SD)			
Weight (kg)	73.6 (15.7)	75.0 (16.6)	74.1 (16.1)
Height (cm)	172.3 (10.0)	173.4 (9.5)	172.5 (9.6)
BMI (kg/m^2)	24.7 (4.3)	24.8 (4.6)	24.8 (4.5)

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Treatment group	Placebo n=338	12 SQ-HDM n=318	Overall N=992
Abbreviations: SQ-HDM, standardised quality house dust mite; BMI, body mass index; SD, standard deviation.			

The trial population consisted of equal proportions of males and females (50% of each). The majority of the subjects were Caucasians (98%), and the mean age of the population was 32 years old.

The countries recruiting most subjects for the trial were Poland, Germany, Romania, and Czech Republic with 25%, 14%, 12%, and 11% of the trial population, respectively, enrolled in these countries. Most of the subjects (81%) were non-smokers.

Table 21: MT-06 baseline disease characteristics [48]

Treatment group	Placebo n=338	12 SQ-HDM n=318	Overall N=992
Lung function, mean (SD)			
FEVI (% of predicted)	98.5 (13.0)	99.3 (13.0)	98.5 (13.0)
HDM allergy status			
HDM AR, n (%)	338 (100%)	318 (100%)	992 (100%)
Years with AR, mean (SD)	10.0 (8.7)	9.8 (8.1)	9.9 (8.7)
HDM AA, n (%)	152 (45%)	152 (48%)	456 (46%)
Years with AA, mean (SD)	9.3 (10.7)	8.1 (8.1)	8.9 (9.4)
Sensitisation status, n (%)			
Mono-sensitised	160 (31%)	109 (34%)	313 (32%)
Poly-sensitised	232 (69%)	209 (66%)	679 (68%)
Symptom score, mean (SD)			
Rhinitis DSS	8.0 (1.7)	7.9 (1.7)	7.9 (1.7)
Conjunctivitis DSS	2.9 (1.4)	2.9 (1.5)	2.9 (1.5)
Rhinoconjunctivitis DSS	10.9 (2.8)	10.8 (2.8)	10.9 (2.8)
Abbreviations: SQ-HDM, standardised quality house dust mite; AA, allergic asthma; AR, allergic rhinitis; SD, standard deviation; DSS, daily symptom score; FEV, forced expiratory volume.			

In accordance with the inclusion criteria, all subjects suffered from HDM AR. In addition, approximately half of the population suffered from concomitant HDM AA. The baseline FEV1 values were within normal ranges and were similar between the 2 treatment groups.

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A total of 313 subjects (32%) were mono-sensitised to HDM. Of the poly-sensitised subjects, most had 1 (20%), 2 (18%), or 3 (12%) additional sensitivities besides HDM. The most common other sensitivities were grass (41% positive), cat dander/hair (41% positive), and dog dander/hair (28% positive).

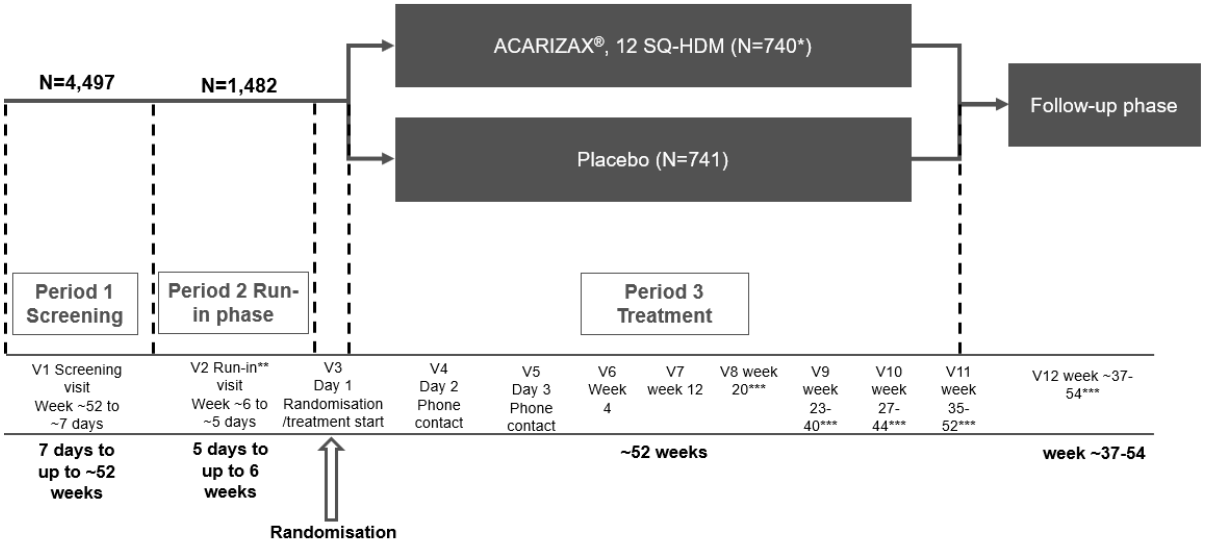
The 3 treatment groups were similar with regard to the baseline rhinitis, conjunctivitis, or rhinoconjunctivitis DSS. Similarly, there were no overall differences in mean values of individual rhinitis and conjunctivitis scores between the 3 treatment groups[48].

B.2.3.3 P001

B2.3.3.1 Trial design

P001 was a 52-week, randomised, double-blind, multicentre study conducted in patients 12 years of age and older with AR/ARC symptoms induced by exposure to HDM [35, 49]. The trial design of the P001 study is presented in Figure 7.

Figure 7: Trial design for P001 study [35, 49]



Telephone contacts between the investigator/designee and the subject occurred between the screening and run-in visits.
*741 subjects in the 12 SQ-HDM treatment group were randomised. 740 subjects were treated with 12 SQ-HDM.
**Selected pre-approved sites did not perform the run-in (refer to inclusion criterion 5 in Appendix O) and combined visits 1 and 2. This visit was to occur 6 weeks to 5 days before randomisation.
***Subjects randomised after 10th August 2014 followed a modified schedule per the trial flowchart (Visit 8 = Week 18, Visit 9 = Week 21, Visit 10 = Week 25, Visit 11 = Week 33, Visit 12 = Week 35)

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The trial consisted of a screening period, a run-in period, and randomisation. This was followed by an approximately 52-week treatment period, of which the last 8 weeks were defined as the efficacy assessment period, and a final follow-up phase.

Participants were required to discontinue their symptomatic allergy medications at Visit 2 and record symptoms until randomisation. From randomisation and throughout the treatment period, participants received 12 SQ-HDM or placebo. All participants could restart their symptomatic allergy medications following the establishment of symptom score eligibility during the run-in period, and participants were provided with rescue medications for their allergy symptoms during approximately the final 12 weeks of the trial.

B2.3.3.2 Eligibility criteria

Table 22: Summary of the inclusion and exclusion criteria of the P001 trial [49]

Inclusion criteria	Exclusion criteria
≥12 years of age	Patients with unstable or severe asthma, as judged by the investigator
Clinical history of AR/ARC when exposed to HDM of 1-year duration or more (with or without asthma), and received anti-allergy treatment during the previous year before the Screening Visit	Sensitised and regularly exposed to non-HDM perennial allergens during the run-in and efficacy assessment periods
Positive skin prick test response (average wheal diameter of 2 tests must be at least 5 mm larger than the saline control after 15 to 20 minutes) to Dermatophagoides pteronyssinus (ALK 10,000 AU/mL) and/or Dermatophagoides farinae (ALK 10,000 AU/mL) at the Screening Visit	History of symptomatic seasonal AR/C to an allergen to which the subject is sensitised and regularly exposed, which potentially overlapped with the run-in and efficacy assessment periods
Specific IgE against Dermatophagoides pteronyssinus and/or Dermatophagoides farinae at the Screening Visit of at least IgE Class 2 (0.7 kU/L)	Any nasal condition that could confound the efficacy or safety assessments; those with a history of anaphylaxis with cardiorespiratory symptoms with prior AIT of an unknown cause or because of an inhalant allergen
Rhinitis DSS of at least 6, or a score of at least 5 with 1 symptom being severe, on 5 of 7 consecutive calendar days before randomisation. A subject receiving anti-allergy medication is required to wash out their medication before and during the run-in period of the trial until the required symptom threshold is met	Receiving a high dose ICS for asthma within 6 months before screening; those with an occurrence of clinical deterioration of asthma that resulted in emergency treatment, hospitalisation, or systemic corticosteroid treatment in the 3-month period before the screening and run-in periods

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Inclusion criteria	Exclusion criteria
FEV1 of at least 80% of predicted value at the Screening, run-in, and randomisation Visits (following at least a 6-hour washout of short-acting β2 agonists and 12-hour washout of long-acting β2 agonists)	
Abbreviations: HDM, house dust mite; AR, allergic rhinitis; FEV, forced expiratory volume; ARC, allergic rhinoconjunctivis; ICS, inhaled corticosteroids; DSS, daily symptom score; IgE, immunoglobulin E; AR/C, allergic rhinitis/rhinoconjunctivitis.	

B2.3.3.3 Settings and locations

P001 was conducted at 182 trial sites across the US and Canada.

B2.3.3.4 Trials drugs

Eligible participants were treated with 12 SQ-HDM or with placebo. Subjects received daily treatment for approximately 12 months.

B2.3.3.5 Permitted and disallowed concomitant medications

Permitted concomitant medications

Subjects could take any medication or vaccine that was not restricted by the protocol, and that would not be expected to interfere with the conduct of the trial. Participants were required to wash out their symptomatic allergy medication prior to and during the run-in period of the study until the required symptom threshold was met. All participants could restart their symptomatic allergy medications following the establishment of symptom score eligibility during the run-in period, and participants were provided with rescue medications for their allergy symptoms during approximately the final 12 weeks of the trial.

Rescue medications

Rescue medications were given to patients as predefined, open-label medications to be taken in a stepwise fashion depending on the persistence, severity, and type of symptoms for allergic ARC during the last 12 weeks of the treatment period starting from Visit 9 [35, 49]. The rescue medications allowed for use in the trial are presented in Table 23.

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Table 23: Rescue medications provided in P001 [35, 49]

Drug	Dose/potency	Route of administration	Use
Self-injectable Epinephrine	Preferred dose = 0.30 mg	Intramuscular	Rescue medication to be dispensed at Visit 3
Loratadine tablet	10 mg	Oral tablet	Rescue medication to be dispensed at Visit 9
Olopatadine hydrochloride	0.10%	Ophthalmic drops	Rescue medication to be dispensed at Visit 10
Mometasone furoate monohydrate nasal spray	50 mcg - 2 sprays in each nostril	Intranasal	Rescue medication to be dispensed at Visit 11

Prohibited concomitant medications

The prohibited concomitant medications in the P001 trial are listed in Appendix N.

B2.3.3.6 Outcomes used in the economic model or specified in the scope

The key outcomes from P001 relevant to this appraisal are presented in Table 24.

Table 24: Outcomes from P001 relevant to this appraisal [35, 49]

Primary outcomes
• Average TCRS during the last 8 weeks of treatment.
Key secondary outcomes
• Average rhinitis DSS during the last 8 weeks of treatment • Average rhinitis DMS during the last 8 weeks of treatment • Average TCS during the last 8 weeks of treatment • Average AR/ARC VAS score during the last 8 weeks of treatment
Safety outcomes
• AEs • AE discontinuations • SAEs • Vital signs • Safety laboratory assessments • FEV1 • Physical examinations
Abbreviations: FEV, forced expiratory volume; AR, allergic rhinitis; AE, adverse event; SAE, serious adverse event; DSS, daily symptom score; DMS, daily medications score; ARC, allergic rhinoconjunctivitis; TCRS, total combined rhinitis score; VAS, visual analogue scale; TCS, total combined rhinoconjunctivitis score.

The primary endpoint for the P001 trial was the average TCRS during the efficacy evaluation period (final 8 weeks of treatment) which ranged from September to April, to avoid overlapping symptoms caused by pollen allergy.

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The TCRS is calculated as the sum of rhinitis symptom and medication score [range, 0-24]. The total AR DSS was the total of 4 rhinitis symptom scores (runny nose, blocked nose, sneezing, and itchy nose) which were measured on a 4-point scale from 0 (no symptoms) to 3 (severe symptoms) and ranged from 0-12. The total AR DMS was the sum of the total daily scores for all rhinitis medication and ranged from 0-12. For the medication score, subjects reported their use of specific pharmacotherapy. To transform the amount of symptomatic medications used into medication scores, the scoring principles detailed in Table 25 were applied.

Table 25: P001 trial scoring of symptomatic medication use [49]

Symptomatic medication	Score/dose unit*	Maximum daily dose	Maximum daily score
Rhinitis medication score			
Loratadine tablets#, 10 mg	4	1 tablet	4
Mometasone nasal spray, 50 µg/dose	2 per puff	2 puffs per nostril	8
Maximum daily rhinitis medication score†			12
Conjunctivitis medication score**			
Loratadine tablets#, 10 mg	2 per tablet	1 tablet	2
Olopatadine hydrochloride, 0.1%	1.5 per drop	2 drops per eye	6
Maximum daily conjunctivitis medication score†			8

*: Scoring scales were not seen by the subjects. # : Loratadine counted 4 in the rhinitis score and 2 in the conjunctivitis score, based on assumed equal efficacy of antihistamine on the 4 nasal symptoms and 2 eye symptoms (Salmun & Lorber 2002). †: If any subject exceeded the recommended daily dose of symptomatic medication, the actual score was used. **

Asthma symptom scores were not part of the TCRS, but were reported separately in participants' electronic diary. The asthma DSS ranged from 0 to 9 points and reflected 3 symptoms (cough, wheeze, and chest tightness/shortness of breath), which were each measured on a 4-point scale from 0 (no symptoms) to 3 (severe symptoms).

The overall severity of rhinoconjunctivitis symptoms were captured by participants using a VAS ranging from 'no symptoms' (0) to 'severe symptoms' (100). The secondary endpoint was calculated based on diary entries over the final 8 weeks of

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treatment. Baseline VAS endpoint value was calculated as the last non-missing VAS value prior to randomisation.

QoL was assessed as an exploratory endpoint by participants by the RQLQ(S). The RQLQ(S) consists of 28 questions, each on a 7-point (0-6) scale, divided into 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional). All items within each domain are weighted equally. The weekly domain scores were calculated as the average of all items scores for each domain. The weekly overall RQLQ score was the average of all 28 item scores, with higher scores indicating worse rhinoconjunctivitis HRQoL. Across selected sites at Visit 10 and 11, participants also completed the EQ-5D-5L questionnaire to collect data on their HRQoL.

Immunological assessments, including D. farinae and D. pteronyssinus specific IgE, and IgG4 at run-in, Week 4, Week 20, and the final week of dosing (Visit 11).

B2.3.3.7 Subject baseline characteristics

Participant baseline demographic and disease characteristics were consistent between the 12 SQ-HDM and placebo groups in P001: see Table 26 and Table 27.

Table 26: Subject baseline patient characteristics of P001 [35, 49]

Treatment group	Placebo n=741	12 SQ-HDM n=741	Total N=1,482
Gender, n (%)			
Female	430 (58.0)	445 (60.1)	875 (59.0)
Male	311 (42.0)	296 (39.9)	607 (41.0)
Age, mean (SD)			
Age (years)	35.2 (13.7)	34.9 (13.8)	35.1 (13.8)
Race, n (%)			
White	564 (76.1)	567 (76.5)	1113 (76.3)
Asian	51 (6.9)	48 (6.5)	99 (6.7)
Black or African American	75 (10.1)	80 (10.8)	155 (10.5)
Multi-racial	46 (6.2)	39 (5.3)	85 (5.7)
American Indian or Alaska Natives	4 (0.5)	6 (0.8)	10 (0.7)
Unknown	1 (0.1)	1 (0.1)	2 (0.1)
Weight, height, and BMI, mean (SD)			
Weight (kg)	80.29 (21.4)	79.02 (22.8)	79.65 (22.1)
Height (cm)	169.94 (9.9)	169.15 (10.1)	169.55 (8.0)
BMI (kg/m^2)	27.68 (6.6)	27.53 (7.4)	27.61 (7.0)

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Treatment group	Placebo n=741	12 SQ-HDM n=741	Total N=1,482
Abbreviations: SD: standard deviation; BMI: body mass index			

The trial population consisted of marginally greater proportions of females to males (59% female). The majority of the subjects were White (76%) and the mean age of the population was 35 years old.

Table 27: Subject baseline disease characteristics of P001 [35, 49]

Treatment group	Placebo n=741	12 SQ-HDM n=741	Total N=1,482
Lung function, mean (SD)			
FEVI (% of predicted)	97.2 (11.1)	98.3 (16.7)	97.7 (14.1)
Asthma status, n (%)			
Subjects with asthma	232 (31.3)	228 (30.8)	460 (31.0)
Subjects with asthma and with ICS use	62 (26.7)	66 (28.9)	128 (27.8)
Subjects with asthma and without ICS use	170 (73.3)	162 (71.1)	332 (72.2)
Rhinitis status			
Years with AR/C, mean (SD)	19.1 (12.9)	18.2 (12.5)	18.6 (12.7)
Sensitisation status, n (%)			
Mono-sensitised	171 (23.1)	184 (24.8)	335 (24.0)
Poly-sensitised	567 (76.5)	555 (74.9)	112 (75.7)
Not sensitised to HDM	3 (0.4)	2 (0.3)	5 (0.3)
Abbreviations: SD, standard deviation; AR/C, allergic rhinitis/rhinoconjunctivitis; HDM, house dust mite; FEV, forced expiratory volume.			

In accordance with the inclusion criteria, all subjects suffered from HDM AR. In addition, 31% of the population suffered from concomitant HDM AA, of which only 28% used ICS. The baseline FEV1 values were within normal ranges and were similar between the two treatment groups.

A total of 335 subjects (24%) were mono-sensitised to HDM, with the three most common additional allergen sensitivities being grass pollen, cat dander, and dog dander.

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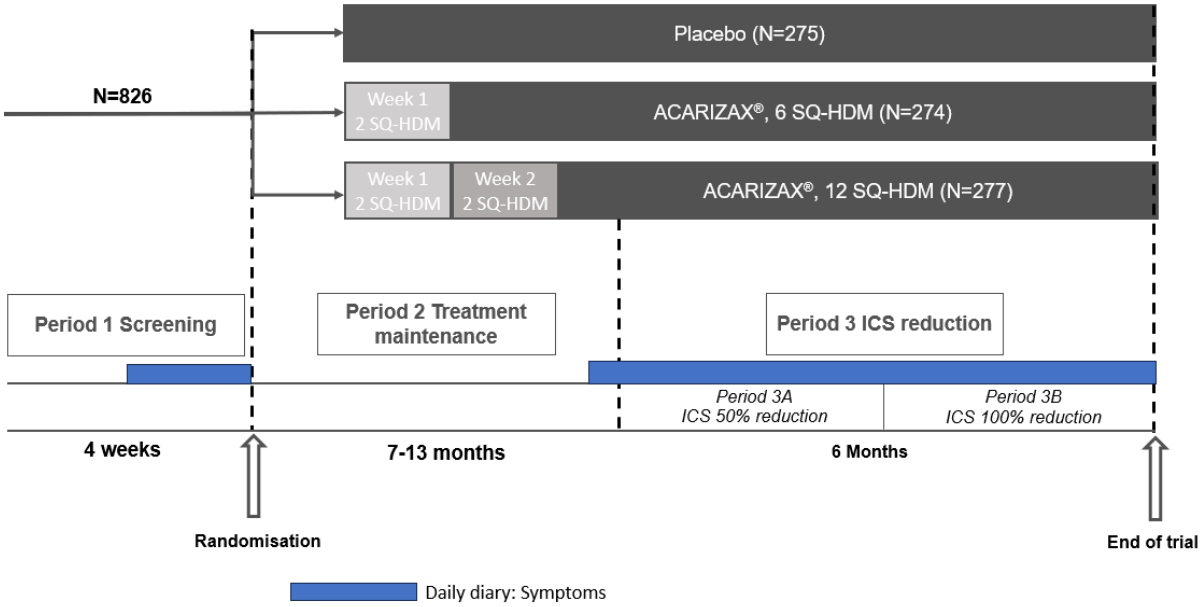
B.2.3.4 TO-203-31

B2.3.4.1 Trial design

TO-203-31 was a placebo-controlled, randomised, double-blind, multicentre, parallel intergroup comparison study conducted in Japan which included patients with an ACQ score of 1.0 to 1.5 and daily ICS use at randomisation [37, 50]. The overall trial design is presented in Figure 8.

Figure 8: Trial design for study TO-203-31 [37, 50]



Abbreviations: ICS, Integrated care system; SQ-HDM, Standardised quality house-dust mite. Subjects were asked to follow a 2-step increase in the SQ-HDM SLIT-tablet dose at the beginning of the treatment period. All subjects entering Period 3 reduced daily ICS use by 50% for 3 months. Those who had no asthma exacerbations in those 3 months completely discontinued their ICS.

After giving informed consent, all subjects were required to switch their usual asthma treatment to fluticasone propionate and SABA as required before screening. Electronic diary (e-diary) recordings, including asthma symptoms (wheezing, coughing, shortness of breath, chest tightness, and nocturnal awakening); medication use; and PEF of the last 2 weeks of Period 1 (baseline period); served as each subject's individual baseline.

Eligible subjects were randomly assigned (1:1:1) to daily treatment with placebo, or the SQ-HDM SLIT-tablet at a dose of 10,000 Japanese Allergy Unit (JAU) (equivalent to 6 SQ-HDM) or 20,000 JAU (equivalent to 12 SQ-HDM), in addition to the required ICS and SABA [37, 50].

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A 2-step up dosing regimen was used during Period 1. 3,300 JAU (2 SQ-HDM) was selected as the initial dose for a week, followed by upward titration of the dose to 10,000 JAU (6 SQ-HDM); for subjects randomised to the 20,000 JAU (12 SQ-HDM) group, a further upward titration was performed again 1 week after treatment with 10,000 JAU. The duration of Period 2 varied from 7 to 13 months depending on the date of randomisation. All subjects with ACQ scores of 1.5 or less at the first visit to the ICS reduction period (Period 3) proceeded on a fixed date in September 2013, and those with ACQ scores of more than 1.5 would not proceed to Period 3 to avoid ICS reduction in subjects with uncontrolled asthma.

During Period 3, daily ICS dose was reduced by 50% for the first 3 months and subsequently withdrawn completely for an additional 3 months for subjects who did not experience asthma exacerbation during the first 3 months. Subjects recorded in the e-diary twice daily during Period 1, the last 4 weeks of Period 2, and Period 3.

B2.3.4.2 Eligibility criteria

Table 28: Summary of the inclusion and exclusion criteria of TO-203-31 [50]

Inclusion criteria	Exclusion criteria
≥18 to <65 years of age	Perennial symptoms of asthma or rhinitis due to regular exposure to antigens (excluding HDM)
Level of HDM-specific IgE antibodies (Dermatophagoides pteronyssinus or Dermatophagoides farinae) measured between the day of informed consent and the first day of observation is assessed as Class 3 or greater	Received immunotherapy with HDM allergen-containing products for at least 1 month during 5 years before the first day of observation
Positive HDM allergen scratch or prick test performed between the day of informed consent and the first day of observation, or within 1 year before the day of informed consent	On immunotherapy other than HDM allergen-containing products on the first day of observation
Asthmatic symptoms treated with ICS(s) including combination drugs for at least 6 months before the first day of observation	History of serious ADRs due to immunotherapy
Daily dose of ICS(s) at the start of study treatment is between 200 and 400 µg as fluticasone propionate	Hospitalised due to worsening of asthma within 3 months before the first day of observation
Patients who experienced reversible airway obstruction before the first day of study treatment. If this is to be checked between	Using or used any of the following drugs: • Within 90 days before the first day of observation: corticosteroids (injections,

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Inclusion criteria	Exclusion criteria
the day of informed consent and the first day of study treatment, at least one of the following criteria should be met: 1. The forced expiratory volume in 1 second (FEV1) on spirometry improves by ≥12% and by ≥200 mL in the absolute volume after administration of a short-acting β2 agonist (SABA) 2. The PEF improves by >20% after administration of an SABA 3. The PEF's circadian variation is >20%	rectal), anti-IgE antibodies, and immunosuppressants • Within 60 days before the first day of observation: corticosteroids (oral) • Within 30 days before the first day of observation: leukotriene receptor antagonists, Chinese medicines for rhinitis or asthma (e.g., Shoseiryuto, Shigyakusan, Kakkontokasenkyushini, Keigairengyoto, Shiniseihaito), and drugs unapproved in Japan • Within 21 days before the first day of observation: monoamine oxidase inhibitors • Within 14 days before the first day of observation: tricyclic antidepressants, mediator release inhibitors, thromboxane A2 inhibitors, Th2 cytokine inhibitors, and anticholinergics • Within 21 days before the scratch/prick test: corticosteroids (external application on the site of the scratch/prick test) • Within 7 days before the scratch/prick test: Antipsychotics with an antihistaminic activity (e.g., Phase 2/3 Clinical Trial of TO-203 (Patients with HDM-induced Allergic Asthma) Clinical Study Report d2 57 chlorpromazine, levomepromazine, clozapine, and olanzapine)) • Within 3 days before the scratch/prick test: Antihistamines
Mean score of ≥1.0 point on the ACQ at the start of observation (a mean score of ≥0.85 LABA are used during the 7 days before the first day of observation)	Infection-related symptoms such as upper respiratory tract infection, acute sinusitis, or acute otitis media, or those who are under treatment of these symptoms at the start of study treatment
Mean score of 1.0 to 1.5 points on the ACQ at the start of study treatment	Ulcerative stomatitis or other oral abnormalities associated with inflammation of Grade 2 or higher (see Appendix 4 "Classification Criteria for Seriousness of Adverse Drug Reactions" of the protocol) at the start of study treatment
FEV1 at the start of observation exceeds 70% of the predicted value	History of anaphylactic shock or angioedema

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Inclusion criteria	Exclusion criteria
Patients who have completed ≥80% of their electronic patient diary for the 2 weeks before the first day of study treatment	History of drug allergies
	Complications with the following diseases or conditions: • Cardiac: treatment-requiring diseases including arrhythmia, angina pectoris, and cardiac failure. • Hepatic: AST (GOT), ALT (GPT), or ALP levels measured between the day of informed consent and the first day of observation exceeding twice the upper limit of the normal reference range • Renal: serum creatinine levels measured between the day of informed consent and the first day of observation exceeding 1.5 times the upper limit of the normal reference range • Other: uncontrolled hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg on the first day of observation or the first day of study treatment) or diabetes mellitus with HbA1c of ≥8.0% measured between the day of informed consent and the first day of observation
	Complications with systemic diseases that affect the immune system (e.g., autoimmune diseases, immune complex diseases, immunodeficiency)
	Complications with respiratory diseases (e.g., COPD) considered to affect the efficacy and safety evaluations of TO-203
	History of hypersensitivity to mannitol or gelatin, the excipients in TO-203 tablets
	Complications with malignant tumours, or who underwent surgery, chemotherapy, radiotherapy, or other treatments of malignant tumours within 5 years before the first day of observation
Abbreviations: PEF, peak expiratory flow; ACQ, asthma control questionnaire; COPD, chronic obstructive pulmonary disease; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase;	

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Inclusion criteria	Exclusion criteria
GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; ICS, inhaled corticosteroid; SABA, short-acting β 2-agonist; ADR, adverse drug reaction; HDM, house dust mite; IgE, immunoglobulin E.	

B2.3.4.3 Settings and locations

TO-203-31 was conducted at 124 trial sites across Japan [50].

B2.3.4.4 Trial drugs

Eligible participants were treated with 6 SQ-HDM, 12 SQ-HDM, or with placebo. Subjects received daily treatment of 1 tablet for up to 19 months [50].

B2.3.4.5 Permitted and disallowed concomitant medications

Permitted concomitant medications:

Subjects were to enter the use of ICS or rescue drugs and the frequency of use in his/her electronic patient diary using a mobile phone (or mobile terminal) on all days of periods specified for reporting. Prior therapies and concomitant medications/therapies were investigated at each visit from the first day of observation (Visit 1) to the last day of treatment (Visit 24) or termination/discontinuation observation, and the contents of the investigation were recorded on a case report form (CRF). The frequency of use of SABA(s) and rescue drugs was evaluated as a secondary efficacy endpoint.

ICS was provided as fluticasone propionate (Flutide® Diskus) for the long-term management of asthma. All ICS use was switched to fluticasone propionate with the equivalent potency. Throughout Period 2, ICS was provided at a fixed dose unless ACQ is >1.5, in which case, the investigator was allowed to consider increasing the dose of ICS.

SABA was provided as rescue medication for asthmatic attacks during the trial period. If SABA failed to control severe asthmatic symptoms or attacks, prednisolone tablets could be used.

Prohibited concomitant medications:

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Concomitant medications that were prohibited during the trial are listed in Appendix N.

B2.3.4.6 Outcomes used in the economic model or specified in the scope

The key outcomes from TO-203-31 relevant to this appraisal are presented in Table 29.

Table 29: Outcomes from the TO-203-31 relevant to this appraisal [37, 50]

Primary outcomes
• Time to first moderate or severe asthma exacerbation in Period 3 measured from randomisation (calculating from the first day of study treatment)
Key secondary outcomes
• Time to first moderate or severe asthma exacerbation in Period 3 measured from the Period 3 started date (calculating from the Period 3 started date)
Safety outcomes
• AEs • AE discontinuations • SAEs • Vital signs • Safety laboratory assessments • FEV1 • PEF • Physical examinations
Abbreviations: FEV, forced expiratory volume; AE, adverse event; SAE, serious adverse event; PEF, peak expiratory flow.

The primary endpoint for the TO-203-31 trial was the time to the first moderate or severe asthma exacerbation measured from randomisation during the primary efficacy evaluation period (Period 3, Visit 18 to 24).

Moderate and severe asthma exacerbation is defined as the patient having met any of the items detailed in Table 23.

Table 30: TO-203-31 trial definition of moderate and severe exacerbation[37, 50]

Criterion	Definition
Moderate exacerbation	
A	SABA-requiring nocturnal awakening due to asthmatic symptoms for at least 2 consecutive nights or an increase in the symptom score (the 4 categories of coughing, wheezing, breathlessness, and chest tightness are each rated on a scale of 0 to 3) by ≥0.75 for at least 2 consecutive days, compared to the mean score for 2 weeks prior to the first day of Period 2

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Criterion	Definition
B	Increase in the frequency of SABA use by ≥4 sprays per day for at least 2 consecutive days compared to the mean frequency for 2 weeks prior to the first day of Period 2
C	Decrease in PEF in the morning or evening by ≥20% for at least 2 consecutive days compared to the mean value for 2 weeks prior to the first day of Period 2 or a decrease in FEV1 by ≥20% compared to that on the first day of Period 2
D	Visit to the emergency outpatient unit on any day or a visit to the trial site on an unscheduled day for the treatment of asthma not requiring systemic corticosteroids
Severe exacerbation	
E	Systemic corticosteroids required to treat asthma
F	A visit to the emergency outpatient unit for the treatment of asthma requiring systemic corticosteroids or admission to the hospital for the treatment of asthma

The key secondary endpoint was the time from the start of Period 3 to the first moderate or severe asthma exacerbation. Several other secondary endpoints were included in the analysis associated with the measurement of exacerbations across different trial time periods, and individual asthma symptom scores.

Lung function was assessed by means of PEF and FEV1 during Period 2B and Period 3.

HDM-specific IgE and IgG4 levels were measured to confirm the specific immunologic response.

Asthma control was assessed by the ACQ, and QoL was assessed by the AHQ-JAPAN during Period 2 and Period 3. Consistent with the MT-04 trial, the ACQ consists of 7 questions referring to the previous week, providing a score between 0 and 6 (higher being worse).

B2.3.4.7 Subject baseline characteristics

Baseline demographic and disease characteristics were generally similar in the 12 SQ-HDM and placebo groups in TO-203-31: see Table 31 and Table 32.

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Table 31: TO-203-31 Baseline patient characteristics [37, 50]

Treatment group	Placebo n=274	12 SQ-HDM n=276	Overall N=824
Gender, n (%)			
Male	149 (54.4%)	130 (47.1%)	421 (51.1%)
Female	125 (45.6%)	146 (52.9%)	403 (48.9%)
Age, mean (SD)			
Age (years)	37.9 (9.4)	38.3 (9.9)	38.2 (10.0)
Weight and height, mean (SD)			
Weight (kg)	63.65 (12.58)	63.81 (13.79)	63.51 (12.83)
Height (cm)	165.41 (8.56)	164.16 (8.57)	164.53 (8.56)

There were no meaningful differences in demographics between groups. The mean age of the population was 38.2 years old, and the median was 38 years old. The maximum age was 64 years old and the distribution of age was similar between groups, as was the weight, height, and BMI.

Table 32: TO-203-31 Baseline disease characteristics [37, 50]

Treatment group	Placebo n=274	12 SQ-HDM n=276	Total N=824
Lung function, mean (SD)			
FEVI (% of predicted)	88.8 (14.7)	87.4 (14.3)	88.5 (14.2)
Asthma duration, mean (SD)			
Asthma duration (years)	17.5 (13.5)	17.4 (13.3)	17.4 (13.3)
Onset, mean (SD)			
Onset (age, years)	19.5 (15.2)	19.9 (15.5)	19.8 (15.4)
Medication use (ICS, fluticasone per day), n (%)			
200 µg	71 (25.9)	68 (24.6)	197 (23.9)
300 µg	2 (0.7)	1 (0.4)	3 (0.4)
400 µg	302 (73.4)	207 (75.0)	624 (75.7)
Sensitisation status, n (%)			
Mono-sensitised	47 (17.2)	31 (11.2)	111 (13.5)
1 other than HDM	41 (15.0)	46 (16.7)	125 (15.2)
2 other than HDM	43 (15.7)	44 (15.9)	137 (16.6)
≥3 other than HDM	143 (52.2)	155 (56.2)	451 (54.7)
Total asthma symptom score*, mean (SD)			
Total asthma symptom score	1.62 (1.45)	1.66 (1.48)	1.70 (1.50)
Asthma control, mean (SD)			
ACQ score	1.19 (0.17)	1.21 (0.17)	1.20 (0.17)

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Treatment group	Placebo n=274	12 SQ-HDM n=276	Total N=824
Abbreviations: SD, standard deviation; SQ, standardised quality; HDM, house dust mite; ACQ, asthma control questionnaire; ICS, inhaled corticosteroid; FEV, forced expiratory volume. * Asthma symptom score correlates with the 'total asthma daytime symptom score' as reported in the MT-04 trial. Total asthma symptom score (range, 0-12): sum of each asthma symptom score (wheezing, coughing, shortness of breath, and chest tightness) during the day on a 0-3 scale (0, no symptom; 1, mild; 2, moderate; 3, severe).			

There were no significant differences in asthma characteristics at baseline. The mean duration of asthma was 17.4 years. Approximately half the subjects had polysensitisation to 3 or more allergens other than HDM, whereas 13.5% of all subjects were HDM mono-sensitised. Overall, 80% of subjects also had AR.

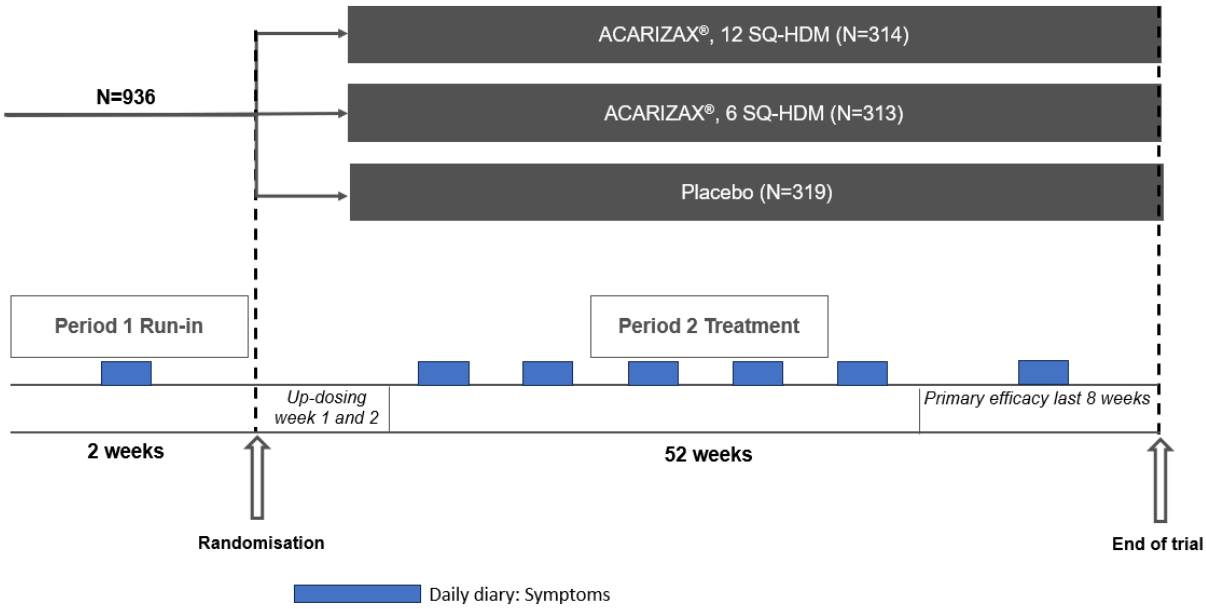
Three-quarters of the subjects used 400 µg of fluticasone propionate per day at randomisation, with the remainder using 200 µg daily.

B.2.3.5 TO-203-32

B2.3.5.1 Trial design

TO-203-32 was a placebo-controlled, randomised, double-blind, multicentre, parallel intergroup comparison study conducted in Japan which included patients with HDM-induced AR [38, 51]. The overall trial design is presented in Figure 9.

Figure 9: The trial design for study TO-203-32 [38, 51]



Abbreviation: SQ-HDM, Standardised quality house dust mite. Subjects were asked to follow a 2-step up dosing regimen at the beginning of the treatment period. The electronic diary collected 14 days of data during the run-in

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period and 5 times after up dosing until the end of the primary evaluation period comprising the last 8 weeks of the treatment period. Black boxes represent electronic diary periods.

The trial consisted of a 2-week observation period for subject selection and randomisation, followed by an approximately 52-week treatment period (364 days), with Day 365 defined as the final observation visit.

Eligible subjects were randomly assigned (1:1:1) to daily treatment with placebo or the SQ-HDM SLIT-tablet at a dose of 10,000 JAU (equivalent to 6 SQ-HDM) or 20,000 JAU (equivalent to 12 SQ-HDM). Subjects followed a 2-step up dosing regimen at the beginning of the treatment period. The electronic diary collected 14 days of data during the run-in period and 5 times after up dosing until the end of the primary evaluation period comprising the last 8 weeks of the treatment period. 3,300 JAU (2 SQ-HDM) was selected as the initial dose for a week, followed by upward titration of the dose to 10,000 JAU (6 SQ-HDM); for subjects randomised to the 20,000 JAU (12 SQ-HDM) group, a further upward titration was performed again 1 week after treatment with 10,000 JAU. During up dosing, patients were provided with weekly packages of the IMP or placebo to maintain blinding. Therefore, subjects received their randomised treatment for approximately 12 months.

B2.3.5.2 Eligibility criteria

Table 33: Summary of the inclusion and exclusion criteria of the TO-203-32 trial [38, 51]

Inclusion criteria	Exclusion criteria
≥12 to <65 years of age	Patients who are evaluated between the day of informed consent and the first day of observation (Visit 1) as Class 5 or greater in the IgE antibody tests specific to any of the following: cedar, cypress, alder, cocksfoot, ragweed, mugwort, Japanese hop, cockroach, Candida, Aspergillus, Alternaria, dog hair, or cat hair
Patients whose level of HDM-specific IgE antibodies (D.pteronyssinus or D.farinae) measured between the day of informed consent and the first day of observation (Visit 1) is assessed as Class 3 or greater	Patients who are evaluated between the day of informed consent and the first day of observation (Visit 1) as Class 2 to 4 in the IgE antibody tests specific to any of the following: cocksfoot, ragweed, mugwort, Japanese hop, cockroach, Candida, Aspergillus, Alternaria, dog hair, or cat hair; and who have symptoms of AR due to the relevant antigen
Patients who test positive on a nasal provocation test (either HDM or house dust)	Patients who are evaluated between the day of informed consent and the first day of

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Inclusion criteria	Exclusion criteria
performed between the day of informed consent and the first day of observation (Visit 1) or within 1 year before the day of informed consent	observation (Visit 1) as Class 2 to 4 in the IgE antibody tests specific to dog hair or cat hair, and who have no symptoms of AR while being constantly exposed to the relevant animal (e.g., pet parenting at home, working at a pet shop)
Patients who have a history of treatment for HDM-induced AR that started more than 1 year before the first day of observation (Visit 1)	Patients who underwent immunotherapy with HDM allergen-containing products for at least 1 month during 5 years before the first day of observation (Visit 1)
Patients who have moderate or severe symptom(s) of HDM-induced AR (total daily rhinitis symptom scores of ≥7) for at least 7 days during the 14-day observation period that starts from the first day of observation (Visit 1)	Patients who are on immunotherapy other than HDM allergen-containing products on the first day of observation (Visit 1)
Patients who score at least 1 point in at least 1 item in the following JRQLQ No. 1 due to HDM-induced AR on the first day of observation (Visit 1) • Reduced productivity at work/home Phase 2/3 Clinical Trial of TO-203 (Patients with HDM-induced Allergic Rhinitis) Clinical Study Report (Jun 24, 2014) 44 • Impaired reading of book/newspaper • Limitation of outdoor life (e.g. sport, picnics) • Limitation on going out • Hesitation visiting friend or relatives • Reduced contact with friends or others by telephone or conversation • Impaired sleeping	Patients who have nasal symptoms that might affect the evaluation of efficacy or safety (e.g., nasal congestion due to chronic sinusitis, nasal polyp, nasal septum deviation, or vasomotor rhinitis) on the first day of observation (Visit 1)
	Patients who used the following drugs (including drugs released for the market during the trial period that are categorised as drugs with the same indications as the following drugs): 1. Corticosteroids 1. Oral, rectal, and pulmonary administration (inhalation) and injection: from 90 days before the first day of observation (Visit 1) until trial completion 2. Nasal and ocular administration and ophthalmic ointment: from the first day of observation until trial completion* 2. Anti-allergic drugs

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Inclusion criteria	Exclusion criteria
	1. Leukotriene antagonist: from 30 days before the first day of observation (Visit 1) until trial completion 2. Other anti-allergic drugs (excluding dermatological preparations and mouthwash): from 7 days before the first day of observation (Visit 1) until trial completion* 3. Anti-IgE antibody: from 90 days before the first day of observation (Visit 1) until trial completion 4. Immunosuppressants: from 90 days before the first day of observation (Visit 1) until trial completion 5. Chinese medicines for the treatment of asthma or rhinitis (e.g., Shoseiryuto, Shigyakusan, Kakkontokasenkyushini, Keigairengyoto, Shiniseihaito): from 30 days before the first day of observation (Visit 1) until trial completion 6. Monoamine oxidase inhibitors (MAOI): from 21 days before the first day of observation (Visit 1) until trial completion 7. Tricyclic antidepressants: from 14 days before the first day of observation (Visit 1) until trial completion 8. Anticholinergic drugs: from 14 days before the first day of observation (Visit 1) until trial completion 9. Antipsychotics with antihistamine effects (e.g., chlorpromazine, levomepromazine, clozapine, olanzapine, thioridazine): from 7 days before the first day of observation (Visit 1) until trial completion 10. Catechol-O-methyltransferase (COMT) inhibitors: from the first day of observation (Visit 1) until trial completion 11. Beta blockers: from 30 days before the first day of observation (Visit 1) until trial completion 12) Nasal vasoconstrictors: from the first day of observation (Visit 1) until trial completion 13) Drugs not approved in Japan: from 30 days before the first day of observation (Visit 1) until trial completion * Except for rescue drugs prescribed during the period of administration of the IMP

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Inclusion criteria	Exclusion criteria
Abbreviations: AR, allergic rhinitis; IgE, immunoglobulin E; HDM, house dust mite; JRQLQ, Japanese allergic rhinitis quality of life standard questionnaire.	

B2.3.5.3 Settings and locations

TO-203-31 was conducted at 90 trial sites across Japan.

B2.3.5.4 Trial drugs

Eligible participants were treated with 6 SQ-HDM, 12 SQ-HDM, or with placebo. Subjects received daily treatment of 1 tablet for approximately 52 weeks.

B2.3.5.5 Permitted and disallowed concomitant medications

Permitted concomitant medications [38, 51]:

Prior therapies and concomitant medications/therapies were investigated from the first day of observation (Visit 1) to the day of the observation after 52 weeks of administration (Visit 12) or discontinuation observation. The contents of the investigation were recorded on the CRFs.

Subjects were to enter the use of rescue drugs and the frequency of use in his/her electronic patient diary using a mobile phone (or mobile terminal) on all days of the periods specified for reporting.

The use of rescue drugs was evaluated as a medication score, which is an efficacy endpoint. Fluticasone propionate nasal solution was permitted to be used for unbearable symptoms of ‘nasal congestion’ and olopatadine hydrochloride ophthalmic solution for unbearable ‘ocular symptoms’ (e.g., itchy eyes or watery eyes) as rescue drugs. If unbearable symptoms persisted after the use of these drugs or if symptoms such as ‘sneezing, nasal discharge, and itchy sensation’ were unbearable, loratadine was used.

Prohibited concomitant medications:

The prohibited concomitant medications are listed in Appendix N.

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B2.3.5.6 Outcomes used in the economic model or specified in the scope

The key outcomes from TO-203-32 relevant to this appraisal are presented in Table 34.

Table 34: Outcomes from TO-203-32 relevant to this appraisal [38, 51]

Primary outcomes
• Average TCRS during the last 8 weeks of treatment.
Key secondary outcomes
• Average AR symptom score (DSS) during the last 8 weeks of treatment
Safety outcomes
• AEs • AE discontinuations • SAEs • ADRs • Vital signs • Safety laboratory assessments • FEV1 • Physical examinations
Abbreviations: FEV, forced expiratory volume; AR, allergic rhinitis; AE, adverse event; SAE, serious adverse event; DSS, daily symptom score; TCRS, total combined rhinitis score; ADR, adverse drug reaction.

The primary endpoint is the mean value of the TCRS in the final 8 weeks of the administration period. As detailed previously, the TCRS is the total of the mean values of the AR DSS and AR DMS. Regarding the medication score, the drugs to be used and the score were specified in reference to the MT-06 trial, as detailed in Table 19.

The key secondary endpoint was the AR DSS. Other secondary endpoints included an evaluation of the independent and combined rhinitis and conjunctivitis medication and symptom scores.

QoL was evaluated using the JRQLQ No. 1. The JRQLQ comprises 24 questions rated on a 5-point scale (0-4), and is designed to measure the impact of AR on various aspects of a person's life, including physical well-being, daily activities, and emotional well-being.

B2.3.5.7 Subject baseline characteristics

Baseline and disease characteristics were generally similar in the 12 SQ-HDM and placebo groups in TO-203-31: see Table 35 and Table 36.

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Table 35: TO-203-32 Baseline patient characteristics [38, 51]

Treatment group	Placebo n=285	12 SQ-HDM n=281	Overall N=851
Gender, n (%)			
Male	121 (42.5%)	131 (46.6%)	391 (45.9%)
Female	164 (57.5%)	150 (53.4%)	460 (54.1%)
Age, mean (SD)			
Age (years)	26.7 (11.7)	26.9 (12.3)	27.0 (12.1)
Weight and height, mean (SD)			
Weight (kg)	56.52 (11.89)	56.33 (11.86)	56.51 (12.15)
Height (cm)	162.47 (8.30)	162.27 (8.56)	162.32 (8.72)
Abbreviations: SD, standard deviation; SQ, standardised quality; HDM, house dust mite.			

This trial was designed to include patients aged 12 to 64 years; those aged 12 to 17 years accounted for 30% or more of the subjects in each group. Across all 3 treatment groups, the mean age of subjects was approximately 27 years.

Table 36: TO-203-32 Baseline disease characteristics [38, 51]

Treatment group	Placebo n=285	12 SQ-HDM n=281	Total N=851
Rhinitis duration, mean (SD)			
Rhinitis duration (years)	10.1 (8.6)	9.8 (8.9)	10.1 (8.9)
Specific IgE antibody (*D. farinae*),			
≤Class 3	108 (37.9)	101 (35.9)	315 (37.0)
Class 4	91 (31.9)	106 (37.7)	293 (34.4)
Class 5	52 (18.2)	32 (11.4)	133 (15.6)
Class 6	34 (11.9)	42 (14.9)	110 (12.9)
Specific IgE antibody (*D. pteronyssinus*),			
≤Class 3	113 (39.6)	102 (36.3)	319 (37.5)
Class 4	87 (30.5)	108 (38.4)	291 (34.2)
Class 5	50 (17.5)	31 (11.0)	129 (15.2)
Class 6	35 (12.3)	40 (14.2)	112(13.2)
Sensitisation status, n (%)			
Mono-sensitised	65 (20.4)	57 (18.2)	198 (20.9)
Poly-sensitised	254 (79.6)	257 (81.8)	748 (79.1)
Symptom score, mean (SD)			
Rhinitis DSS	8.42 (1.32)	8.49 (1.27)	8.48 (1.29)
Conjunctivitis DSS	2.66 (1.35)	2.64 (1.35)	2.66 (1.36)
Rhinoconjunctivitis DSS	11.08 (2.27)	11.13 (2.23)	11.14 (2.27)

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Treatment group	Placebo n=285	12 SQ-HDM n=281	Total N=851
Abbreviations: SD, standard deviation; DSS, daily symptom score; IgE, immunoglobulin E; SQ, standardised quality; HDM, house dust mite.			

The mean duration of HDM-induced AR was approximately 10 years. The percentage of subjects with mono-sensitisation to HDM was 18.2% in the 12 SQ-HDM group. In poly-sensitised, subjects the most common 'other' allergen based on specific IgE antibody levels was Japanese cedar pollen (67%), followed by Japanese cypress pollen (34%), cats (26%), orchard grass (23%), and dogs (15%).

B.2.3.6 Summary of methodologies

See Table 37 for a summary of the methodologies of the included trials.

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Table 37: Methodology summary of included trials

Trial name	MT-04 [36, 47]	MT-06 [34, 48]	P001 [35, 49]	TO-203-31 [37, 50]	TO-203-32 [38, 51]
Settings and Location	109 sites across 13 European countries	100 trial sites across 12 European countries	182 trial sites across the US and Canada	124 trial sites across Japan	90 trial sites across Japan
Trial design	Phase 3, randomised, parallel-group, double-blind, placebo-controlled, multicentre trial	Phase 3, randomised, parallel-group, double-blind, placebo-controlled, multicentre trial	Phase 3, randomised, parallel-group, double-blind, placebo-controlled, multicentre trial	Phase 2/3, placebo-controlled, randomised, double-blind, multicentre, parallel intergroup comparison trial	Phase 2/3, placebo-controlled, randomised, double-blind, multicentre, parallel intergroup comparison trial
Duration of study and follow-up	13-18 months	12 months	12 months	19 months	12 months
Eligibility criteria for participants	• Subjects ≥18 years • Clinical history consistent with HDM-induced asthma of at least 1 year prior to trial entry • Asthma control questionnaire (ACQ) score ≥1.0 at screening • 1.0≤ACQ≤1.5 at Visit 3 (randomisation) • A clinical history consistent with mild-severe HDM-induced AR for at least 1 year	• Subjects 18-65 years • A clinical history with moderate-to-severe persistent HDM AR (with or without asthma) for at least one year prior to trial entry, with AR symptoms despite having received symptomatic treatment • Use of symptomatic medication for treatment of HDM AR during at least 8 days of	• Subjects 12 years and older • A clinical history of HDM-induced AR/ARC of 1 year duration or more, with or without asthma • Sensitised to HDM with a positive skin test ≥5 mm compared with saline control and serum specificIgE of ≥0.7 kU/L to either Dermatophagoides (D.) farinae or	• Patients ≥18 to <65 years of age on day of informed consent • Level of HDM-specific IgE antibodies (Dermatophagoides pteronyssinus or Dermatophagoides farinae) measured between the day of informed consent and the first day of observation assessed as Class 3 or greater • Positive HDM allergen scratch or prick test performed between the day of informed	• Subjects ≥12 to <65 years of age on day of informed consent • Patients whose level of HDM-specific IgE antibodies (D.pteronyssinus or D.farinae) measured between the day of informed consent and the first day of observation (Visit 1) is assessed as Class 3 or greater • Patients who test positive on a nasal provocation test (either HDM or house dust)

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	• Positive skin prick test response to Dermatophagoides pteronyssinus and/or Dermatophagoides farinae • Positive specific IgE levels (>0.70kU/L) against Dermatophagoides pteronyssinus and/or Dermatophagoides farinae	the baseline period • Presence of one or more of the ARIA quality of life items due to HDM AR during the baseline period • If subject has asthma, daily use of ICS should be ≤400mcg budesonide or equivalent (i.e. corresponding to GINA treatment Steps 1 or 2) • Positive skin prick test response (wheal diameter ≥3 mm) to Dermatophagoides pteronyssinus (Dermatophagoides pteronyssinus) and/or Dermatophagoides farinae (Dermatophagoides farinae) • Positive specific IgE against Dermatophagoid	Dermatophagoides pteronyssinus • Forced expiratory volume in 1 second (FEV1) >80% of predicted at screening, run-in, and randomisation visits • A rhinitis daily symptom score (DSS) of at least 6 (or a score of at least 5 with 1 symptom being severe) out of 12 on 5 of 7 consecutive calendar days before randomisation	consent and the first day of observation, or within 1 year before the day of informed consent • Asthmatic symptoms were treated with ICS(s) including combination drugs for at least 6 months before the first day of observation • Daily dose of ICS(s) at the start of study treatment is between 200 and 400 µg fluticasone propionate • Patients who experienced reversible airway obstruction before the first day of study treatment. If this is to be checked between the day of informed consent and the first day of study treatment, at least one of the following criteria should be met:	performed between the day of informed consent and the first day of observation (Visit 1) or within 1 year before the day of informed consent • Patients who have a history of treatment for HDM-induced AR that started more than 1 year before the first day of observation (Visit 1) • Patients who have moderate or severe symptom(s) of HDM-induced AR (total daily rhinitis symptom scores of ≥7) for at least 7 days during the 14-day observation period that starts from the first day of observation (Visit 1) • Patients who score at least 1 point in at least 1 item in the following JRQLQ No. 1 due to HDM-induced AR on the first day of

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		es pteronyssinus and/or Dermatophagoides farinae (defined as ≥IgE Class 2; i.e. ≥0.70 kU/L)		1. The forced expiratory volume in 1 second (FEV1) on spirometry improves by ≥12% and by ≥200 mL in the absolute volume after administration of a short-acting β2 agonist (SABA) 2. The PEF improves by >20% after administration of an SABA 3. The PEF's circadian variation is >20% • Mean score of ≥1.0 point on the ACQ at the start of observation (a mean score of ≥0.85 if long-acting β2 agonists [LABA] are used during the 7 days before the first day of observation) • Mean score of 1.0 to 1.5 points on the ACQ at the start of study treatment • FEV1 at the start of observation exceeds 70% of the predicted value • Patients who have completed ≥80% of their electronic patient diary for the 2 weeks before the	observation (Visit 1): 1. Reduced productivity at work/home Phase 2/3 Clinical Trial of TO-203 (Patients with HDM-induced Allergic Rhinitis) Clinical Study Report (Jun 24, 2014) 2. Impaired reading of book/newspaper 3. Limitation of outdoor life (e.g. sport, picnics) 4. Limitation on going out 5. Hesitation visiting friend or relatives 6. Reduced contact with friends or others by telephone or conversation 7. Impaired sleeping • Patients who have completed ≥80% of their electronic patient diary during the observation period • Men and women of childbearing potential who are willing to practice appropriate contraception during the trial • Women of childbearing potential who have

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				first day of study treatment • Men and women of childbearing potential who are willing to practice appropriate contraception during the trial period • Women of childbearing potential who have a negative pregnancy test both on the first day of observation and on the first day of study treatment	a negative pregnancy test on the first day of observation (Visit 1) and the first day of study treatment (Visit 2)
Trial drugs	6/12 SQ-HDM, placebo	6/12 SQ-HDM, placebo	12 SQ-HDM, placebo	6/12 SQ-HDM, placebo	6/12 SQ-HDM, placebo
Permitted concomitant medication	Concomitant medications were to be kept to a minimum during the trial. However, if considered necessary for the subject's well-being and unlikely to interfere with the IMP, concomitant medications were allowed to be prescribed at the discretion of the investigator according to the local standard of care. Symptomatic medications were	Concomitant treatments and medications were to be kept to a minimum during the trial. However, if considered necessary for the subject's well-being and unlikely to interfere with the trial medication, they could be given at the discretion of the investigator according to the local standard of care. Subjects were provided with nasal steroid, oral antihistamine, and	Subjects could take any medication or vaccine not restricted by the protocol (refer to Table 9-1 and Table 9-2) and that would not be expected to interfere with the conduct of the trial. Chronic medications should have been dosed on a stable regimen. All concomitant medications were to be appropriately	Concomitant medications were to be kept to a minimum during the trial. ICS was provided as fluticasone propionate (Flutide® Diskus) for the long-term management of asthma. When asthmatic attacks occur during the trial, SABA was used as appropriate. When SABA fails to control severe asthmatic symptoms or attacks, prednisolone tablets were used.	Concomitant medications were to be kept to a minimum during the trial. However, if unbearable symptoms occur, the following rescue drugs were used: • Fluticasone propionate nasal solution was used for unbearable symptoms of "nasal congestion". • Olopatadine hydrochloride ophthalmic solution was

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	allowed to be used as needed, in addition to the IMP to which the patients had been randomised.	antihistamine eye drops to be used as needed. Symptomatic medications were allowed in the trial. It was considered reasonable to adjust the reported symptom score to account for the symptomatic medications used, in order to get a more accurate representation of symptomatology.	documented on the eCRF.		used for unbearable "ocular symptoms (e.g., itchy eyes or watery eyes)". If unbearable symptoms persist after the use of these drugs or if symptoms such as "sneezing, nasal discharge, and itchy sensation" are unbearable, loratadine was used.
Disallowed concomitant medication	• Glucocorticoids • Antihistamines • Nedocromil/cromolyn sodium • Leukotriene antagonists, synthase inhibitors, LABA, LAMA • MAOIs • Pizotifene • Theophylline • Beta blockers • Anti-IgE treatment • Immunotherapy to other allergens • High dose ICS • Tricyclic antidepressants or antipsychotic	• Glucocorticoids • Antihistamines • Nedocromil/cromolyn sodium • Leukotriene antagonists, synthase inhibitors, LABA, LAMA • MAOIs • Pizotifene • Theophylline • Beta blockers • Anti-IgE treatment • Immunotherapy to other allergens • High dose ICS • Tricyclic antidepressants or antipsychotic	• Immunosuppressive therapy (except steroids for allergic and asthma symptoms) • Beta blockers • Anti-IgE treatment • Immunotherapy to HDM • High dose ICS • Tricyclic antidepressants or antipsychotic with antihistaminic effects • Investigational drugs	• Corticosteroids • Leukotriene receptor antagonists • LABAs • SABAs • Theophylline • Antihistamines • Antipsychotics with antihistaminic effects (e.g., chlorpromazine, levomepromazine, clozapine, olanzapine) • Monoamine oxidase inhibitors • Tricyclic antidepressants • Mediator release inhibitors, thromboxane A2	• Corticosteroids • Anti-allergic drugs • Anti-IgE antibody • Immunosuppressants • Chinese medicines for the treatment of asthma or rhinitis (e.g., Shoseiryuto, Shigyakusan, Kakkontokasenkyushini, Keigairengyoto, Shiniseihaito) • MAOI • Tricyclic antidepressants • Anticholinergic drugs • Antipsychotics with antihistamine effects (e.g.,

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	with antihistaminic effects • Investigational drugs	with antihistaminic effects • Investigational drugs		inhibitors, Th2 cytokine inhibitors • Anticholinergics • Anti-IgE antibody • Immunosuppressants • Chinese medicines for rhinitis or asthma (e.g., Shoseiryuto, Shigyakusan, Kakkontokasenkyushini, Keigairengyoto, Shiniseihaito) • Drugs not approved in Japan	chlorpromazine, levomepromazine, clozapine, olanzapine, thioridazine) • COMT inhibitors • Beta blockers • Nasal vasoconstrictors • Drugs not approved in Japan
Primary outcomes used in the economic model or specified in the scope	• Time to first moderate or severe asthma exacerbation during Period 3 (ICS reduction/ withdrawal)	• Average TCRS during the efficacy evaluation period	• Average TCRS during the last 8 weeks of treatment	• Time to the first moderate or severe asthma exacerbation in Period 3 measured from randomisation (calculating from the first day of study treatment)	• Average TCRS during the last 8 weeks of treatment
Secondary outcomes used in the economic model or specified in the scope	• Time to first asthma exacerbation with deterioration in asthma symptoms • Immunology measured as change from baseline to end	• Average total AR DSS during the efficacy evaluation period • Average total AR DMS during the efficacy evaluation period	• Average rhinitis DSS during the last 8 weeks of treatment • Average rhinitis DMS during the last 8 weeks of treatment • Average TCS during the last 8	• Time to the first moderate or severe asthma exacerbation in Period 3 measured from the Period 3 started date (calculating from the Period 3 started date)	• Rhinitis DSS • Rhinitis DMS • Rhinoconjunctivitis DSS, rhinoconjunctivitis DMS, total combined rhinoconjunctivitis score • Conjunctivitis DSS, conjunctivitis DMS,

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	of trial in terms of specific IgG4 against HDM allergens • Proportion of patients with a MID change in AQLQ(S) controlled for change in ICS • Proportion of patients with a MID change in AQLQ(S) controlled for change in ICS • Time to first asthma exacerbation with increased use of SABA • Time to first asthma exacerbation with deterioration in lung function • Time to first severe asthma exacerbation • Number of first asthma exacerbations during Period 3 • Total number of asthma	• Average overall RQLQ score during the efficacy evaluation period • Average total combined allergic ARC score during the efficacy evaluation period • Average total allergic ARC DSS during the efficacy evaluation period • Average total allergic ARC DMS during the efficacy evaluation period • Average total combined conjunctivitis score during the efficacy evaluation period • The average total AR DSS, average total AR DMS and average TCRS	weeks of treatment • Average AR/ARC VAS score during the last 8 weeks of treatment • Average asthma DSS during the last 8 weeks of treatment • Percentage of minimal symptom days (defined as a day without the use of any rescue medication and with rhinoconjunctivitis DSS of ≤2) during the last 8 weeks of treatment • Average rhinoconjunctivitis symptoms assessed by RQLQ(S) 12+ during the last 8 weeks of treatment • Descriptive summary of EQ-5D-5L	• Time to moderate worsening of asthma • Time to severe worsening of asthma • Frequency of worsening of asthma during the ICS dose tapering period • Mean symptom score for the duration until worsening of asthma during the first 12 weeks of the ICS dose tapering period • Mean symptom score for the duration until worsening of asthma during the ICS dose tapering period • The number of symptom-free days during the ICS dose tapering period A symptom-free day is defined as a day on which: the symptom score is 0, SABAs are not used, and oral corticosteroids are not used.	and total combined conjunctivitis score • Symptom scores • QoL (JRQLQ No. 1) • Symptom-free days in the final 8 weeks of the study treatment period • Symptom-severe days in the final 8 weeks of the study treatment period • Discontinuation due to lack of efficacy • Overall evaluation by physicians • Overall evaluation by subjects

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	exacerbations during Period 3 • The average morning PEF, evening PEF, and diurnal variability during Period 2B and the first asthma exacerbation-free period of Period 3 • Change from baseline in FEV1 and FEV1 in % of predicted value • The average total asthma daytime symptom score and the average nocturnal asthma symptom score during Period 2B and the first asthma exacerbation-free period of Period 3 • Average nocturnal awakenings during Period 2B and the first asthma	during one week diary periods at Visits 3, 4, 5, and 6 • The average individual allergic rhinoconjunctivitis DSS during the efficacy evaluation period • Frequency of symptom-free days • Global evaluation for efficacy • Average individual domains in the RQLQ score during the efficacy evaluation period • The average overall RQLQ score at Visit 3, 4, 5, and 6 • The change from baseline of overall RQLQ during the efficacy evaluation period and at	domain scores and EQ-VAS during the last 8 weeks of treatment • Immunological assessments, including D. farinae and D. pteronyssinus specific IgE, and IgG4 at run-in, Week 4, Week 20, and final week of dosing (Visit 11) • WPAI+CIQ:AS outcome at Visits 2, 3, and 6	• Changes in pulmonary function test results (FEV1 and PEF) • ACQ (including FEV1 data) • QoL (AHQ-JAPAN) • Frequency of SABA use	

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	exacerbation-free period of Period 3 • SABA use during Period 2B and the first asthma exacerbation-free period of Period 3 • Proportion of symptom-free days, -nights and 24-hour periods during Period 2B and the first asthma exacerbation-free period of Period 3 (symptom-free is defined as asthma symptom score =0 and SABA intake =0) • Average morning PEF, evening PEF, and diurnal variability during Period 2B and the first asthma exacerbation-free period during Period 3	Visit 3, 4, 5, and 6 • Change from baseline to end of treatment of log10(IgE) for both HDM species • Change from baseline to end of treatment of log10(IgG4) for both HDM species			

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	• Change from baseline in FEV1 and FEV1 in % of predicted value • ACQ score • AQLQ score • Proportion of subjects with MID change in ACQ/AQLQ(S) controlled for change in ICS at visit 9 (ICS reduction) and visit 11 (ICS withdrawal) • Specific IgE • Development and changes SF-36, TSQM II, WPAI:ASTHMA, health care resource use, and rate of hospitalisation				
Safety outcomes used in the economic model or specified in the scope	• AEs • AE discontinuations • SAEs • Vital signs • Safety laboratory assessments • FEV1 • Physical examinations	• AEs • AE discontinuations • SAEs • Vital signs • Safety laboratory assessments • FEV1 • Physical examinations	• AEs • AE discontinuations • SAEs • Vital signs • Safety laboratory assessments • FEV1 • Physical examinations	• AEs • AE discontinuations • SAEs • Vital signs • Safety laboratory assessments • FEV1 • PEF • Physical examinations	• AEs • AE discontinuations • SAEs • ADRs • Vital signs • Safety laboratory assessments • FEV1 • Physical examinations

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Pre-planned subgroups	No formal statistical subgroup analyses were planned.	No formal statistical subgroup analyses were planned.	Subgroup analyses of the average TCRS during the last 8 weeks of treatment included age, gender, race, asthma status, ICS use, allergen sensitivity, geographic location, and the occurrence of local application site reactions.	Subgroup analyses of the primary and key secondary endpoint during the last 8 weeks of treatment included age and allergen sensitivity.	Subgroup analyses of the average TCRS during the last 8 weeks of treatment included age and allergen sensitivity.

Abbreviations: AE, adverse event; SAE, serious adverse event; FEV, forced expiratory flow; ADR, adverse drug reaction; ICS, inhaled corticosteroid; TCRS, total combined rhinitis score; ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; Ig, immunoglobulin; JRQLQ, japanese allergic rhinitis quality of life standard questionnaire; DMS, daily medications score; DSS, daily symptom score; RQLQ, rhinitis quality of life questionnaire LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonistic; MAOI, monoamine oxidase inhibitors; ARC, allergic rhinoconjunctivitis; AR, allergic rhinitis; SABA, short-acting β 2-agonist; PEF, peak expiratory flow.

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B2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Description of study populations

Please see Table 38 for a description of the analysis populations for efficacy and safety outcomes for the MT-04, MT-06, P001, TO-203-31, and TO-203-32 trials.

Table 38: Overview of the study populations of the included trials

Study		Description
MT-04 [36, 47]	**Total**	All patients who entered the trial. This analysis set includes screening failures and was used to list reasons for screening failures and AEs before randomisation.
	FAS	All randomised patients in accordance with the ICH intent-to-treat principle. The FAS was considered the primary analysis set for the primary, secondary, and exploratory efficacy analyses.
	FAS-MI	All randomised patients who discontinued from the trial during Period 2 were included in this analysis set as if they were following the same distribution, with regards to the first asthma exacerbation, as the observed placebo group during the efficacy assessment period (Period 3), i.e., as if they were having no treatment effect. Thus, all subjects who discontinued during Period 2 were included as sampled from the placebo distribution of time to first asthma exacerbation during Period 3. The primary efficacy analysis was conducted based on the FAS-MI analysis set.
	PP	All patients in the FAS with no major protocol violations which might influence the primary endpoint. The per-protocol (PP) analysis set was used as a supportive analysis of the primary endpoint.
	Safety	Identical to the FAS. All randomised patients who discontinued from the trial during Period 2 were included in this analysis set as if they were following the same distribution, with regards to the first asthma exacerbation, as the observed placebo group during the efficacy assessment period (Period 3), i.e., as if they were having no treatment effect.
MT-06 [34, 48]	**Total**	All patients who entered the trial. This analysis set includes screening failures and was used to list reasons for screening failures and AEs before randomisation.
	FAS	All randomised patients in accordance with the ICH intent-to-treat principle. The FAS was the primary set for all efficacy analyses.
	FAS-MI	Identical to the FAS dataset, except with multiple imputation of missing data.
	PP	All patients in the FAS with no major protocol violations which might influence the primary endpoint. The PP analysis set was used as a supportive analysis of the primary endpoint.
	Safety	All randomised patients, i.e., the SS is identical to the FAS. The SS was used for safety tables and listings.
P001 [35, 49]	**FAS**	The FAS population considered all randomised patients who had received at least 1 dose of study drug. The FAS was considered the primary analysis set for the primary, secondary, and exploratory efficacy analyses.
	PP	The PP population included all randomised patients who did not have major prespecified protocol violations. The PP analysis set was used as a supportive analysis of the primary endpoint and key secondary efficacy endpoints.

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Study		Description
	ASaT	The all-subjects-as-treated (ASaT) population included all randomised patients who received at least 1 dose of the study drug. This population was used for the analysis of the safety data.
TO-203-31 [37, 50]	**FAS**	FAS included subjects who received IMP and had undergone efficacy assessment irrespective of compliance with the protocol. The primary analysis of the primary endpoint was performed in the FAS study group.
	FAS-MI	FAS-MI included subjects in FAS, and data on subjects who did not move to Period 3 were imputed with data of the placebo group in Period 3. The FAS-MI study group was used for the analyses of the key secondary endpoint.
	FAS-OC	FAS-OC included subjects who moved to Period 3 in FAS (data on subjects who did not move to Period 3 were not imputed with data of the placebo group in Period 3). The FAS-OC study group was used for the sensitivity analyses of key secondary analysis of the key secondary endpoint.
	PPS	Included subjects who met the following criteria in FAS: • Treatment compliance of 80% or greater • Subjects who were judged to have no significant protocol deviation by the blind review meeting Sensitivity analyses of the primary analysis of the primary endpoint were performed in the PPS study group.
	PPS-OC	Subjects who moved to Period 3 in PPS. The PPS-OC study group was used for the sensitivity analyses of the key secondary analysis of the key secondary endpoint.
TO-203-32 [38, 51]	**FAS**	Subjects who received the IMP and recorded at least 80% (at least 45 days) of symptom scores and medication scores in the final 8 weeks of the study treatment period, regardless of compliance to the protocol. The FAS set was used for primary analyses.
	ITT	Subjects who received the IMP and recorded symptom and medication scores at least once. The ITT study group was used for sensitivity analyses.
	PPS	Subjects without a significant protocol deviation who were included in FAS and met the following criteria: • Treatment compliance of 80% or greater • Subjects who were judged to have no significant protocol deviation by the blind review meeting The PPS study group was used for sensitivity analyses.
Abbreviations: PPS, per-protocol set; ITT, intent-to-treat, PP, per-protocol; FAS, full analysis set; OC, observed cases; MI, multiple imputation; ASaT, all-subjects-as-treated.		

B.2.4.2 Patient dispositions

B2.4.2.1 MT-04

The patient disposition and study participation of patients in MT-04 are presented by treatment group in Table 39, and participant disposition throughout the trial is outlined in Figure 10.

The FAS comprised a total of 834 patients: 277 patients in the placebo group, 275 patients in the 6 SQ-HDM group, and 282 patients in the 12 SQ-HDM group.

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The PP analysis set comprised a total of 664 patients (80% of the FAS), with 228 in the placebo group, 218 in the 6 SQ-HDM group, and 218 in the 12 SQ-HDM group. 175 patients were excluded from the PP analysis. 92 patients were excluded as they discontinued the trial prior to Visit 9 (ICS reduction) and thus did not provide data on the primary efficacy endpoint. Besides this, the most common reason for exclusion from the PP set was the use of prohibited concomitant medication during baseline, or during Period 3 (ICS reduction/withdrawal) prior to the first asthma exacerbation (n=36). 10 patients (1%) were excluded due to IMP compliance deviations (<75% from Visit 3 and until the end of trial).

Table 39: MT-04 patient disposition and study participation [36, 47]

Treatment group	**Placebo**	**12 SQ-HDM**	**Overall**
Subjects screened	-	-	1262
Screening failures	-	-	428
FAS	277 (100%)	282 (100%)	834 (100%)
PP	228 (82%)	218 (77%)	664 (80%)
Entering Period 3 [a]	257 (93%)	248 (88%)	742 (89%)
Completed trial [b]	209 (75%)	205 (73%)	617 (74%)
Discontinuation			
During entire trial	68 (25%)	77 (27%)	217 (26%)
Reason for discontinuation			
Adverse event	8 (3%)	25 (9%)	45 (5%)
Lack of efficacy	2 (<1%)	1 (<1%)	4 (<1%)
Lost to follow-up	5 (2%)	3 (1%)	14 (2%)
Non-compliance with protocol	8 (3%)	7 (2%)	21 (3%)
Pregnancy	6 (2%)	1 (<1%)	8 (<1%)
Withdrawal of consent	13 (5%)	15 (5%)	44 (5%)
Other [c]	26 (9%)	25 (9%)	81 (10%)
Discontinuations following an asthma exacerbation [d]	24 (9%)	19 (7%)	65 (8%)

a. Patients who attended Visit 9 (ICS reduction) and thereby provided data for the primary efficacy analysis
b. 693 attended Visit 13 or had an asthma exacerbation fulfilling the primary endpoint (considered trial completers)
c. 65 of the 81 'other reasons' were due to asthma exacerbations (see below) during Period 3; the remaining reasons included travel, use of prohibited medication, or planning of pregnancy.
d. An asthma exacerbation during Period 3A (ICS reduction) was not per se requiring trial discontinuation and patients had the possibility of continuing in the trial up to a maximum of 3 exacerbations. During Period 3B (ICS withdrawal) the protocol specified that patients should be discontinued following an exacerbation.
Abbreviations: SQ, standardised quality; HDM, house dust mite; FAS, full analysis set; PP, per-protocol.

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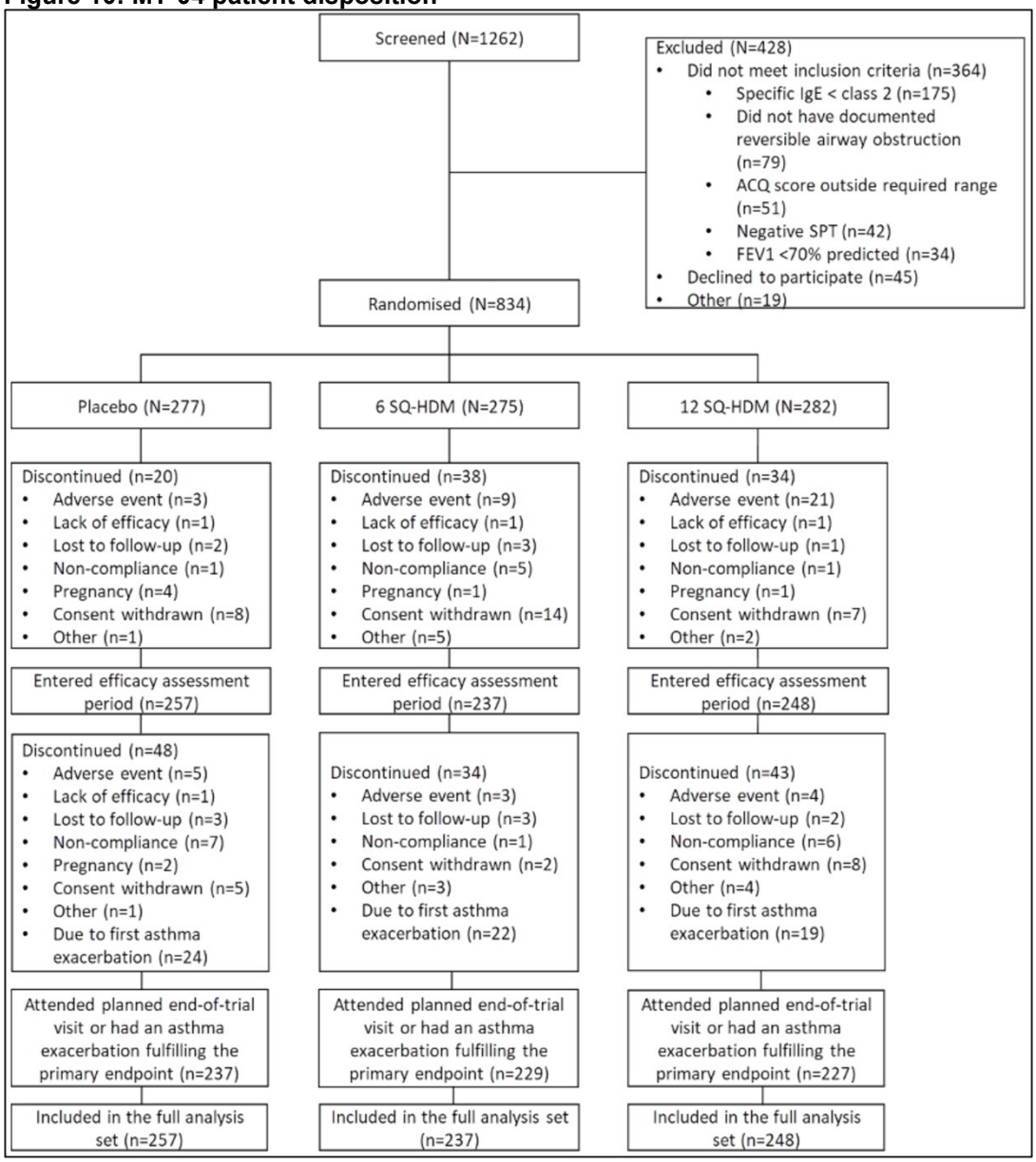
Figure 10: MT-04 patient disposition [36, 47]



Abbreviations: IgE, immunoglobulin E; FEV, forced expiratory volume; ACQ, asthma control questionnaire; SPT, skin prick test.

B2.4.2.2 MT-06

The patient disposition and study participation of patients in MT-06 are presented by treatment group in Table 40, and participant disposition throughout the trial is outlined in Figure 11.

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A total of 1,425 patients were screened for the trial. Of the screened patients, 433 (30%) were screening failures, which resulted in 992 patients being eligible for randomisation. Of the randomised patients, 877 (88%) completed the trial; there was no material overall difference between the 3 treatment groups.

Table 40: MT-06 patient disposition and study participation [34, 48]

Treatment group	**Placebo**	**12 SQ-HDM**	**Overall**
Subjects screened	-	-	1425
Screening failures	-	-	433
FAS	338 (100%)	318 (100%)	992 (100%)
FAS with observations [a]	298 (88%)	284 (89%)	879 (89%)
PP	272 (80%)	264 (83%)	805 (81%)
Completed trial	296 (89%)	284 (89%)	877 (88%)
Discontinuation			
All discontinued	42 (12%)	34 (11%)	115 (12%)
Reason for discontinuation			
Adverse event	7 (2%)	13 (4%)	30 (3%)
Lack of efficacy	2 (<1%)	-	4 (<1%)
Lost to follow-up	5 (1%)	1 (<1%)	12 (1%)
Non-compliance with protocol	6 (2%)	4 (1%)	11 (1%)
Other	6 (2%)	6 (2%)	15 (2%)
Pregnancy	4 (1%)	1 (<1%)	6 (<1%)
Withdrawal of consent	12 (4%)	9 (3%)	37 (4%)

[a] FAS with observations are subjects in FAS with observations of the primary endpoint.
Abbreviations: SQ, standardised quality; HDM, house dust mite; FAS, full analysis set; PP, per-protocol.

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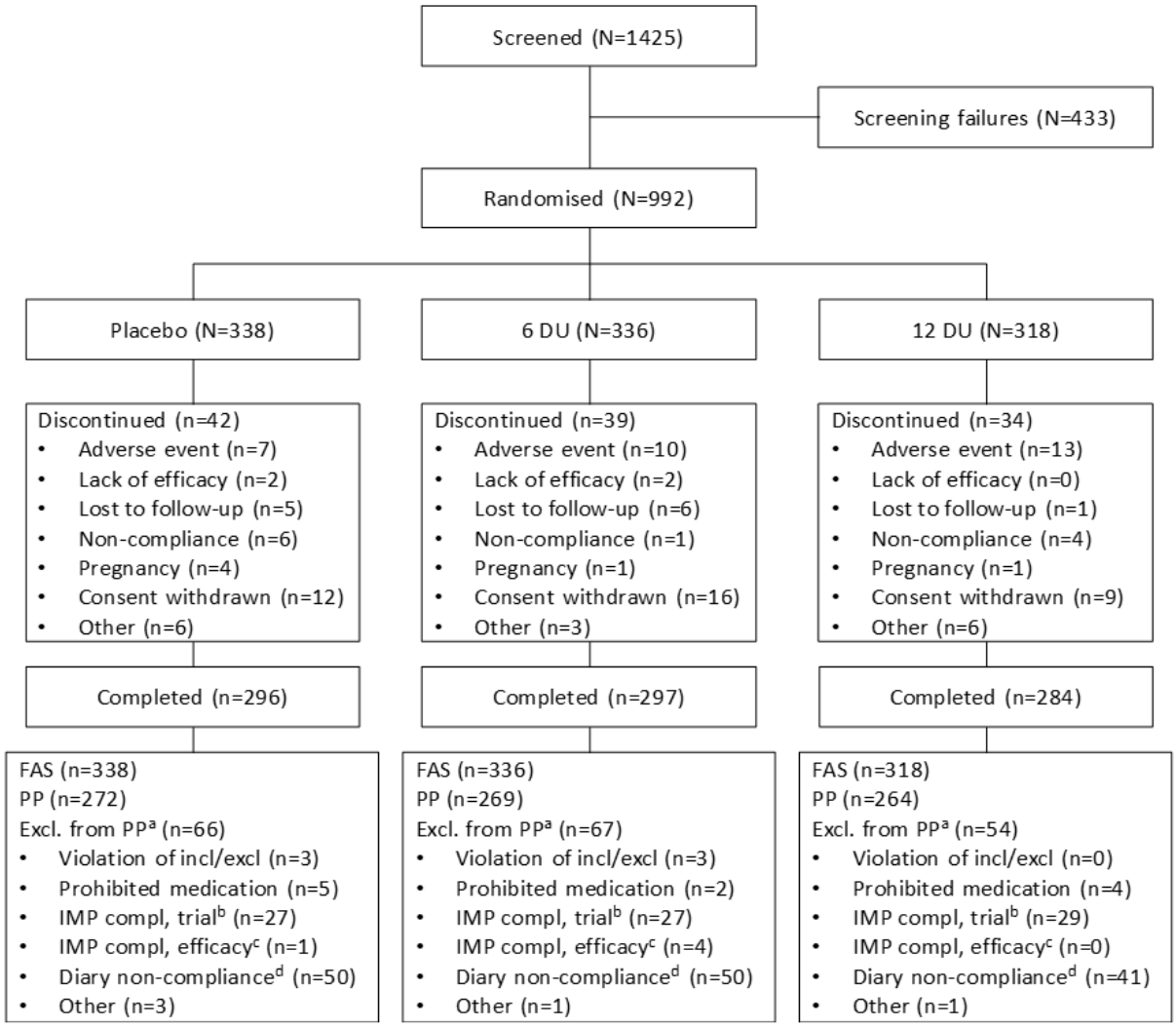
Figure 11: MT-06 patient disposition



Abbreviations: FAS=Full Analysis Set; PP=Per-protocol; IMP=Investigational Medicinal Product; incl=inclusion; excl=exclusion; compl=compliance; DU, development unit.

[a]: One or more subjects had more than one reason for PP exclusion.

[b]: To be included in the PP, the IMP compliance in the entire trial should be above or equal to 75%.

[c]: To be included in the PP, the IMP compliance during the efficacy evaluation period should comply with the treatment stop date being less than a month (i.e 30 days) prior to the last diary record in the efficacy evaluation period.

[d]: Diary non-compliance is defined as providing fewer than 21 daily diary records in the efficacy evaluation period.

B2.4.2.3 P001

The patient disposition and study participation of patients in P001 are presented by treatment group in Table 41, and participant disposition throughout the trial is outlined in Figure 12.

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The majority of randomised patients (79.2%) completed the double-blind treatment period. There were more discontinuations in the 12 SQ-HDM group than in the placebo group, with AEs notably being a major contributor to the difference in rates of discontinuations. The primary reasons for trial discontinuation were withdrawal by the subject, discontinuation due to AE, and loss to follow-up. The percentage of patients who discontinued from the trial was higher in the 12 SQ-HDM group than in the placebo group.

Table 41: P001 patient disposition and study participation [35, 49]

	Placebo	**12 SQ-HDM**	**Overall**
Subjects screened	-	-	4497
Screening failures	-	-	3015
FAS	741 (100%)	740 (99%)	1481 (99%)
PP	645 (87%)	651 (88%)	1296 (87%)
Safety set (ASaT) [a]	738 (99%)	743 (101%)	1481 (99%)
Completed trial	613 (83%)	561 (76%)	1174 (79%)
Discontinuation			
During entire trial	128 (17%)	179 (24%)	307 (21%)
Reason for discontinuation			
Adverse event	18 (24%)	73 (10%)	91 (6%)
Lack of efficacy	-	1 (0%)	1 (0%)
Lost to follow-up	29 (4%)	42 (6%)	71 (5%)
Non-compliance with study drug	5 (1%)	-	5 (3%)
Physician decision	3 (%)	2 (3%)	5 (3%)
Pregnancy	4 (1%)	1 (1%)	5 (3%)
Progressive disease	-	1 (1%)	1 (1%)
Protocol violation	4 (1%)	3 (4%)	7 (5%)
Technical problems	1 (%)	-	1 (1%)
Withdrawal by subject	64 (9%)	56 (8%)	120 (8%)

[a] Three subjects randomised to receive placebo received the incorrect treatment during the trial; these three subjects were analysed as 12 SQ-HDM treated subjects in the ASaT population
Abbreviations: SQ, standard quality; HDM, house dust mite; FAS, full analysis set; PP, per-protocol; ASaT, all-subjects-as-treated.

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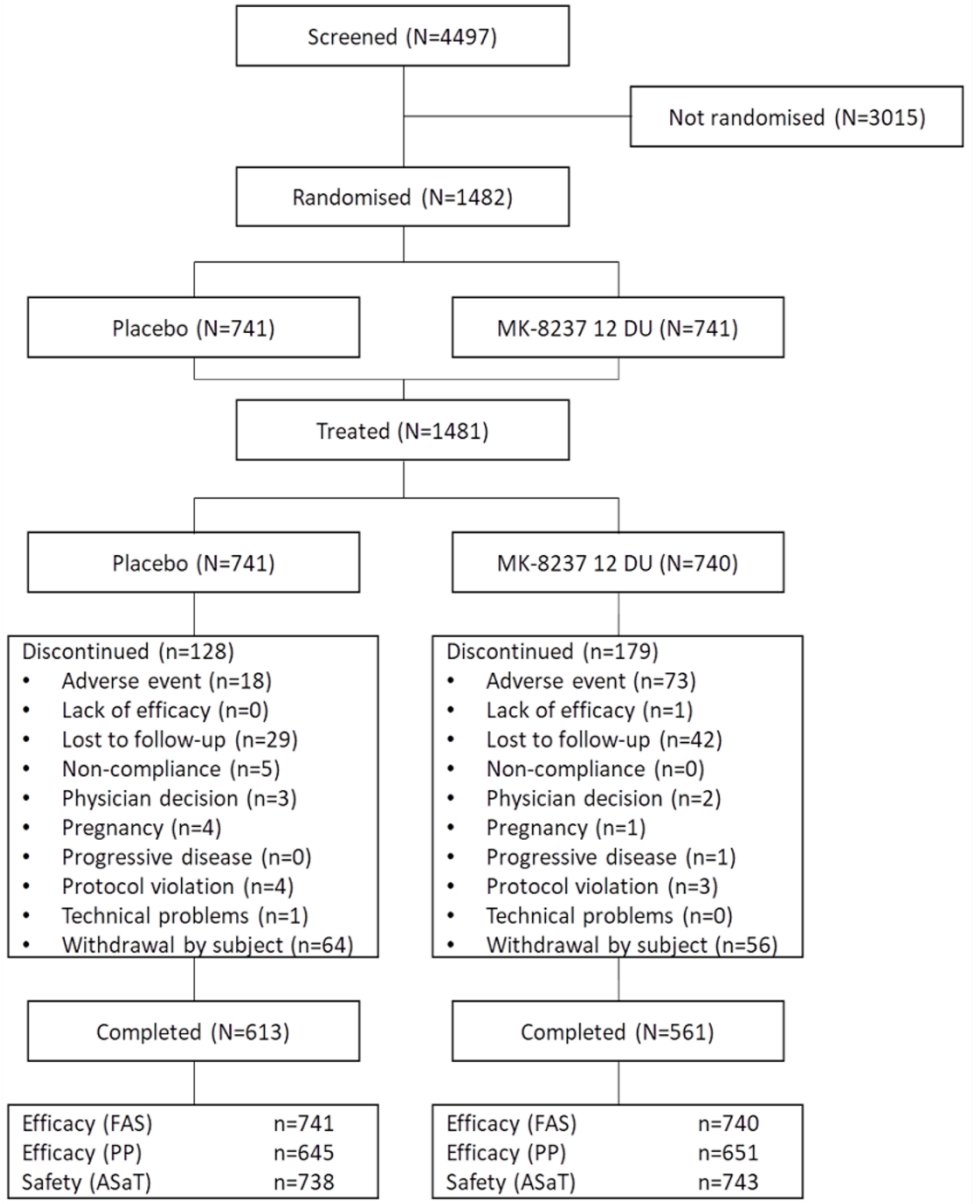
Figure 12: P001 patient disposition [35, 49]



Abbreviations: DU, development unit; FAS, full analysis set; PP, per protocol; ASaT, all subjects as treated.

B2.4.2.4 TO-203-31

The patient disposition and study participation of patients in TO-203-31 are presented by treatment group in Table 42, and participant disposition throughout the trial is outlined in Figure 13.

A total of 1,335 patients were screened for the trial. Of the screened patients, 509 (38%) were screening failures, which resulted in 826 patients eligible for

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randomisation. Of the randomised patients, 693 (84%) completed the trial with no material overall difference between the 3 treatment groups.

There were more discontinuations in the 12 SQ-HDM group than in the placebo group, with AEs most notably contributing to the difference in rates of discontinuations. The primary reasons for trial discontinuation were withdrawal by the subject, personal reasons, and discontinuation due to AE. The percentage of patients who discontinued from the trial was higher in the 12 SQ-HDM group than in the placebo group.

Table 42: TO-203-31 patient disposition and study participation[37, 50]

	Placebo	12 SQ-HDM	Overall
Subjects screened	-	-	1335
Screening failures	-	-	509
FAS[†]	274 (100%)	276 (100%)	824 (100%)
PPS	225 (82%)	240 (87%)	689 (84%)
Entered Period 3	246 (90%)	238 (86%)	721 (88%)
Completed trial	237 (86%)	227 (82%)	693 (84%)
Discontinuation			
During entire trial	32 (12%)	42 (15%)	113 (14%)
Reason for discontinuation			
Adverse event	4 (1%)	10 (4%)	22 (3%)
Asthma exacerbation (Period 2)	4 (1%)	6 (2%)	11 (1%)
Withdrawal consent	8 (3%)	6 (2%)	30 (4%)
Judged to be unsuitable for the trial	1 (0%)	3 (1%)	7 (1%)
Personal reasons	6 (2%)	9 (3%)	23 (3%)
Pregnancy	2 (1%)	1 (%)	3 (0%)
Lost to follow-up	1 (0%)	4 (1%)	6 (1%)
Other	6 (2%)	3 (1%)	11 (1%)

[†] Duplicate enrolment: 1 subject was enrolled at 2 different sites and assigned to the placebo and 12 SQ-HDM groups (2 subjects excluded from overall population).
Abbreviations: SQ, standard quality; HDM, house dust mite; FAS, full analysis set; PPS, per-protocol set.

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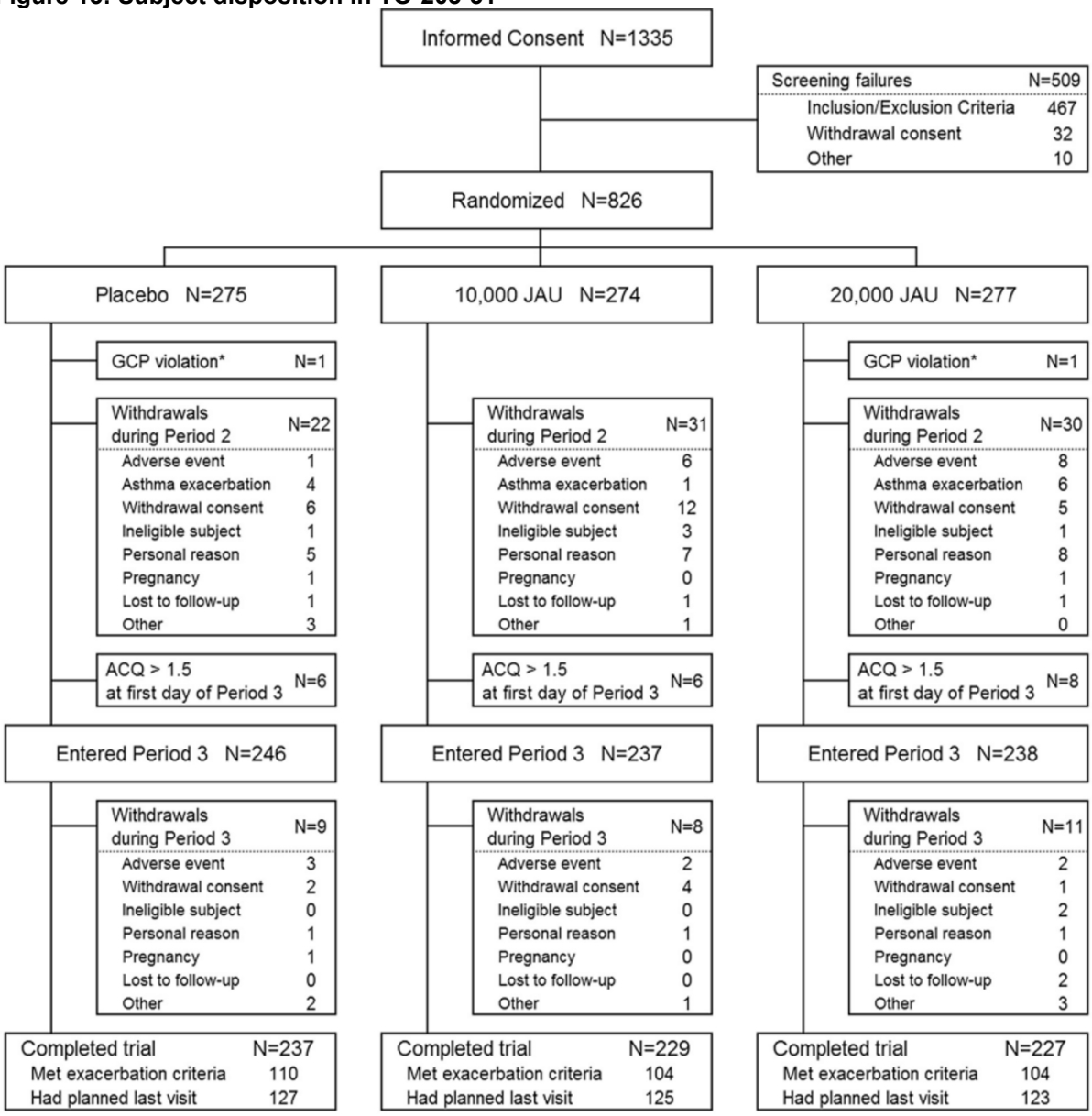
Figure 13: Subject disposition in TO-203-31[37, 50]



Abbreviations: JAU, Japanese allergy unit; ACQ, asthma control questionnaire; GCP, good clinical practice.

B2.4.2.5 TO-203-32

The patient disposition and study participation of patients in TO-203-32 are presented by treatment group in Table 43, and participant disposition throughout the trial is outlined in Figure 14.

A total of 1,740 patients were screened for the trial. Of the screened patients, 794 (46%) were screening failures, which resulted in 946 patients eligible for

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randomisation. Of the randomised patients, 852 (90%) completed the trial with no material overall difference between the 3 treatment groups.

As detailed in Table 38, FAS was used for primary analysis. ITT and PPS were used for sensitivity analyses. ITT included subjects who received the study drug and underwent efficacy assessment at least once. FAS included subjects who received the study drug and recorded at least 80% (at least 45 days) of symptom scores and medication scores during Period A, regardless of compliance to the protocol. PPS included subjects without a significant protocol deviation whose treatment compliance rate was at least 80% in FAS.

There were no material differences in discontinuations between the placebo group and the 12 SQ-HDM group. The primary reasons for trial discontinuation were withdrawal by the subject, personal reasons, and discontinuation due to AE. The percentage of patients who discontinued from the trial due to AEs was higher in the placebo group compared with the 12 SQ-HDM group. Of subjects who started study treatment (n = 946), discontinuation due to lack of efficacy occurred in 1 subject in the placebo group only.

Table 43: TO-203-32 patient disposition and study participation [38, 51]

	Placebo	12 SQ-HDM	Overall
Subjects screened	-	-	1740
Screening failures	-	-	794
Randomised	319 (100%)	314 (100%)	946 (100%)
ITT	317 (99%)	307 (98%)	928 (98%)
FAS	285 (89%)	281 (89%)	852 (90%)
PPS	276 (87%)	274 (87%)	829 (88%)
Completed trial	285 (89%)	281 (89%)	852 (90%)
Discontinuation (% of FAS)			
During entire trial	34 (12%)	33 (12%)	94 (11%)
Reason for discontinuation (% of FAS)			
Adverse event	9 (3%)	5 (2%)	21 (22%)
Rhinitis exacerbation	1 (0%)	0 (0%)	1 (1%)
Withdrawal consent	13 (5%)	13 (5%)	34 (36%)
Judged to be unsuitable for the trial	2 (1%)	3 (1%)	5 (5%)
Personal reasons	5 (2%)	9 (3%)	20 (21%)
Pregnancy	1 (0%)	1 (0%)	5 (5%)
Lost to follow-up	2 (1%)	1 (0%)	5 (5%)
Other	1 (0%)	1 (0%)	3 (3%)

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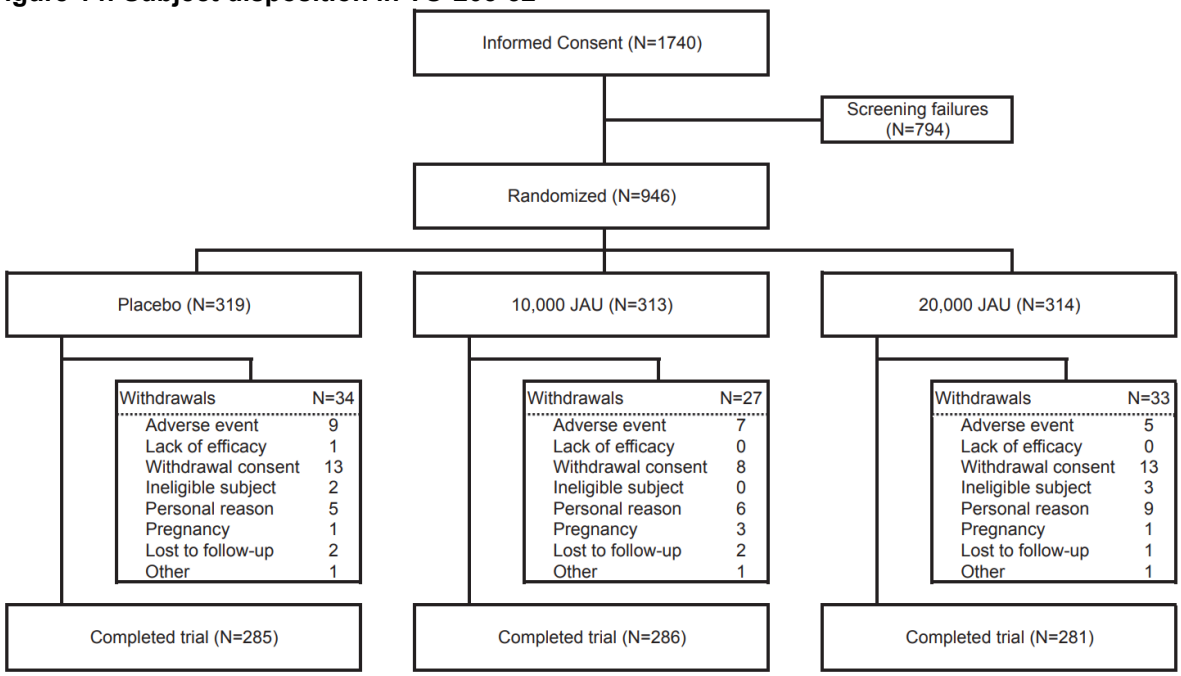
	Placebo	12 SQ-HDM	Overall
Abbreviations: SQ, standard quality; HDM, house dust mite; FAS, full analysis set; PPS, per-protocol set; ITT, intention-to-treat.			

Figure 14: Subject disposition in TO-203-32[38, 51]



B.2.4.3 Statistical analysis

The statistical analyses performed in the MT-04, MT-06, P001 TO-203-31 and TO-203-32 trials are summarised in Table 44.

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Table 44: Summary of the statistical analysis carried out in the MT-04, MT-06, P001, TO-203-31, and TO-203-32 trials

Study	MT-04 [36, 47]	MT-06 [34, 48]	P001 [35, 49]	TO-203-31 [37, 50]	TO-203-32 [38, 51]
Hypothesis objective	**Primary efficacy outcome:** • Time to first moderate or severe asthma exacerbation during Period 3 (ICS reduction/withdrawal) **Key secondary efficacy outcomes:** • Time to first asthma exacerbation with deterioration in asthma symptoms (time in days from start of Period 3 to the first asthma exacerbation fulfilling criterion a[a]) • Immunology measured as change from baseline to end of trial in terms of specific IgG4	**Primary efficacy outcome:** • Average TCRS during the efficacy evaluation period **Key secondary efficacy outcomes:** • Average total AR DSS during the efficacy evaluation period • Average total AR DMS during the efficacy evaluation period • Average overall RQLQ score during the efficacy evaluation period • Average total combined allergic ARC score during the efficacy evaluation period	**Primary efficacy outcome:** • Average TCRS during the final 8 weeks of treatment **Key secondary efficacy outcomes:** • Average rhinitis DSS during the final 8 weeks of treatment • Average rhinitis DMS during the final 8 weeks of treatment • Average TCS during the final 8 weeks of treatment • Average AR/ARC symptoms assessed by VAS during the final 8 weeks of treatment	**Primary efficacy outcome:** • Time to the first moderate or severe asthma exacerbation in Period 3, measured from randomisation (calculating from the first day of study treatment) **Key secondary efficacy outcome:** • Time to the first moderate or severe asthma exacerbation in Period 3, measured from the Period 3 started date (calculating from the Period 3 started date)	**Primary efficacy outcome:** • Average TCRS during the final 8 weeks of treatment **Key secondary efficacy outcome:** • Average AR symptom score (DSS) during the final 8 weeks of treatment

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Study	MT-04 [36, 47]	MT-06 [34, 48]	P001 [35, 49]	TO-203-31 [37, 50]	TO-203-32 [38, 51]
	against HDM allergens • Proportion of patients with a MID change in ACQ controlled for change in ICS (end of trial evaluation) • Proportion of patients with MID change in AQLQ(S) controlled for change in ICS (end of trial evaluation)				
Statistical analysis	Kaplan-Meier–estimated absolute risk for first exacerbation for the FAS. Primary and key secondary end points were daily scores averaged over the 8-week end of treatment efficacy assessment period. Significant difference procedure for the FAS group – Kaplan-Meier –estimated absolute risk for first	The primary analysis compared treatment groups by using a linear mixed effects (LME) model, including the average AR symptoms score at baseline as a fixed effect, and country as a random effect. The FAS included all randomised patients in accordance with the ICH intent-to-treat principle. The primary	The primary end point was analysed by using a prespecified nonparametric approach in which a between-treatment comparison was performed with the Wilcoxon rank sum test. The Hodges-Lehmann estimate of treatment difference and the corresponding 2-sided 95% confidence intervals	FAS was used for primary analyses and PPS was used for sensitivity analyses. For the primary endpoint, a log rank test was performed in FAS. The Cox proportional hazard model was used for the calculation of the hazard ratio. For the secondary endpoint, An analysis using the Cox proportional	FAS was used for primary analyses. ITT and PPS were used for sensitivity analyses. FAS included subjects who received the IMP and recorded at least 80% (at least 45 days) of symptom scores and medication scores in the final 8 weeks of the study treatment period, regardless of compliance to the protocol. ITT included

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Study	MT-04 [36, 47]	MT-06 [34, 48]	P001 [35, 49]	TO-203-31 [37, 50]	TO-203-32 [38, 51]
	exacerbation for the FAS.	analysis set was the FAS with multiple imputations for missing data (FAS-MI), which conservatively treated all patients with missing data as having no treatment effect. Additional analyses for the primary end point were performed on the full analysis set, observed data (FAS), and PP analysis set. Key secondary end points were similarly analysed by means of LME models on FAS-MI and FAS.	(CIs) were also reported. Treatment difference relative to placebo was calculated as follows: 100%*((12 SQ-HDM-placebo)/placebo) based on medians (or means for rhinitis DMS); the 95% CI was based on the bootstrap method using 10,000 iterations. Key secondary endpoints were analysed in the following order for purposes of multiplicity control: rhinitis DSS, rhinitis DMS, TCS, and VAS AR/C score. All of these used the same method as the primary end point, except for rhinitis DMS. For analysis of rhinitis DMS, the zero-inflated log-normal model was used (with treatment, baseline asthma status, age group, and region as fixed effects)	hazard model was performed in FAS-MI (the data of subjects who moved to Period 3 in the placebo group was randomly imputed as data of subjects who did not move to Period 3 irrespective of the assigned treatment group). The primary analysis of the primary endpoint and the key secondary analysis of the key secondary endpoint were adjusted for multiplicity.	subjects who received the IMP and recorded symptom and medication scores at least once. Analyses of all the items, including the primary analysis of the primary endpoint, were performed using the LME model with the values of the primary endpoint transformed to square roots as the dependent variables, the treatment group and baseline DSS transformed to square roots as the fixed effects, and the trial site as the random effect.

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Study	MT-04 [36, 47]	MT-06 [34, 48]	P001 [35, 49]	TO-203-31 [37, 50]	TO-203-32 [38, 51]
			because more than 30% of the rhinitis DMS values were zero. 95% CIs were calculated by using the D method. The primary and key secondary end points were tested in a stepwise manner to control for type I error under multiple hypotheses.		
Sample size, power calculation	1,262 patients were screened. 428 patients failed screening and 834 patients were randomised. The power calculation was based on the assumption that roughly 65% of patients in the placebo group would experience an asthma exacerbation. The clinically relevant effect size was based on the available literature on other asthma treatments and unpublished data from	1,425 patients were screened. 433 patients failed screening and 992 patients were randomised. The power calculation was based on the following assumptions: 1. Analysis was performed based on multiple imputations. Patients who did not contribute any diary data during the last 8 weeks of treatment were imputed as sampled from the observed placebo	4,497 patients were screened. 3,015 patients failed screening and 1,482 were randomised. The power calculation assumed that approximately 645 subjects per treatment group would be eligible for the evaluation period and the absolute treatment difference would be based off the MT-06 trial results: a median TCRS reduction of 1.66.	1,335 patients were screened. 509 patients failed screening and 826 patients were randomised. Based on the results of the MT-02 trial conducted by ALK, assuming that 65% of placebo-treated subjects experience worsening of asthmatic symptoms during Period 3, that the difference in the absolute value and the HR compared to placebo are 13% and 0.70	1,740 patients were screened. 794 patients failed screening and 946 patients were randomised. In an analysis of the subgroup of cases with a total dose of ICS of ≤600 µg at randomisation and with TCRS of >0 before administration in the MT-02 trial conducted by ALK, the difference was 24% in the 6SQ-HDM group and 21% in the 3SQ-HDM group. The mean value of TCRS in the placebo

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Study	MT-04 [36, 47]	MT-06 [34, 48]	P001 [35, 49]	TO-203-31[37, 50]	TO-203-32[38, 51]
	a previous HDM tablet trial (the MT-02 trial). The expected effect size was estimated in the protocol and formed the basis for the power calculations. A reduction in the hazard rate for time to first asthma exacerbation of approximately 30%, corresponding to a Hazard ratio (HR) of 0.70, was considered clinically relevant.	distribution of the TCRS. 2. Equal proportions of 10% were imputed in each treatment group. 3. A pooled SD corresponding to a coefficient of variation (CV) of 82%. 4. The global hypothesis was tested with an F-test on 2 degrees of freedom at 5% level of significance. 5. The pairwise hypotheses were tested with a 2-sided t-test at 5% level of significance.	With this expected treatment difference, the study would have a >99% power for the primary analysis at the 5% level of significance. Additionally, there would be approximately 85% power to have the upper bound of the 95% CI below 10%, assuming a median TCRS score in the placebo are of 7.54 (MT-06 results).	for 6SQ-HDM and 16% and 0.64 for 12 DU, and the proportion of censored subjects is 10% in Period 2 and 4% in Period 3. In a simulation performed based on these assumptions using the log rank test for the period from the start of Period 2 until worsening of asthma in Period 3, the power for rejecting the null hypothesis with 300 subjects per treatment group was as shown in the table below. Therefore, the target sample size was set at 300 subjects per treatment group (a total of 900 subjects).	group was 4.9 and the (CV=SD/mean value) was 0.82 in the same subgroup. In a simulation with SAS under the hypothesis above, the power of about 92% was obtained, which rejects the global null hypothesis that there is no difference among treatment groups based on the F-test with a significance level of 5% in the analysis population of 270 subjects in a group of 300 subjects with a 10% dropout rate.
Data management, patient withdrawals	The FAS-MI data set was identical to the FAS set but had missing data for Period 3 imputed. The FAS-MI data set was used to analyse the primary	The primary efficacy analysis was based on an LME model and performed on the FAS by using a multiple imputation strategy for missing data by Rubin	The primary analysis methods for the subject reported outcomes were based on observed data only. Patients with no data on a given endpoint	Analyses of FAS-Multiple Imputation (FAS-MI), FAS-Observed Case (FAS-OC), and PPS-Observed Case (PPS-OC) were appropriately	No missing data were imputed. The primary analysis of the primary endpoint and the key secondary analysis of the key

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Study	MT-04 [36, 47]	MT-06 [34, 48]	P001 [35, 49]	TO-203-31 [37, 50]	TO-203-32 [38, 51]
	efficacy endpoint. The multiple imputation methodology included all prematurely discontinued patients as if they belonged to the placebo group (i.e. all randomised patients who discontinued from the trial during Period 2 were included in this analysis set as if they were following the same distribution, with regards to the first asthma exacerbation, as the observed placebo group during the efficacy assessment period (Period 3). This is as if they were having no treatment effect).	(data set denoted FAS-MI). Missing data in all treatment groups were sampled from the observed data of the primary end point in the placebo group by using the method of unrestricted random sampling with replacement. Multiplicity for the primary and key secondary analyses were controlled for by using the Fisher least significant difference procedure and a hierarchic testing strategy.	during the efficacy assessment period were not evaluable for that specific endpoint under this approach. Sensitivity analyses were implemented to address different aspects of the missing data issues for the primary efficacy endpoint, including multiple imputation, last observation carried forward (LOCF), and the longitudinal data analysis (LDA) model. The multiple imputation approach focused on the missing data due to early dropout before the efficacy assessment period. All patients in the FAS population were evaluable in the multiple imputation analysis if the subject had non-missing baseline value. Within each imputation, missing endpoint values for patients from	performed. FAS-MI included subjects in FAS. Data on subjects who did not move to Period 3 were imputed with data of the placebo group in Period 3. FAS-OC included subjects who moved to Period 3 in FAS (data on subjects who did not move to Period 3 were not imputed with data of the placebo group in Period 3). PPS-OC included subjects who moved to Period 3 in PPS. In other secondary analyses, analyses without imputation of missing values and analyses at the last administration point using LOCF were performed.	secondary endpoint were adjusted for multiplicity. To adjust multiplicity, Fisher's least significant difference was used to perform a test.

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Study	MT-04 [36, 47]	MT-06 [34, 48]	P001 [35, 49]	TO-203-31 [37, 50]	TO-203-32 [38, 51]
			both treatment groups were imputed by random samples drawn from the distribution of average TCRS from placebo-treated patients.		

[a] Criterion a defines a moderate asthma exacerbation as that the patient should experience nocturnal awakening(s) due to asthma requiring SABA use for at least 2 consecutive nights or an increase of minimum 0.75 in DSS from baseline value on at least 2 consecutive days.
Abbreviations: SQ, standard quality; HDM, house dust mite; FAS, full analysis set; PP, per-protocol; CV, coefficient of variation; CI, confidence interval; MI, multiple imputations; PPS, per-protocol set; OC, observed case; DSS, daily symptom score; DMS, daily medication score; VAS, visual analogue scale; TCRS, total combined rhinitis score; ICS, inhaled corticosteroid; Ig, immunoglobulin; RQLQ, rhinoconjunctivitis quality of life questionnaire; AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis; LOCF, last observation carried forward; LDA, longitudinal data analysis; IMP, investigational medicinal product; HR, hazard ratio.

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B2.5 Critical appraisal of the relevant clinical effectiveness evidence

Table 45 assesses the relevant clinical effectiveness evidence, using criteria taken from the NICE User Guide [8]. Please see Appendix P for a full quality assessment.

Table 45: Quality assessment of the MT-04, MT-06, and P001 trials

Question	MT-04 [36, 47]	MT-06 [34, 48]	P001 [35, 49]	TO-203-31 [37, 50]	TO-203-32 [38, 51]
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes	Yes

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B2.6 Clinical effectiveness results of the relevant studies

The following sections outline the clinical effectiveness results for the primary and secondary endpoints for the MT-04 and TO-203-31 (adult AA population), MT-06 (adult AR population), and P001 and TO-203-32 (adolescent and adult AR population) trials.

B.2.6.1 MT-04

Primary endpoint

The primary endpoint for the MT-04 trial was the time to first moderate or severe asthma exacerbation during period three (the ICS reduction/withdrawal phase). The primary efficacy analysis was conducted based on the FAS-MI, the FAS, and the PP analysis set (see Table 46).

12 SQ-HDM was associated with a statistically significant reduction in the risk of a moderate or severe asthma exacerbation compared with placebo, as measured by a 31% risk reduction (HR: 0.69 [95% CI, 0.50-0.96], p=0.03) of the probability of a moderate-to-severe asthma exacerbation in FAS-MI population compared to placebo. These results were similarly significant for 12-SQ-HDM compared to placebo in the FAS population with a 34% risk reduction (HR: 0.66 [95% CI, 0.47-0.93], p=0.02), as shown in Table 46 . For 12 SQ-HDM, both the FAS-MI and FAS results for the primary analysis met the prespecified clinically relevant reduction in HR for time to first asthma exacerbation of 30% (HR ≤0.70).

The efficacy analysis of time to first moderate or severe asthma exacerbation for the PP analysis set supported the efficacy estimate of the primary analysis; however, this was without power to reach statistical significance. For the comparison of 12 SQ-HDM versus placebo, the HR was 0.73 (p=0.0867).

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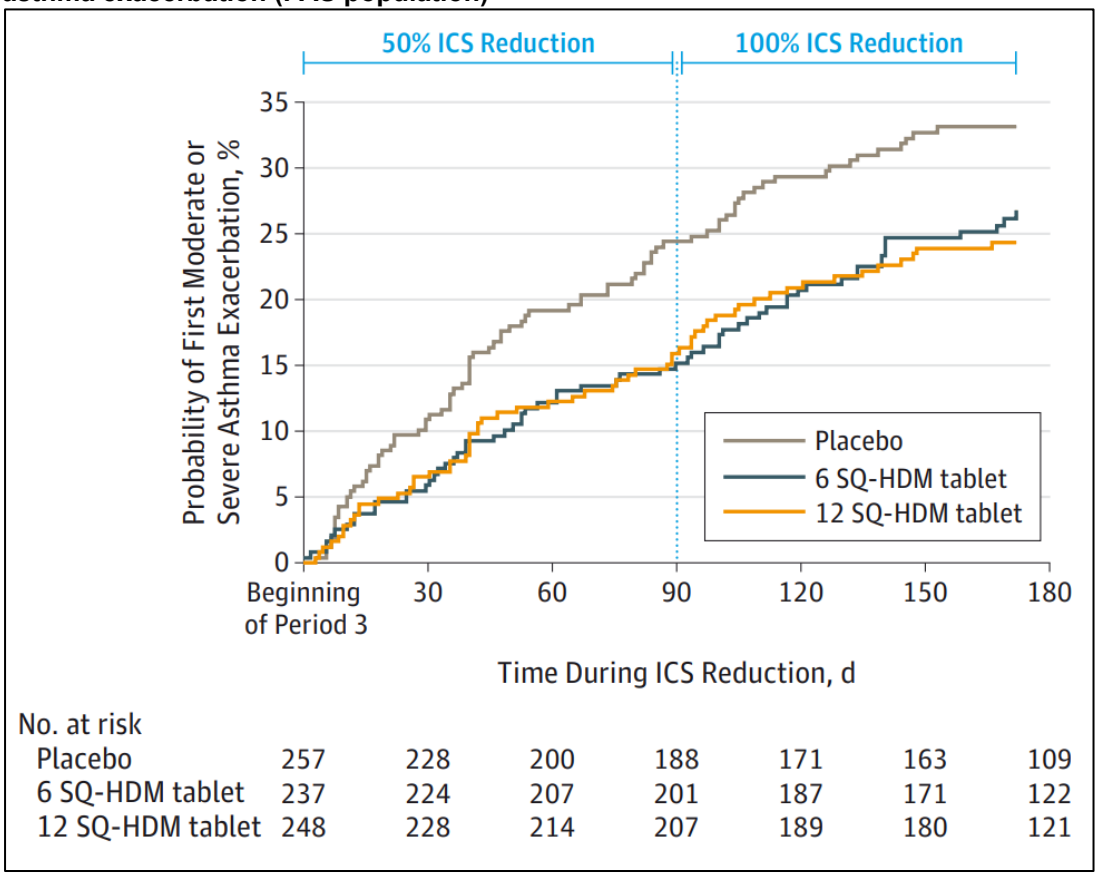
Figure 15: MT-04 – Kaplan-Meier plot of the probability of having the first moderate or severe asthma exacerbation (FAS population) [36]



From early on in the ICS reduction/withdrawal period, there was a difference between the active groups and placebo. The Kaplan-Meier plot shows evidence that the time to the first exacerbation experienced by 25% of the subjects was between 90 and120 days for placebo, and above 180 days for 12 SQ-HDM.

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Table 46: MT-04 - Summary of the main efficacy results in AA adults [36, 47]

MT-04 (MITRA) results	12 SQ-HDM		Placebo		Efficacy 12 SQ-HDM over placebo		
	N	n (%)	N	n (%)	HR [95% CI]	Risk reduction[a]	p-value
Primary endpoint							
Any exacerbation. moderate or severe (FAS-MI) [b]	282	59 (21%)	277	83 (30%)	0.69 [0.50,0.96]	31%	0.027
Any exacerbation, moderate or severe (FAS)[c]	248	59 (24%)	257	83 (32%)	0.66 [0.47,0.93]	34%	0.017
Predefined analyses of components of the primary endpoint							
Nocturnal awakening or increase in symptoms [c]	248	39 (16%)	257	57 (22%)	0.64 [0.42;0.96]	36%	0.031
Time to first asthma exacerbation with increased use of SABA [c]	248	18 (7%)	257	32 (12%)	0.52 [0.29,0.94]	48%	0.029
Time to first asthma exacerbation with deterioration in lung function [c]	248	30 (12%)	257	45 (18%)	0.58 [0.36,0.93]	42%	0.022
Time to first severe asthma exacerbation [c]	248	10 (4%)	257	18 (7%)	0.49 [0.23,1.08]	51%	0.076

N: number of subjects in treatment group with data available for the analysis.
n (%): number and percentage of subjects with first exacerbation
CL: confidence limits.
[a] Estimated by HR.
[b] FAS-MI: full analysis set with multiple imputations. The analysis treats subjects who discontinued the trial before the efficacy assessment period as placebo subjects.
[c] FAS: full analysis set. All available data used to its full extent, i.e., including all subjects who provided data during the efficacy assessment period.

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Secondary endpoints

For all three predefined analyses of the components of a moderate asthma exacerbation, there was a statistically significant treatment effect of 12 SQ-HDM over placebo.

For 12 SQ-HDM, there was a statistically significant reduction compared with placebo in the time to first asthma exacerbation, with: deterioration in asthma symptoms (HR: 0.64 [95% CI, 0.42-0.96], p= 0.03), increased SABA use (HR: 0.52 [95% CI, 0.29-0.94], p=0.03), and deterioration in lung function (HR: 0.58 [95% CI, 0.36-0.93] p=0.02) in the FAS population, as shown in Table 46 .

Furthermore, 12 SQ-HDM was also associated with a meaningful numerical 51% risk reduction (HR: 0.49 [95% CI, 0.23-1.08], p=0.08) in the time to first severe asthma exacerbation compared with placebo in the FAS population. This relationship was not statistically significant. However, the trial was not powered to investigate this endpoint; the low number of recorded events may be the primary reason for failing to reach statistical significance.

The analysis of change from baseline to Visit 13 (end of trial) for specific IgG4 against D. pteronyssinus and D. farinae, showed highly statistically significant changes associated with 12 SQ-HDM (p<0.0001) (see Table 47). There were almost no changes from baseline in the placebo group over the trial, whereas the specific IgG4 levels for both HDM species were significantly increased from baseline after approximately 4 weeks of treatment in the 12 SQ-HDM group. Additionally, specific IgE remained largely unchanged in the placebo group throughout the trial, and the analysis of change from baseline in log10(IgE) showed statistically significant differences to placebo for 12 SQ-HDM at every timepoint measured (p<0.001).

Table 47: Efficacy analysis of specific IgG4 against HDM allergens[36, 47]

	12 SQ-HDM vs. placebo	
	Difference in change from baseline to end of trial	p-value
Specific IgG_4 (*D. pteronyssinus)*	0.595	<0.0001
Specific IgG_4 (*D. farinae)*	0.595	<0.0001

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For the analysis of asthma control, more subjects in the 12 SQ-HDM group had a clinically relevant improvement in ACQ score than in placebo at Visit 13 (50% for 12 SQ-HDM and 43% for placebo). However, as shown in Table 48, in the analysis controlled for change from baseline in ICS, there were no statistically significant differences between the 12 SQ-HDM and placebo in the proportion of subjects with improvement.

For the analysis of asthma QoL, more subjects in the 12 SQ-HDM groups had a clinically relevant improvement in AQLQ(S) score than in placebo at Visit 13 (55% for 12 SQ-HDM and 47% for placebo). However, in the analysis controlled for change from baseline in ICS, there were no statistically significant differences between the groups in the proportion of subjects with improvement (see Table 48).

Table 48: Efficacy analysis of ACQ and AQLQ (FAS dataset) [47]

	12 SQ-HDM vs. placebo	
	Odds ratio	p-value
ACQ controlled for ICS	1.31	0.215
AQLQ(S) controlled for ICS	0.97	0.893

A post-hoc analysis was conducted on the SF-36 data collected during the trial. Detail on the results of this analysis is provided in Section B.3.5.

B.2.6.2 MT-06

Primary endpoint [34, 48]

The primary endpoint for the MT-06 trial was the average TCRS during the primary efficacy evaluation period (Period 3; between Visit 7 and Visit 8).

The primary efficacy analysis was based on an LME model and performed on the FAS-MI analysis set. Supporting analyses of the primary endpoint used the same LME model in the FAS, PP, and FAS with imputation of missing data using the LOCF method (FAS-LOCF).

As shown in Figure 16 and Table 49, 12 SQ-HDM was associated with a significant reduction in AR medication use and symptoms in AR patients, as demonstrated by a significant reduction in the TCRS compared with placebo in the FAS-MI population

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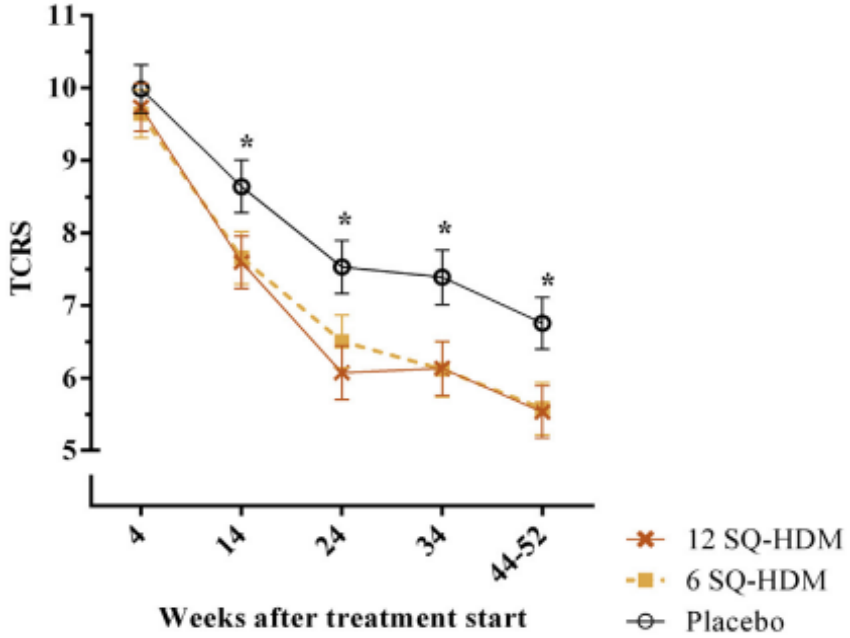
(absolute difference: 1.09 [95% CI 0.35-1.84], p=0.004). These results were similarly significant for the FAS population, with a relative reduction of 18.2% (absolute difference: 1.22 [95% CI, 0.49-1.96], p=0.001) in the TCRS compared with placebo.

Figure 16: MT-06 - Adjusted means of the TCRS over time (FAS population) [34]



Error bars represent pairwise comparisons between each of the active dose and placebo groups. Asterisks designate statistically significant differences from placebo.

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Table 49: MT-06 - Summary of the main efficacy results in AR adults [34, 48]

MT-06 (MERIT) results	12 SQ-HDM		Placebo		Treatment effect		p-value
	n	Score	n	Score	Absolute difference (95%CI) [c]	Relative difference[d]	
Total combined rhinitis score (TCRS)							
FAS-MI [a] (adjusted mean)	318	5.71	338	6.81	1.09 [0.35,1.84]		0.004
FAS [b] (adjusted mean)	284	5.53	298	6.76	1.22 [0.49,1.96]	18%	0.001
FAS [b] (median)	284	5.88	298	7.54	1.66	22%	
Rhinitis symptoms score (DSS)							
FAS-MI (adjusted mean)	318	2.84	338	3.31	0.47 [0.11;0.82]	14%	0.01
FAS [b] (adjusted mean)	284	2.76	298	3.30	0.54 [0.18,0.89]	16%	0.003
FAS [b] (median)	284	2,98	298	3.98	1	25%	
Rhinitis medication score (DMS)							
FAS-MI	318	2.32	338	2.86	0.54 [0.01;1.07]	19%	0.045
FAS [b] (adjusted mean)	284	2.22	298	2.83	0.60 [0.08,1.13]	21%	0.024
FAS [b] (median)	284	2.83	298	4	1.17	29%	
Total combined rhinoconjunctivitis score (TCS)							
FAS [b] (adjusted mean)	241	7.91	257	9.12	1.21 [0.13,2.28]	13%	0.029
FAS [b] (median)	241	8.38	257	10.05	1.67	17%	
Rhinoconjunctivitis quality of life questionnaire (RQLQ(S)) score							
FAS [b] (adjusted mean)	229	1.38	240	1.58	0.19 [e] [0.02;0.37]	12%	0.031
FAS [b] (median)	229	1.25	240	1.46	0.21	14%	

n: number of subjects in treatment group with data available for the analysis. CL: confidence limits.
[a] FAS-MIT full analysis set with multiple imputations. The analysis treats subjects who discontinued the trial before the efficacy assessment period as placebo subjects. For the primary analysis (FAS-MI), only the absolute difference was prespecified.
[b] FAS: full analysis set. All available data used to its full extent, i.e., subjects who provided data during the efficacy assessment period.
[c] Absolute difference placebo minus 12 SQ-HDM, 95% confidence limits.
[d] Relative difference to placebo: placebo minus 12 SQ-HDM divided by placebo.
[e] The difference between 12 SQ-HDM and placebo was primarily driven by differences in three domains: sleep problems, practical problems, and nose symptoms.
[f] Odds ratio for having a rhinitis exacerbation: 12 SQ-HDM over placebo.

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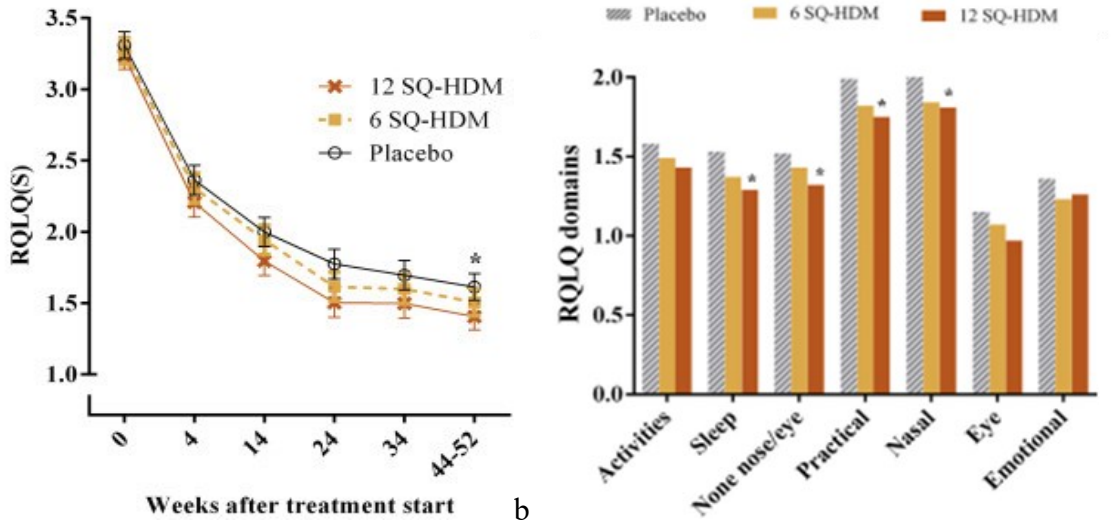
Secondary endpoints

For the predefined key secondary endpoints evidencing the impact on AR medication use and AR symptoms in AR patients, treatment with 12 SQ-HDM was shown to result in a significant improvement in both DSS (FAS-MI absolute difference: 0.47 [95% CI 0.11,0.82], p=0.001) and DMS (FAS-MI absolute difference: 0.54 [95% CI 0.01,1.07], p=0.045) compared with placebo. These results were similarly significant for the FAS population (DSS absolute difference: 0.54 [95% CI 0.18,0.89], p=0.003; DMS absolute difference: 0.60 [95% CI 0.08,1.13], p=0.024).

In addition, 12 SQ-HDM was associated with a significant improvement in the QoL, as demonstrated by an improvement in RQLQ score compared with placebo (absolute difference: 0.19 [95% CI 0.02,0.37], p=0.031) in the FAS population. The significant reduction in RQLQ score with 12 SQ-HDM compared to placebo was evident after 24 weeks of treatment and onwards to Week 52, as shown in Figure 17a. Figure 17b also shows that 12 SQ-HDM's significant reduction in overall RQLQ score when compared to placebo is apparent for 4 of the 7 RQLQ individual domains: nasal symptoms, non-nose/eye symptoms (this measures fatigue, thirst, reduced productivity, tiredness, poor concentration, headache and feeling worn out), practical problems, and sleep impairment.

Figure 17: MT-06 - RQLQ scores (FAS population) [34] .



B.1.1 a. Scores are shown as adjusted means. Asterisks designate statistically significant differences from placebo. b. Adjusted means of the overall RQLQ(s) score over time for the 3 treatment groups (FAS). Error bars represent pairwise comparisons between each of the active dose and placebo groups. Asterisks designate statistically significant differences from placebo.

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The TCS, which includes conjunctivitis symptoms and medications, was significantly reduced by 1.21 (p=0.029) in the 12 SQ-HDM group compared to placebo.

The pharmacodynamic endpoints were analysed for a limited subset of the overall trial population, i.e., only for subjects in Germany who consented (n=74; 7.5% of the overall trial population). Specific IgE and IgG4 against D. pteronyssinus and D. farinae, respectively, were assessed at Visit 1 (Week 0), 3 (Week 4), 4 (Week 14), 5 (Week 24) and 8 (Week 52). Immediately after initiation of 12 SQ-HDM, the level of specific IgG4 followed a steady increase during the entire trial, and the level of specific IgE increased and reached a peak 4 weeks after treatment start, after which the level slightly decreased. No changes over time in the level of specific IgG4 or IgE were observed for the placebo group. The difference between 12 SQ-HDM and placebo was statistically significant at all visits after initiation of treatment.

Post-hoc analyses of days with a rhinitis exacerbation were also conducted. This post-hoc endpoint was analysed with or without the use of rhinitis symptomatic mediation. A rhinitis exacerbation was defined as a day where the subject returned to the high level of symptoms required for trial inclusion: a rhinitis symptom score of at least 6, or at least 5 with one symptom rated severe. Rhinitis symptomatic medication included desloratadine tablets and/or nasal steroid. In the 12 SQ-HDM group, the percentage of days with a rhinitis exacerbation was significantly reduced by more than 50% (OR: 0.45 [95% CI 0.28,0.72], p=0.001) compared to placebo**.** Similarly, days with a rhinitis exacerbation despite the use of symptomatic medication were statistically significantly reduced by 47% (OR: 0.51 [95% CI 0.32,0.81], p=0.005) in the 12 SQ-HDM group compared to placebo.

The percentage of symptom-free days in the efficacy evaluation period was increased in the 12 SQ-HDM group compared to placebo. This increase compared to placebo was statistically significant for 12 SQ-HDM (OR: 2.28 [95% CI 1.28, 4.07], p = 0.005).

A post-hoc analysis was conducted on the EQ-5D data collected during the trial. Detail on the results of this analysis is provided in Section B.3.5

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B.2.6.3 P001

Primary endpoint

The primary endpoint for the P001 trial was the average TCRS during the primary efficacy evaluation period, performed on observed data during the final approximately 8 weeks of treatment for the FAS population.

As shown in Table 50, the average TCRS during the last 8 weeks of treatment was lower in the 12 SQ-HDM group than in the placebo group. The relative treatment difference between the groups was -17.2% (95% CI -25.0% -9.7%), and the between-treatment difference based on medians was statistically significant (Hodges-Lehmann estimate of shift, median: -0.80 [95% CI -1.20,-0.4], p<0.001).

The results of the primary analysis were also corroborated by 4 parametric supportive analyses based on the FAS population: the ANCOVA model, the LDA model, the ANCOVA model with multiple imputation method, and the ANCOVA model with LOCF. The ANCOVA model (with observed data only) provided an alternative approach to the primary nonparametric approach to analyse the data. The other 3 supportive analyses – ANCOVA-based with multiple imputation and with LOCF imputation as well as the LDA method – assessed the impact of missing data to the primary analysis result (Table 51).

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Table 50: P001 - Summary of the main efficacy results in AR adolescents and adults [35, 49]

Treatment	n	Total combined rhinitis score (TCRS)		Relative treatment difference [b] (95% CI)	Hodes-Lehman estimate of shift [a] (95% CI)	p-value
		Mean score	Median score [lower, upper]			
Total Combined Rhinitis Score (TCRS), nonparametric analysis						
12 SQ-HDM	566	4.67	4.10 [2.0, 6.4]	-17.2% (-25.0, -9.7)	-0.80 (-1.20, -0.40)	<0.001
Placebo	620	5.49	4.95 [2.7, 7.6]			
Rhinitis symptoms score (DSS), nonparametric analysis						
12 SQ-HDM	566	3.83	3.55 [1.9, 5.3]	-15.5% (-24.4, -7.3)	-0.60 (-1.00, -0.30)	<0.001
Placebo	620	4.46	4.20 [2.3, 6.3]			
Total combined rhinoconjunctivitis score (TCS), nonparametric analysis						
12 SQ-HDM	566	6.40	5.50 [2.5. 8.8]	-16.7% (-24.6, -4.0)	-1.10 (-1.70, -0.60)	<0.001
Placebo	620	7.62	6.60 [3.6, 10.4]			
Average VAS score, nonparametric analysis						
12 SQ-HDM	540	42.29	41.40 [24.9, 59.3]	-16.0% (-22.7, -8.3)	-6.10 (-9.10, -3.10)	<0.001
Placebo	685	47.96	49.30 [29.4, 65.2]			
		Mean score	**Estimated mean [c] (95% CI)**	**Relative treatment difference [b] (95% CI)**	**Difference in estimate means (95% CI) [c]**	**p-value**
Rhinitis medication score (DMS), zero-inflated log-normal analysis						
12 SQ-HDM	566	0.84	0.65 (0.45. 0.85)	-18.4% (-41, 4.3)	-0.15 (-0.35, 0.05)	0.154
Placebo	620	1.03	0.79 (0.56, 1.02)			

[a] The 95% confidence interval for median difference was based on the Hodges-Lehmann estimator.
[b] Treatment difference relative to placebo based on medians was calculated as (12 SQ-HDM – placebo)/placebo*100%; confidence interval was calculated by the bootstrap method using 10,000 iterations
c Analysis via zero-inflated log-normal model with treatment, baseline asthma status, age group, and region as fixed effects. Model estimate mean and the associated 95% CI based on delta method were reported

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Table 51: Sensitivity analysis of average Total Combined Rhinitis Score (FAS) [35, 49]

Treatment	n	Least squares (LS) mean	Relative treatment difference [a] (95% CI)	Treatment difference [a] (95% CI)	p-value
Average Total Combined Rhinitis Score (TCRS) during last 8 weeks of Treatment (ANCOVA model)					
12 SQ-HDM	566	4.67	-17.5% (-25.2, -8.8)	-0.75 (-1.18, -0.32	<0.001
Placebo	620	5.49			
Average Total Combined Rhinitis Score (TCRS) during last 8 weeks of Treatment (LDA model)					
12 SQ-HDM	566	4.66	-18.4% (-31.0,-6.5)	-0.71 (-1.22,-0.20)	<0.001
Placebo	620	5.42			
Average Total Combined Rhinitis Score (TCRS) during last 8 weeks of Treatment (Multiple Imputation Method)					
12 SQ-HDM	740	4.67	-12.3% (-17.8, -6.9)	-0.54 (-0.96, -0.11)	0.031
Placebo	741	5.49			
Average Total Combined Rhinitis Score (TCRS) during last 8 weeks of Treatment (LOCF Method)					
12 SQ-HDM	566	4.67	-17.3% (-25.2, -8.5)	-0.74 (-1.17, -0.31)	<0.001
Placebo	620	5.48			

[a] Back-transformed LS means, treatment difference and the associated 95% CI were reported. Treatment difference relative to placebo based on LS means was calculated by (12 SQ-HDM – placebo)/placebo*100%; the confidence interval was calculated by the bootstrap method using 10,000 iterations or delta method.
ANCOVA model with square root transformed daily TCRS scores as response. The model included treatment, day, treatment-by-day interaction, baseline asthma status, age group, and region as fixed effects and subjects as random effects, and included baseline endpoint value as a covariate. The Toeplitz covariance matrix was used to model the correlation among repeated measurements.
For the multiple imputation method, missing data in both treatment groups were imputed using the sample distribution of TCRS observed from the placebo group. The same ANCOVA model was applied. Rubin's strategy was used to combine multiple estimates.
For the LOCF method, missing daily data during the last 8 weeks of treatment from both groups were imputed with the last observation carried forward. Only the TCRS recorded during the last 8 weeks of treatment was used to impute the missing scores. The same ANCOVA model was applied.

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Secondary endpoints

For the predefined key secondary endpoints evidencing the impact of 12 SQ-HDM on AR medication use and AR symptoms in AR patients, results of the rhinitis DSS analysis showed a statistically significant and lower average rhinitis DSS in the 12 SQ-HDM group when compared with the placebo group during the last 8 weeks of treatment. The relative treatment difference between the groups was -15.5% (95% CI, -24.4%, -7.3%), and the between-treatment difference based on medians was statistically significant (Hodges-Lehmann estimate of shift, Median: -0.60 [95% CI -1.00,-0.30], p<0.001) (Table 50).

The average rhinitis DMS was numerically lower in the 12 SQ-HDM group than in the placebo group. However, the treatment difference was not statistically significant compared to placebo. In a review of the data, it was determined that rescue medications were not utilised by the majority of subjects: 337 (59.5%) and 336 (54.2%) subjects in the 12 SQ-HDM and placebo treatment groups, respectively, had a rhinitis DMS equal to zero. Due to a large proportion of subjects not using any rescue medication, the zero-inflated log-normal model was used, as prespecified in the protocol, to analyse the average rhinitis DMS for the FAS population during the last 8 weeks of treatment. The relative treatment difference between the groups was -18.4% (95% CI, -41.0%, 4.3%), and the between-treatment difference based on means was not statistically significant (Hodges-Lehmann estimate of shift, mean: -0.15 [95% CI -0.35,0.05], p=0.154) (Table 50).

Subjects from the 12 SQ-HDM group reported fewer symptoms on the VAS compared to the placebo group. These results correspond with the reduction in the DSS observed in the 12 SQ-HDM-treated subjects. Treatment with 12 SQ-HDM was associated with a significant improvement (p<0.001) in patient QoL (as measured by average AR/ARC VAS scores). However, the relative treatment difference between the groups (-16.0%; 95% CI, -22.7%, -8.3%) cannot be considered confirmatory due to the prespecified multiplicity control strategy for this trial.

The average TCS, which includes conjunctivitis symptoms and medications, was statistically lower (p<0.001) in the 12 SQ-HDM group than in the placebo group.

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However, this result cannot be considered confirmatory due to the prespecified multiplicity control strategy for this trial.

Specific IgE and IgG4 against D. pteronyssinus and D. farinae, respectively, were assessed at Visit 2 (baseline), 6 (Week 4), 8 (Week 20), and 11 (final week of dosing). Compared with baseline, treatment with 12 SQ-HDM resulted in an increase in HDM-specific IgE levels, followed by a slight decrease over time. Similarly, IgG4 levels increased over time.

The RQLQ(S) was statistically lower ($p<0.001$) in the 12 SQ-HDM group than in the placebo group, and there were no notable differences between treatment groups for any of the EQ-5D-5L dimensions or for the EQ-VAS.

B.2.6.4 TO-203-31

Primary endpoint

The primary endpoint for the TO-203-31 trial was consistent with the primary endpoint of the MT-04 trial: the objective was to analyse the time from randomisation to the first moderate or severe asthma exacerbation during Period 3. The primary efficacy analysis was conducted based on the FAS analysis set. A summary of the results of primary and key secondary endpoints is provided in Table 52.

No significant difference was found between 12 SQ-HDM and placebo in the time from randomisation to first moderate or severe asthma exacerbation during Period 3 of the TO-203-31 trial (HR:0.97 [95% CI: 0.74–1.27] p=0.8285).

The Japanese guidelines for well-controlled adult asthma [57] differ from the GINA guidelines [31]. The TO-203-31 trial included patients with a mean score of 1.0 to 1.5 points on the ACQ at randomisation. However, 27% of those patients had no daytime asthma symptoms and nocturnal awakening for a week before randomisation. As reported in Tanaka et al., 2020 [37], the GINA criteria allow asthma symptoms or SABA use twice a week or less in the definition of ‘well-controlled’ asthma, whereas the Japanese guidelines includes only those patients who have no asthma symptoms and do not need to use SABA meaning they were patients with likely well-controlled asthma on the basis of GINA criteria.

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To account for this difference, Tanaka et al., 2020 conducted a subgroup analysis on the primary endpoint for the subgroup of subjects who required SABA during the baseline period to more closely align with European guidelines. In this subgroup, 12 SQ-HDM was associated with a reduction in the risk of a moderate or severe asthma exacerbation compared with placebo (HR: 0.71 [95% CI, 0.49-1.02], p=0.061), similar to the results in the European MT-04 trial [36]. The inclusion of subjects considered to have sufficiently controlled asthma according to GINA criteria may be the reason the TO-203-31 trial did not meet its primary and secondary endpoints.

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Table 52: TO-203-31 - Summary of the main efficacy results in AA adults with or without AR[37, 50]

TO-203-31 results	12 SQ-HDM		Placebo		Efficacy 12 SQ-HDM over placebo		
	N	n (%)	N	n (%)	HR [95% CI][a]	Risk reduction	p-value[b]
Primary endpoint							
Any exacerbation, moderate or severe (FAS)	276	104 (38%)	274	110 (40%)	0.971 [0.74,1.27]	NR	0.8285
Any exacerbation, moderate or severe (PPS)	240	88 (37%)	225	87 (39%)	0.984 [0.73,1.32]	NR	0.9158
Secondary endpoint							
Any exacerbation, moderate or severe, from Period 3 (FAS-MI)	276/238[†]	104 (38%)	274/246[†]	110 (40%)	0.945 [0.73,1.23]	NR	0.6750
Any exacerbation, moderate or severe, from Period 3 (FAS-OC)	238	104 (44%)	246	110 (45%)	0.924 [0.71,1.21]	NR	0.5653
Other secondary endpoints (FAS)							
Any exacerbation due to asthmatic symptoms score	276	46 (17%)	274	63 (23%)	0.753 [0.52,1.10]	NR	0.1409
Any exacerbation due to lung function test value	276	30 (11%)	274	22 (8%)	1.410 [0.81,2.45]	NR	0.2379
Moderate exacerbation	276	84 (30%)	274	95 (35%)	0.909 [0.68,1.22]	NR	0.5248
Severe exacerbation	276	20 (7%)	274	15 (6%)	1.366 [0.70,2.70]	NR	0.3361

N: number of subjects in treatment group with data available for the analysis.
n (%): number and percentage of subjects with first exacerbation
CL: confidence limits.
[a]: Cox proportional hazard model
[b]: log rank test
[†]:number of subjects analysed/number of subjects who started Period 3
Abbreviations: FAS, full analysis set; PPS, per-protocol set; MI, multiple imputations; OC, observed case; NR, no reduction.

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Secondary endpoints

The key secondary endpoint was the time to the first moderate or severe asthma exacerbation in Period 3, measured from the Period 3 start date. This analysis was performed on the FAS-MI and the FAS-OC data sets.

For the FAS-MI, the observed data of placebo-treated subjects who moved to Period 3 were randomly imputed for subjects who discontinued the study treatment in Period 2 and subjects who did not move to Period 3 because ACQ was >1.5 immediately before the start of Period 3. The HR of the 12 SQ-HDM group versus the placebo group was 0.945 (95% CI: 0.725–1.232). No significant difference was found (p=0.6750).

For the FAS-OC, data were not imputed for subjects who were censored in Period 2 and who started Period 3 in FAS. The analysis results in FAS-OC were similar to those in FAS-MI. No significant difference was found in the analyses of the 12 SQ-HDM group versus the placebo group using the Cox proportional hazard model (p=0.5653). Although there was no difference among dose groups in the proportion of subjects who did not experience an asthma exacerbation until 90 days after the start of Period 3 (i.e., ICS 50% tapering period), the active groups had a greater number of subjects who did not experience an asthma exacerbation than the placebo group thereafter (i.e., ICS 100% withdrawal period).

Additional secondary endpoints included the frequency of moderate or severe asthma exacerbations and the reason for the exacerbation in Period 3. The frequency of moderate or severe asthma exacerbation was similar between the treatment groups for entire Period 3, Period 3A, and Period 3B. The most common reason for moderate asthma exacerbation was Reason “a” (SABA-requiring nocturnal awakening due to asthmatic symptoms for at least 2 consecutive nights or an increase in the symptom score* by ≥0.75 for at least 2 consecutive days compared to the mean score for 2 weeks prior to the first day of Period 2) in all treatment groups. The majority of reasons for severe asthma exacerbation were Reason “e” (systemic corticosteroids required to treat asthma).

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For the analysis of asthma control, the adjusted mean of individual ACQ scores at the final observation was slightly higher than 1.0 in the placebo and 12 SQ-HDM groups. In the analysis using the linear mixed-effect model, no significant difference was found in the 12 SQ-HDM group compared to the placebo group (p=0.6124).

The results of the analysis of QoL (as measured by AHQ-JAPAN) found no significant difference for the mean QoL scores by category between the 12 SQ-HDM group and the placebo group.

For the assessment of lung function, there was no significant difference found between the 12 SQ-HDM group and the placebo group for the adjusted mean of FEV1, %FEV1, PEF in the morning, or PEF in the evening.

B.2.6.5 TO-203-32

Primary endpoint

The trial's primary endpoint was consistent with the primary endpoint of the MT-06 and P001 trials, with the objective to analyse the average TCRS during the efficacy evaluation period (last 8 weeks of treatment) in the FAS analysis set. A summary of the results of primary and key secondary endpoints is provided in Table 53.

12 SQ-HDM was associated with a significant reduction in AR medication use and symptoms in AR patients, as demonstrated by an adjusted mean difference of -0.99 (p=0.0001), and a ratio of the adjusted mean TCRS for 12 SQ-HDM to placebo of 0.81 [95% CI: 0.72, 0.90], indicating a 19% relative reduction. These results were supported by LME and Mixed Models for Repeated Measures (MMRM) analyses in the PPS and ITT populations.

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Table 53: TO-203-32: Summary of the main efficacy results in AR adults and adolescents [38, 51]

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

Abbreviations: MMRM, mixed model repeated measures; LMEM, linear mixed effects model; CI, confidence interval; FAS, full analysis set; PPS, per-protocol set; ITT, intention-to-treat; SQ, standard quality; HDM, house dust mite.
For the primary endpoint, the linear mixed effects model includes the square-rooted average of the values during period A as the dependent variable, treatment groups and square-rooted average of DSS during baseline period as fixed effect, and clinical sites as random effect. Back-transformed adjusted mean, differences, and ratios are calculated.
[a] Relative difference to placebo: placebo minus 12 SQ-HDM divided by placebo.

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Secondary endpoints

The key secondary endpoint was analysis of the average AR DSS during the last 8 weeks of treatment in FAS. Similar to the primary analysis of the primary endpoint, the adjusted mean of rhinitis DSS in patients receiving 12 SQ-HDM was reduced compared with patients receiving placebo, with an adjusted mean difference of -0.87 (p=0.0001) and a ratio of the adjusted mean of 0.82 [95% CI: 0.73,0.90], indicating a 18% relative reduction.

For the analysis of AR DMS during Period A in FAS, although the adjusted mean in 12 SQ-HDM group was reduced compared with that in the placebo group, no significant differences were found in analyses of the 12 SQ-HDM versus placebo (p=0.1244).

The TCS, which includes conjunctivitis symptoms and medications, was significantly reduced by an adjusted mean difference of 1.34 (p=0.0002), with a demonstrated 20% relative reduction compared to placebo.

Additional secondary endpoints included the analysis of symptom-free days during the assessment period. The proportion of subjects with more than one ‘rhinitis symptom-free day’ in the 12 SQ-HDM group was significantly increased compared to the placebo group (odds ratio=1.46, p=0.0413). Additionally, the proportion of subjects with no ‘rhinitis symptom-severe days’ in the 12 SQ-HDM group was significantly increased compared to the placebo group (Odds ratio=1.52, p=0.0232).

The mean JRQLQ No.1 score was lower in the 12 SQ-HDM group compared with the placebo group in 6 categories, with significant differences in scores in 4 of the categories (daily life [p=0.0147], outdoor [p=0.0251], sleep [p=0.005], and body [p=0.0223]).

B.2.6.6 Supportive evidence

The efficacy of SQ-HDM SLIT-tablets for AR and AA is further supported by evidence from the P003 trial, an allergen exposure chamber trial as well as the MT-02 trial which was conducted with lower doses of SQ-HDM-tablets than the licensed 12 SQ-HDM-tablet considered in this appraisal. The MT-02 trial is a double-blind,

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randomised, placebo-controlled, Phase 2 trial, which enrolled 604 adults and adolescent subjects 14 years or older with mild-to-moderate HDM AA and a clinical history of house dust mite AR. The MT-02 trial is used as supportive evidence, as the 1,3, and 6 SQ-HDM doses were investigated (all of which lower than the licensed dose of 12 SQ-HDM). The P003 trial is a randomised, double-blind, placebo-controlled, Phase 2 trial conducted in an allergen exposure chamber in 124 adults with HDM AR with or without AA/ARC. P003 is used as supportive evidence due to the controlled setting in which patients were exposed.

B2.6.6.1 MT-02

The MT-02 trial was a double-blind, randomised, placebo-controlled Phase 2 trial, which enrolled 604 adults and adolescent subjects 14 years or older with mild-to-moderate HDM AA and a clinical history of HDM AR. Subjects were randomised to approximately 1 year of treatment with 1, 3, or 6 SQ-HDM, or placebo. Subjects' use of ICS was standardised and adjusted at baseline and the end of treatment to the lowest dose providing asthma control [44, 45].

The primary endpoint was a reduction in ICS dose from the individual subject's baseline dose after 1 year of treatment. Other asthma-related endpoints were ICS dose, ACQ score, FEV1, PEF, AQLQ score, and the number of asthma exacerbations [44, 45].

At the 4-week end-of-trial efficacy evaluation period, the mean difference between 6 SQ-HDM and placebo in the reduction in daily ICS dose was significantly different with a reduction from baseline of 207.6 µg budesonide in the 6 SQ-HDM group and 126.3 µg in the placebo group corresponding to an absolute difference of 81 µg budesonide per day (95% CI, 27-136 µg/d, p=0.004). Relative mean and median reductions from baseline were, respectively, 42% and 50% for 6 SQ-HDM and 15% and 25% for placebo [44, 45].

In a post-hoc analysis of the subgroup (n=108) with lower asthma control and ICS ≥400 µg budesonide, the mean reduction from baseline in daily ICS dose was 384.4 µg for 6 SQ-HDM and 57.8 µg for placebo. This indicated a significant absolute difference of 327 µg budesonide per day between 6 SQ-HDM and placebo (95% CI,

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182-471], p<0.0001, post-hoc analysis). No significant differences were found between placebo and 1 and 3 SQ-HDM. No statistically significant differences were observed for the other assessed asthma parameters (ACQ score, PEF, FEV1, asthma exacerbations, and AQLQ score), reflecting the intended controlled status of trial subjects [44, 45].

While the trial did not examine the licensed 12 SQ-HDM dose, the effectiveness of SQ-HDM tablets has been demonstrated to significantly reduce the ICS dose required to maintain asthma control at the lower dose of 6 SQ-HDM, with results implying that investigation of a dose higher than 6 SQ-HDM would be well-tolerated and potentially lead to better efficacy [44, 45].

B2.6.6.2 P003

The P003 trial is a randomised, double-blind, placebo-controlled Phase 2 trial that was conducted in an allergen exposure chamber with the objective to determine the dose-related efficacy and onset of action of the HDM sublingual immunotherapy.124 adults with house dust mite AR with or without house dust mite allergic asthma/allergic rhinoconjunctivitis were randomised and received at least 1 dose of the study drugs: 12 SQ-HDM, 6 SQ-HDM, or placebo daily for 24 weeks. Participants underwent 6-hour exposure challenges at screening and Weeks 8, 16, and 24, preceded by a washout of all allergy pharmacotherapy [42].

The primary endpoint was the total nasal symptom score during chamber challenges at Week 24. The results from the allergen challenge at Week 24 showed that the placebo group had a mean rhinitis symptoms score of 7.45 [95% CI: 6.57,8.33], while the 12 SQ-HDM group scored 3.83 [95% CI: 2.94,4.72], corresponding to a 3.62 absolute difference and a 49% relative difference (95% CI [35%,60%], p<0.001). The 12 SQ-HDM group also showed a statistically significant difference compared to placebo at Week 16, with mean scores of 4.82 and 6.90, reflecting a 2.08 (30%) difference (95% CI [17%-42%], p<0.001). Additionally, at 8 weeks, the mean scores were 5.34 and 6.71 for 12 SQ-HDM and placebo, respectively, resulting in a 1.37 (20%) difference (95% CI [7%;33%], p=0.007).

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The trial's findings demonstrated that 12 SQ-HDM in a controlled setting reduced nasal and ocular symptoms and exceeded the World Allergy Organization's established clinical efficacy criteria (>20% improvement vs placebo). The onset of action for 12 SQ-HDM of MK-8237 was at Week 8.

B2.7 Subgroup analysis

B.2.7.1 MT-04

Prespecified subgroup analyses were presented for the primary efficacy endpoint and included gender (male/female), allergen sensitisation type (HDM only/HDM and others), other indoor sensitisations (with animal hair and dander or moulds (Cladosporium herbarium and Alternaria alternata)/without)), and age group (<30 years old, >30 years old).

Figure 18 displays the forest plot for the estimated HRs by the above subgroups. The plot displays the estimated HR to placebo (and corresponding confidence interval) for each subgroup by treatment. The estimated HR was calculated using the Cox regression stratified by country, and was based on all observed data in the FAS.

There were no statistically significant interactions at a significance level of $p<0.05$ between treatment and any subgroup variable.

No additional formal statistical subgroup analyses were planned, and the trial was not powered to detect treatment effects within a subgroup [36, 47].

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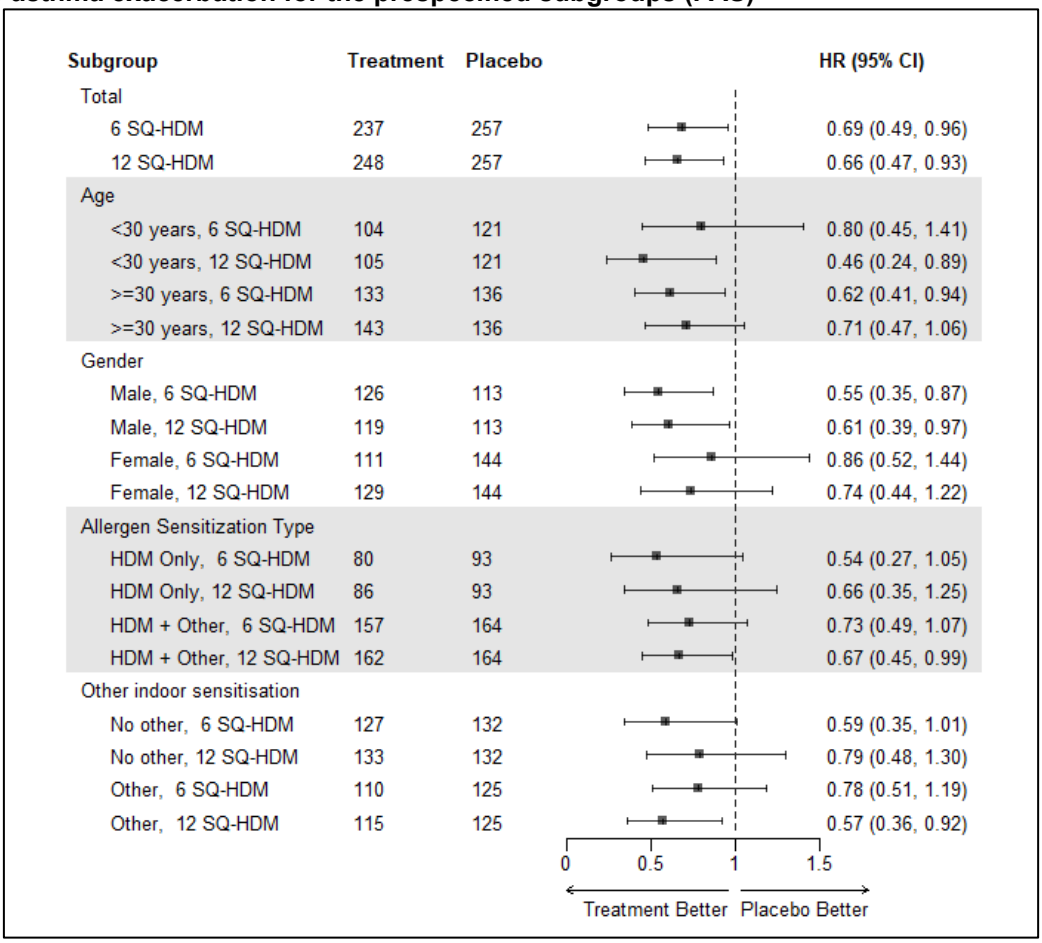
Figure 18: MT-04 forest plot of HR for the comparison to placebo of time to first moderate or severe asthma exacerbation for the prespecified subgroups (FAS)[36, 47]



CI, confidence interval; HDM, house dust mite; HR, Hazard ratio.
Interactions between treatment and subgroup variables were evaluated at a significance level of p<0.05; however, no apparent differences were observed.

B.2.7.2 MT-06

Prespecified subgroup analyses were presented for the primary efficacy endpoint and included gender (male, female), asthma status (with, without), allergen sensitisation type (mite only, mite + others), other indoor sensitisation (with, without), and age group (<30 years old, >30 years old).

Figure 19 displays the forest plot produced for the average TCRS during the efficacy evaluation period by the above subgroups. The plot displays the adjusted mean difference from placebo (and corresponding CI) for each subgroup by treatment. The adjusted mean difference was calculated using the LME model and was based on all observed data in FAS.

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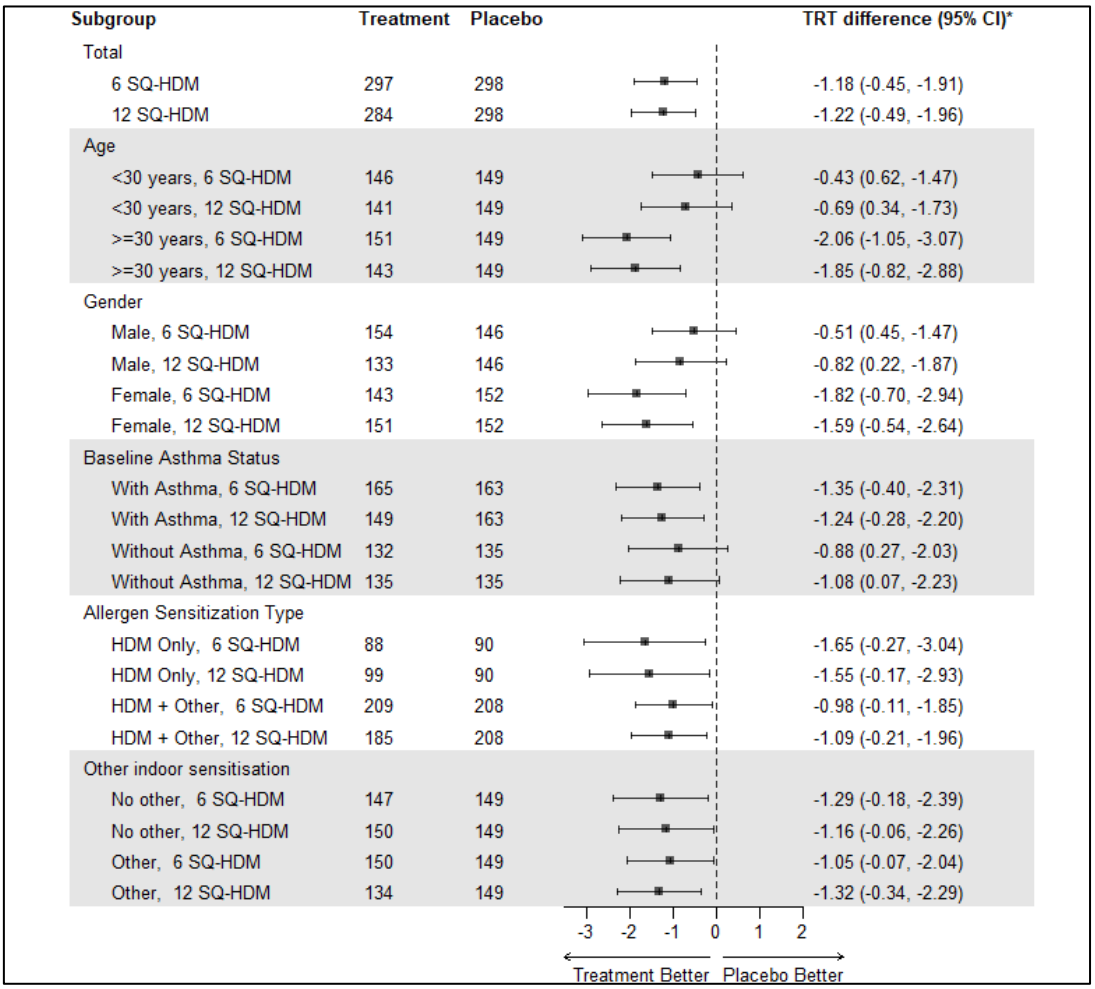
For the age subgroups, the difference to placebo in the TCRS was numerically higher for subjects ≥30 years compared to subjects <30 years old. In addition, for the gender subgroups, the difference to placebo was numerically higher for male patients than for female patients. These observed differences were not statistically significant (p=0.11 and p=0.2, respectively), meaning it is possible the difference was due to random variation. For the remaining subgroups, no apparent differences were observed [34, 48].

Figure 19: MT-06 forest plot of the difference in average TCRS during the efficacy evaluation period by subgroup (FAS) [34, 48]



CI, confidence interval; TCRS = Total Combined Rhinitis Score; HDM, house dust mite; TRT, Treatment.
*The treatment difference represents the mean adjusted change in TCRS. Note that the trial was not powered for such subgroup analyses. Interactions between treatment and subgroup variables were evaluated at a significance level of p<0.05, however, no apparent differences were observed.

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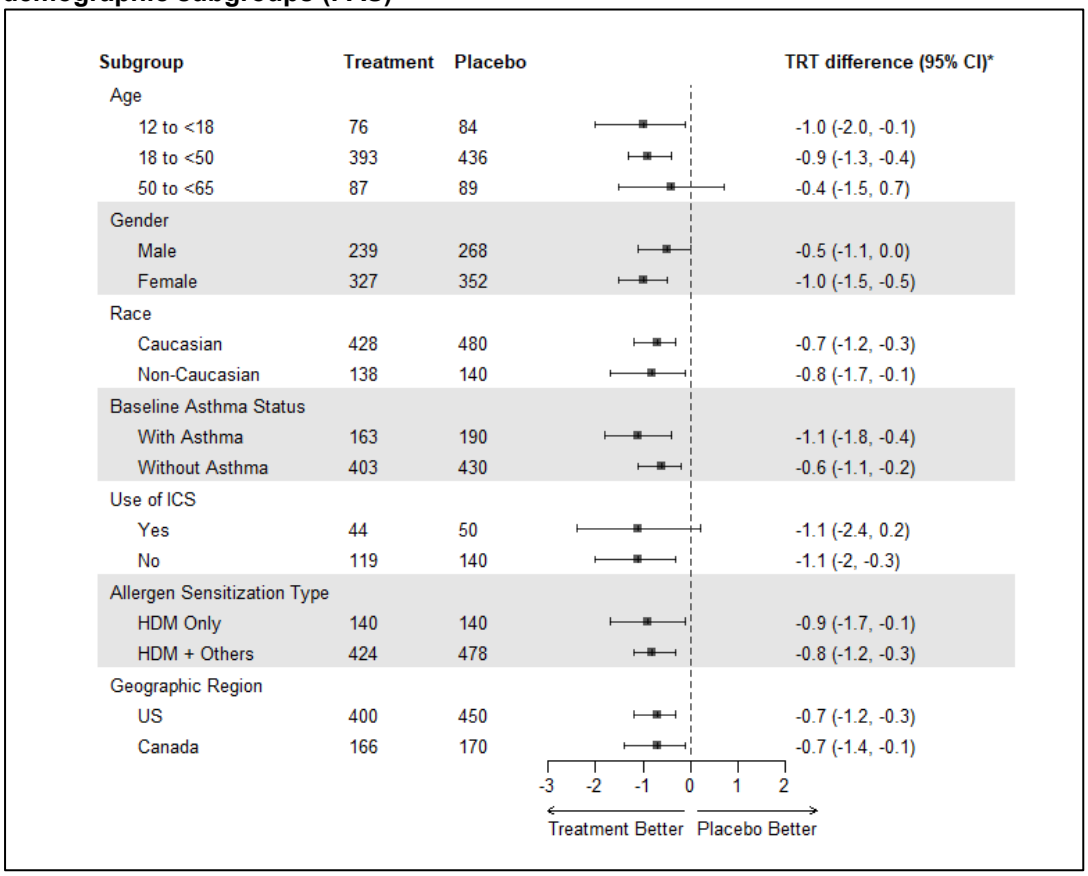
B.2.7.3 P001

Subgroup analyses of the average TCRS during the last 8 weeks of treatment included age, gender, race, asthma status, ICS use, allergen sensitivity, geographic location, and the occurrence of local application site reactions. Although the trial was not powered to show efficacy in specific subgroups, efficacy was consistent between the various subgroups.

Figure 20 displays a forest plot produced to summarise the average TCRS during the last 8 weeks of treatment by the above subgroups. The plot displays the Hodges-Lehmann estimate of treatment difference from placebo (and corresponding CIs) for each subgroup by treatment[35, 49].

Figure 20: P001 forest plot of the average TCRS during the last 8 weeks of treatment by demographic subgroups (FAS)[35, 49]



CI, confidence interval; TCRS = Total Combined Rhinitis Score; ICS = Inhaled corticosteroid.
'Treatment' refers to 12 SQ-HDM.
The trial was not powered to show efficacy in specific subgroups.
*The relative effect was based on the median TCRS calculated by (12 SQ-HDM – Pbo)/Pbo*100. Median treatment difference and 95% CI were based on Hodges-Lehmann estimate. For the age subgroups, results from subjects >=65 are not plotted due to the small number of available subjects (21).

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Subgroup analysis of the primary endpoint was conducted for the adolescent and adult subgroups respectively. The FAS adult subgroups included 829 patients aged 18 to 50 years, and the FAS adolescent subgroup included 189 adolescents aged 12 to 18 years.

The adolescent and adult subgroup both saw a similar reduction in the average daily TCRS with 12 SQ-HDM treatment compared to placebo. For adults, a 19.2% reduction in TCRS was shown for 12 SQ-HDM compared with placebo (Hodges-Lehmann estimate of shift: -0.9 [95% CI -1.30,-0.40]). For adolescents, a 22.4% reduction in TCRS was shown for 12 SQ-HDM compared with placebo (Hodges-Lehmann estimate of shift: -1.0 [95% CI -2.00,-0.10]) [35, 49].

B.2.7.4 TO-203-31

Subgroup analyses of the primary and key secondary endpoint during the last 8 weeks of treatment included age and HDM-specific IgE antibody class.

Table 54 presents the results of the analysis of percentage of moderate or severe asthma exacerbations from the start of the study treatment to end of Period 3 (primary endpoint) by age group. No specific trend between the treatment groups was noted in the percentage of asthma exacerbation by age group. The percentage tended to be lower in younger subjects (≥18 years old and <30 years old) in all treatment groups [37, 50].

Table 54: TO-203-31 - Percentage of moderate or severe asthma exacerbations by age[37, 50]

Subgroup analysis (FAS)	N		n (%)	
	Placebo	12 SQ-HDM	Placebo	12 SQ-HDM
Full population	274	276	110 (40.1%)	104 (37.7%)
Age subgroup (years)				
18-30	54	51	16 (29.6%)	12 (23.5%)
30-40	96	104	40 (41.7%)	37 (35.6%)
40-50	99	89	41 (41.4%)	45 (50.6%)
>50	25	32	13 (52.0%)	10 (31.3%)

N: number of subjects analysed
n: number of subjects who experienced an asthma exacerbation
Abbreviations: SQ-HDM, standard quality house dust mite; FAS, full analysis set

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B.2.7.5 TO-203-32

Subgroup analyses of the primary endpoint – the average TCRS during the last 8 weeks of treatment – included age and HDM-specific IgE antibody class.

The adjusted mean TCRS by age group was estimated in the FAS dataset using the LME model and are reported in Table 55. The minor point difference between the 'Full population' TCRS results and the TCRS results presented as the primary endpoint in Table 53 is expected to be due to the exclusion of clinical sites as a random-effects factor in the LME model used in the examination of subgroups [38, 51].

Table 55: TO-203-32 - adjusted mean TCRS age subgroup analysis[38, 51]

Subgroup analysis	N		LME model*		
			Adjusted mean		Difference in adjusted mean
	Placebo	12 SQ-HDM	Placebo	12 SQ-HDM	
Full population	285	281	5.09	4.13	-0.96
Age subgroup (years)					
<18	92	99	5.04	4.04	-0.99
18<30	85	69	5.25	4.37	-0.88
30<40	54	57	4.89	4.12	-0.77
40<50	47	48	5.15	4.04	-1.11
>50	7	8	6.21	4.01	-2.19

*The model includes the square-rooted average of the values during the Period A as the dependent variable, treatment groups and square-rooted average of DSS during baseline period as fixed effect. Back-transformed adjusted mean, differences, and ratios are calculated.
Abbreviations: SQ-HDM, standard quality house dust mite; LME, linear mixed effects.

Notably, in each treatment group, the adjusted mean TCRS was similar across age groups. The adjusted mean TCRS in subjects aged 12-18 years was similar to that in other age groups in all treatment groups [15]. The ≥50 years old category includes 7 patients in placebo and 8 in 12 SQ-HDM, covering 2% of the total placebo population and 3% of the total 12 SQ-HDM patient population, respectively. A relative difference of 17% (adjusted mean difference: -0.88), 16% (adjusted mean difference: -0.77), and 22% (adjusted mean difference: -1.11) for 12 SQ-HDM compared to placebo can be observed in the 12-18, 18-30, and 30-40 age subgroups, respectively. Both adults and adolescents demonstrated a significant improvement in TCRS compared with placebo, regardless of age group, suggesting similar efficacy in adults and adolescents [38, 51].

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B2.8 Meta-analysis

There were two pivotal trials identified for the AA+AR population (MT-04 and TO-203-31), and three pivotal trials for the AR only population (MT-06, TO-203-32, and P001). Full details of these trials are provided above.

Fixed-effect and random-effect meta-analyses were preformed, pooling estimates of treatment effect across the identified trials for each of the respective populations (AA+AR and AR only).

The following section outlines an assessment of trial comparability, focusing on key differences in study design, baseline characteristics, and endpoints, and describes the methods and results of the meta-analyses. Limitations of the meta-analyses are also discussed.

B.2.8.1 Trial comparability

B2.8.1.1 AA+AR trials

Table 56 provides an overview of the key differences between the MT-04 trial and the TO-203-31 trial.

Table 56: Key trial differences for the AA+AR population

Category	MT-04	TO-203-31
Study population		
Country	European cohort (99% Caucasian)	Japanese cohort
Allergy diagnosis	Positive specific IgE level of >0.70 kU/L or assessed as Class 2 or greater	Positive specific IgE level of >3.5 kU/L or assessed as Class 3 or greater
Study design		
Up dosing	None	Dose escalation from 2, 6, 12 SQ-HDM during first 4 weeks
Efficacy assessment period	None	Required ACQ score <1.5
Inclusion and exclusion criteria		
Allergic rhinitis	Required HDM AR (mild-to-severe)	No requirement
Baseline characteristics (mean)		

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Category	MT-04	TO-203-31
AR, %	100% with HDM AR	25% perennial or seasonal AR 20.9% perennial AR 33.9% seasonal AR 20.3% no AR
Lung function	FEV1 (% of predicted) = 92.7% Diurnal variation of PEF = 8.6%	FEV1 (% of predicted) = 88.5% Diurnal variation of PEF = 3.7%
Mono-sensitisation	34%	14%
Asthma symptom score	2.64	1.70
Asthma duration, yrs	12.9	17.4
Daily ICS dose	588 µg budesonide	352 µg fluticasone propionate (equivalent to 704 µg budesonide)
Primary efficacy endpoint: Time to first moderate or severe asthma exacerbation		
Dataset	FAS and FAS-MI	FAS
Abbreviations: IgE, immunoglobulin E; HDM, house dust mite; ACQ, asthma control questionnaire; AR, allergic rhinitis; FEV, forced expiratory volume; PEF, peak expiratory flow; ICS, inhaled corticosteroid		

The TO-203-31 study was conducted in Japan, and the MT-04 study was conducted across Europe (with 99% of subjects being Caucasian). Both studies required a positive skin prick test response to D.pteronyssinus or D.farinae, but there were differences in the minimum required IgE levels against D.pteronyssinus and/or D.farinae. The MT-04 trial required a positive specific IgE level of >0.70 kU/L or assessed as Class 2 or greater, while, the TO-203-31 required a positive specific IgE level of >3.5 kU/L or assessed as Class 3 or greater. A higher IgE level may suggest that a person is more sensitised to the specific allergen being tested.

A key difference in study design was that the TO-203-21 study employed a dose escalation method for the first 4 weeks up to the first day of study treatment. Subjects who were to receive 6 SQ-HDM started on 2 SQ-HDM for the first week, and up-dosed to 6 SQ-HDM at Week 2 onwards. Subjects to receive 12 SQ-HDM followed the same pattern, escalating to 12 SQ-HDM from Week 3 onwards.

An additional implication of differences in study location were the criteria for well-controlled asthma as defined by the GINA criteria (used in Europe), and the Japanese guidelines for adult asthma. As reported in Tanaka et al., 2020, the GINA criteria allow asthma symptoms or SABA use twice a week or less, whereas the Japanese guidelines includes only those patients who have no asthma symptoms

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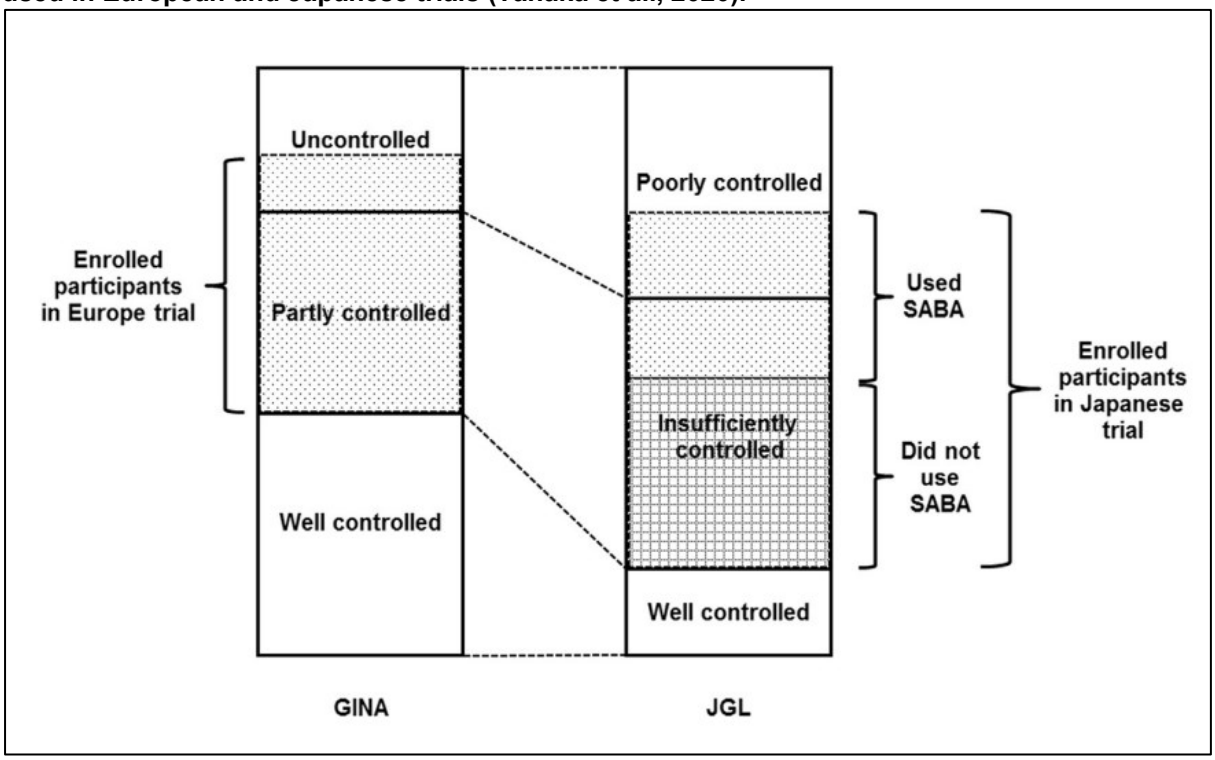
and do not need to use SABA (see Figure 21). As a result, 27% of patients in the TO-203-31 trial had no daytime asthma symptoms and nocturnal awakening for a week before randomisation. For this reason, Tanaka et al., 2020 conducted a subgroup analysis on the primary endpoint for the subgroup of subjects who required SABA during the baseline period to align with European guidelines more closely. As 12 SQ-HDM is only indicated in AA in patients not well-controlled with ICS, the differences in the definition of subject backgrounds enrolled in TO-203-31 may have material implications for the results of the study and limit its generalisability to the licensed European population. Consequently, it is believed that the subgroup analysis reported by Tanaka et al., 2020 using data on patients who required SABA at baseline is more applicable and representative of the target population in this submission.

Figure 21: Asthma control level of enrolled TO-203-31 subjects in compliance with guidelines used in European and Japanese trials (Tanaka et al., 2020).



Additionally, the TO-203-31 trial specified more restrictive conditions on allowing subjects to proceed to Period 3 (the efficacy assessment period): subjects were not allowed to have an ACQ score of >1.5 immediately before Period 3. This indicates that during the TO-203-31 efficacy assessment period, patients could not have had

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uncontrolled asthma, and may therefore have been less likely to experience an asthma exacerbation. This criterion was not applied in the MT-04 trial.

The main difference in inclusion criteria concerns the presence of AR. In the TO-203-21 trial, trial subjects were patients with HDM-induced AA regardless of the presence or absence of complications of HDM-induced AR. However, in the MT-04 trial, it was required that subjects had a clinical history consistent with mild-to-severe HDM-induced AR for at least 1 year. As a result, at baseline, 100% of patients in the MT-04 trial had HDM-induced AR, compared with only 25% (perennial and seasonal) or 20.9% (perennial only) of patients in the TO-203-31 trial with concurrent AR.

The notable differences in the baseline characteristics between the two trials are as follows:

- The FEV1 (% of predicted) score. Across the two trial populations, the FEV1 (% of predicted) score was 88.5% in the TO-203-31 trial and 92.7% in the MT-04 trial. A lower score is indicative of reduced lung function.
- The diurnal variation of PEF. Across the two trial populations, the diurnal variation of PEF score was 3.70% in the TO-203-31 trial and 8.61% in the MT-04 trial. A higher score suggests greater variability in lung function and is indicative of poorly managed asthma.
- The proportion of patients who were mono-sensitised and poly-sensitised. Across the two trial populations, the proportion of patient's mono-sensitised was 14% in the TO-203-31 trial and 34% and MT-04 trial.
- The asthma symptom score. Across the two trial populations, the asthma symptom score was 1.70 in the TO-203-31 trial and 2.64 in the MT-04 trial. A lower score indicates a subject experiences fewer and milder asthma symptoms.
- The duration of a patient's asthma. Across the two trial populations, the average number of years with an asthma diagnosis was 17.4 in the TO-203-31 trial and 12.9 in the MT-04 trial.

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- Average daily ICS dose. The include criteria for dose of ICS at randomisation for the MT-04 trial required a range of budesonide between 400 and 1200µg. Similarly, the TO-203-31 trial required a dose of ICS at the start of study treatment of fluticasone propionate between 200 and 400µg (equivalent to 400 to 80µug budesonide). At baseline, patients in the MT-04 trail had an average total daily dose of 588µg ICS budesonide. At the start of study treatment in the TO-203-31 trial, ICS dosage was reported as a proportion at doses of 200µg (23.9%), 300µg (0.4%), and 400µg (75.7%). Using a weighted average as an estimate, this equates to a dose of 352µg of fluticasone propionate, equivalent to 704µg budesonide. The higher ICS dosage maybe explained by Japanese treatment guidelines which have no recommendations on stepping down in asthma controller dose, which is contrary to GINA and British Thoracic Society (BTS)/SIGN guidelines (European guidelines).

No notable differences were observed in the analysis and reporting of the primary endpoints across two trials.

B2.8.1.2 AR trials

Table 57 provides an overview of the key differences between the MT-06 trial, P001 trial, and the TO-203-32 trial.

Table 57: Key trial differences for the AR population

Category	MT-06	TO-203-32	P001
Study population			
Country	European cohort (98% Caucasian)	Japanese cohort	US and Canada (71% White, 7% Asian, 11% Black or African American)
Allergy diagnosis	Positive skin prick test (wheal diameter ≥3 mm) Positive specific IgE level of >0.7 kU/L or assessed as Class 2 or greater	Nasal provocation test Positive specific IgE level of >3.5 kU/L or assessed as Class 3 or greater	Positive skin prick test (wheal diameter ≥5 mm) Positive specific IgE level of >0.7 kU/L or assessed as Class 2 or greater
Inclusion and exclusion criteria			
Allergic asthma	ICS were ≤400 mcg budesonide or equivalent.	No asthma	ICS cannot be high dose Cannot be unstable or

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Category	MT-06	TO-203-32	P001
	Cannot be uncontrolled. FEV1 ≥70% predicted.		severe. FEV1 ≥80% of predicted
Rhinitis DSS	Rhinitis DSS of ≥6 or a score of ≥5 with one symptom being severe	Rhinitis DSS of ≥7	Rhinitis DSS of ≥6, or a score of ≥5 with one symptom being severe
Rhinitis QoL	1 of 3 ARIA quality of life items	1 point across 1 of 7 items from the JRQLQ No.1	None
Baseline characteristics (mean)			
AA, %	46%	None	31%
Mono-sensitisation, %	32%	21%	24%
Rhinitis duration, yrs	9.9	10.1	18.6
Primary efficacy endpoint: Average TCRS			
Dataset	FAS, adjusted means FAS-MI, adjusted means	FAS, adjusted means	FAS, adjusted means FAS-MI, adjusted means
Abbreviations: IgE, immunoglobulin E; HDM, house dust mite; AA, allergic asthma; AR, allergic rhinitis; FEV, forced expiratory volume; PEF, peak expiratory flow; ICS, inhaled corticosteroid.			

The TO-203-32 study was conducted in Japan. The MT-06 study was conducted across Europe with 98% of subjects being Caucasian. The P001 study was conducted across the US and Canada, with 71%, 7%, and 11% of subjects being White, Asian, and Black or African American, respectively. The TO-203-32 and P001 study included adolescents (≥12) and adults (≥18), whereas the MT-06 trial included adults (≥18) only. For the P001 trial, 13% were adolescents. For the TO-203-32 trial, 33% were adolescents.

For the diagnosis of HDM AR and as inclusion criteria, the P001 trial required a positive skin prick test response (wheal diameter ≥5mm) to D.pteronyssinus or D.farinae, the MT-06 trial required a positive skin prick test response (wheal diameter ≥3mm) to D.pteronyssinus or D.farinae, and the TO-203-23 trial required a positive nasal provocation test. Additionally, the P001 trial and MT-06 required a positive specific IgE level of >0.70kU/L or assessed as Class 2 or greater, while the TO-203-32 required a positive specific IgE level of >3.5kU/L or assessed as Class 3 or greater. A higher IgE level may suggest that a person is more sensitised to the specific allergen being tested. A wheal diameter of at least 5mm in a skin prick test indicates sensitisation to an allergen, whereas a positive nasal provocation test indicates a specific response in the respiratory system.

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The main difference in inclusion criteria between the trials concerns the presence of AA. In the MT-06 trial, subjects with asthma could only enter the trial if daily use of ICS was ≤400mcg budesonide or equivalent, with subjects excluded if asthma was diagnosed as uncontrolled within 3 months prior to screening, or if they had reduced lung function (defined as FEV1 <70% of predicted). For the P001 trial, subjects required a FEV1 ≥80% of predicted to enter the trial and were excluded if a subject had unstable or severe asthma within 3 months prior to screening, or asthma requiring high dose ICS within 6 months prior to screening. The TO-203-32 trial did not allow enrolment of patients with a medical history of asthma, including use of asthma medication and/or an asthma exacerbation within 2 years prior to study start. As a result, at baseline, 46% of patients had asthma in the MT-06 trial, and 31% of patients had asthma in the P001 trial.

Additional differences in the trials' inclusion criteria included rhinitis symptom score and impact on QoL. The MT-06 and P001 trial required a rhinitis DSS of ≥6 or a score of ≥5 with one symptom being severe, for at least 8 days (MT-06) or t 5 days (P001) prior to randomisation. The TO-203-32 trial was more restrictive, requiring a rhinitis DSS of ≥7 for at least 7 days prior to randomisation. Furthermore, the MT-06 trial required the presence of at least 1 of 3 ARIA QoL items, while the TO-203-32 trial required subjects to score at least 1 point across 1 of 7 items from the JRQLQ No.1.

The notable differences in the baseline characteristics between the two trials are as follows:

- The proportion of patients who were mono-sensitised and poly-sensitised. Across the three trial populations, the proportion of patients mono-sensitised was 32% in MT-06, 24% in P001, and 21% in TO-203-32.
- The duration of rhinitis. Across the three trial populations, the mean duration of patients' rhinitis was 9.9 years in MT-06, 18.6 years in P001, and 10.1 years in TO-203-32.

Regarding outcomes, there were differences in the calculation of the primary endpoint (change in average TCRS) between studies. The MT-06 study reports the

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difference of adjusted means for the FAS and FAS-MI dataset, estimated based on a LME model. The P001 study reports the difference of adjusted means in the FAS and FAS-MI dataset estimated based on an ANCOVA model. The TO-203-32 study reports the difference of adjusted means in the FAS dataset estimated based on a LME model, but does not provide any analysis accounting for missing data.

B.2.8.2 Methods

B2.8.2.1 Trial datasets

Efficacy estimands for time to first asthma exacerbation were extracted from the MT-04 and TO-203-31 trials. To account for the material difference between the trial populations relating to definitions of well-controlled asthma in the European and Japanese asthma guidelines used in the trials, data on a subgroup of the TO-203-31 trial based on subjects that used SABA during the 14-day baseline period was used. This combination of reported outcomes was considered to result in the least bias when pooling treatment effects. Estimates corresponded to those reported for the FAS (no MI) of MT-04, and the SABA subgroup of the TO-203-31 trial (FAS, no MI).

Estimated treatment effects for the total TO-203-31 population (not stratified by SABA usage) were also extracted and used in a sensitivity analysis.

Efficacy estimands for the average TCRS versus placebo were taken from MT-06, P001, and TO-203-32. Estimates corresponded to those reported for FAS of each trial, with no imputation of missing data.

B2.8.2.2 Statistical analysis

Fixed-effect and random-effects models were both used to pool estimated treatment effect across the trials, adopting a restricted maximum likelihood approach for estimating the between-study variance.

Statistical heterogeneity was assessed using the I^2 statistic, describing the percentage of the variability in the treatment effects reported for each trial which is due to between-study differences rather than sampling error.

All analyses were performed in R (v 4.2.2), using the ‘meta’ package.

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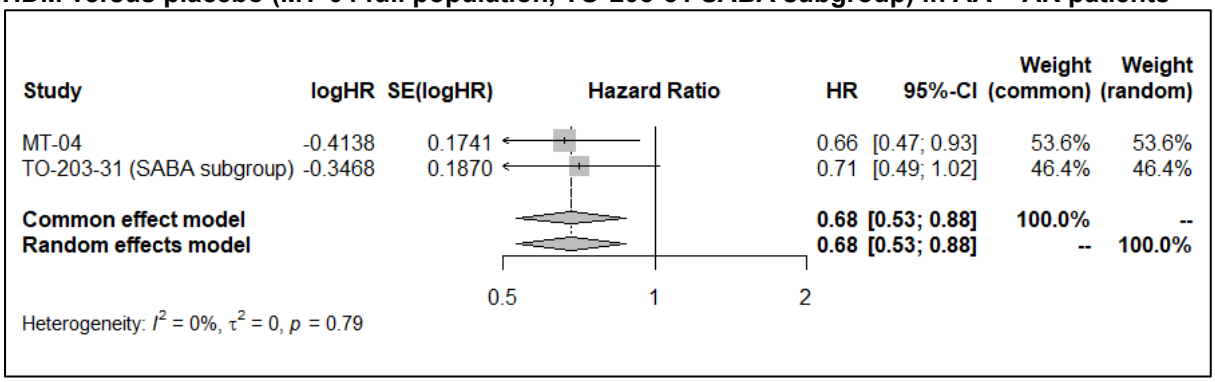
B.2.8.3 Results

B2.8.3.1 AA+AR trials

Results of the meta-analyses for the AA+AR trials are displayed in Figure 22. Based on the pooling of results from MT-04 and the SABA sub-population of TO-203-31, there was evidence to support a statistically significant difference in time to first exacerbation among patients treated with 12 SQ-HDM and those receiving the placebo. The pooled treatment effect was 0.68 (95% CI 0.53,0.88; p=0.0027).

The I^2 statistic returned a value of 0%, suggesting a high degree of alignment in the reported outcomes of the studies.

Figure 22: Meta-analysis showing hazard ratio for time to first asthma exacerbation in 12 SQ-HDM versus placebo (MT-04 full population, TO-203-31 SABA subgroup) in AA + AR patients



Sensitivity analyses combining estimates for MT-04 and the full population of TO-203-31, were consistent with the main analysis, showing a positive treatment effect associated 12 SQ-HDM; however, estimates were accompanied by a much greater degree of uncertainty (Figure 23). Pooled HRs from the fixed and random-effects models were 0.84 (95% CI 0.68,1.03; p=0.0986) and 0.81 (95% CI 0.55,1.18; p=0.2765), respectively.

The I^2 statistic returned a value of 66%, indicating the presence of substantial statistical heterogeneity [58]. This is expected given the fundamental difference between the population of the two trials.

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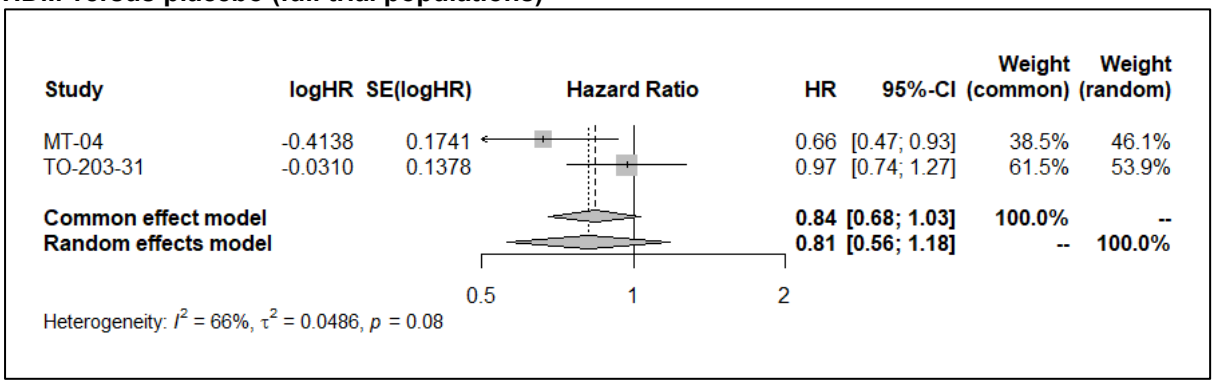
Figure 23: Meta-analysis showing hazard ratio for time to first asthma exacerbation in 12 SQ-HDM versus placebo (full trial populations)

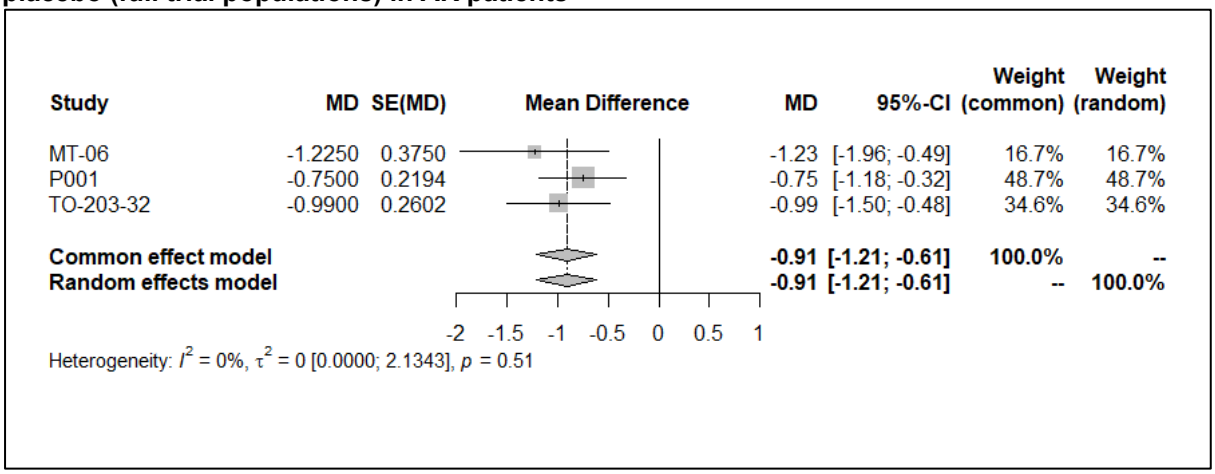


B2.8.3.2 AR trials

Figure 24 shows results from the meta-analysis for the AR trials. The pooled estimate from MT-06, P001, and TO-203-32 demonstrated a statistically significant improvement in TCRS score in patients treated with 12 SQ-HDM versus placebo (-0.91 (95% CI -1.21, -0.61)).

The I^2 statistic returned a value of 0%, indicating minimal statistical heterogeneity between studies.

Figure 24: Meta-analysis showing Mean difference (MD) in average TCRS in 12 SQ-HDM versus placebo (full trial populations) in AR patients



B.2.8.4 Discussion and limitations

The meta-analysis, combining estimated treatment effects from the MT-04 and TO-203-31 (SABA subgroup) trials to align with the target population of this appraisal, supported a statistically significant difference in time to first asthma exacerbation for 12 SQ-HDM versus placebo. Results from the sensitivity analyses which combined

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treatment effects for the full trial populations of both trials also demonstrated a positive treatment effect, albeit non-statistically significant. However, the results of the meta-analysis for the sensitivity analysis indicate the presence of substantial statistical heterogeneity. Despite differences observed between trials stemming from differences in study population, study design, and various disease-specific baseline characteristics, a positive treatment effect was demonstrated in the primary and sensitivity meta-analyses. When subgroup data were used to better match the TO-203-31 trial population to those in the MT-04 trial, a high degree of alignment could be reported in the outcomes of the studies (I^2 = 0%). For both analyses, effect sizes from both random and fixed effects models were consistent.

The comparative assessment of MT-06, P001, and TO-203-32 highlighted some areas of heterogeneity regarding study population and study design of each trial, namely the inclusion of adolescents in the TO-203-32 and P001 trials, the presence of AA at baseline, and duration of rhinitis. However, there was good alignment between the reported outcomes of the trials (I^2 = 0%). The meta-analysis for average TCRS demonstrated a statistically significant treatment effect versus placebo when pooling the results of the 3 trials.

B2.9 Indirect and mixed treatment comparisons

Not applicable.

B2.10 Adverse reactions

In the MT-04, MT-06, and TO-203-31 trials, all AE analyses were performed for the safety analysis set, which was identical to the FAS. In the TO-203-32 trial, AE analyses were performed for the safety analysis set, which was identical to the number of subjects randomised. In the P001 trial, the safety analysis set included all randomised subjects who took at least 1 dose of the IMP.

For the MT-04 and MT-06 trials, all AEs were assessed by the investigator as being possibly or unlikely causally related to the IMP. AEs assessed as having a possible causal relationship to the IMP were termed treatment-related AEs (TRAEs). For the TO-203 trials, the causal relationship of an AE with the IMP was classified into 3 categories (related, possibly related, and not related), with an AE classified as

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possibly related or related being regarded as an adverse drug reaction (ADR). In the P001 trial, drug-related AE were determined by the investigator.

Unsolicited adverse events (AEs) were recorded by subjects in the MT-04, MT-06, TO-203 trials. In contrast, the P001 trial actively solicited 15 local AEs, identified by the World Allergy Organization, from subjects. Solicited AEs refer to AEs collected via a structured questionnaire regarding specific AEs, whereas unsolicited AEs refer to open-ended questioning of AEs in general without specifying individual AEs (22).

Unsolicited data capture may lead to underreporting due to hesitancy by the patient to report an AE, or the possibility they might forget specific AE occurred. In contrast, AEs collected by structured questionnaires may enhance detection of a safety signal but may also lead to inflated reporting rates due to the suggestive nature of questioning the presence of an AE. Studies have demonstrated that the number of events for solicited AEs collected either by a data collection system or by structured questionnaire is generally several fold higher compared with unsolicited AEs [59] .

Details of the AE analyses performed in the MT-04, MT-06, P001, and TO-203 trials are provided in the following sections. The company also note the recent publication of the MT-18 study [60], a Phase 3, open-label, single-arm, 28-day safety trial of daily HDM SLIT-tablet (12 SQ-HDM dose) in European adolescents (12-17 years) with HDM AR/C, with or without asthma. In summary, most TRAEs were mild in intensity and were typically experienced the first 1 to 2 days of treatment. There were no asthma-related TEAEs with the 12 SQ-HDM. Horn et al., 2023 conclude that the safety profile appears similar between adolescents with or without asthma at baseline. The results of this study have been provided in Appendix F.

B.2.10.1 MT-04

Overall, 599 participants (72%) reported AEs in the MT-04 trial. The number of subjects reporting AEs was higher in the 12 SQ-HDM treatment group (222, 79%) compared with the placebo group (174, 63%). An overview of AEs is presented in Table 58 [36, 47].

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Table 58: Summary of adverse events in the MT-04 trial [36, 47]

	MT-04			
	Placebo, n=277		12 SQ-HDM, n=282	
	n (%)	E (%)	n (%)	E (%)
All AEs	174 (63%)	508 (100%)	222 (79%)	829 (100%)
All TRAEs	48 (17%)	69 (14%)	130 (46%)	351 (42%)
Severity of all AEs (% of n, % of E)				
Mild	137 (49%)	315 (62%)	181 (64%)	549 (66%)
Moderate	92 (33%)	176 (35%)	125 (44%)	255 (31%)
Severe	14 (5%)	17 (3%)	20 (7%)	25 (3%)
Most common TRAEs (occurring in ≥2% of patients) (% of nTRAE, % of ETRAE)				
Throat irritation	4 (8%)	4 (6%)	27 (21%)	32 (9%)
Oral pruritis	8 (17%)	8 (12%)	55 (42%)	78 (22%)
Tongue pruritis	1 (2%)	1 (1%)	13 (10%)	15 (4%)
Oedema mouth	0 (%)	0 (%)	28 (22%)	35 (10%)
Oral paraesthesia	0 (%)	0 (%)	12 (9%)	15 (4%)
Lip swelling	0 (%)	0 (%)	6 (5%)	7 (2%)
Ear pruritis	2 (4%)	2 (3%)	11 (8%)	2 (1%)
Nausea	0 (%)	0 (%)	8 (6%)	8 (2%)
Lip oedema	0 (%)	0 (%)	9 (7%)	10 (3%)
Pharyngeal oedema	0 (%)	0 (%)	5 (4%)	6 (2%)
Swollen tongue	0 (%)	0 (%)	5 (4%)	6 (2%)
Lip pruritis	0 (%)	0 (%)	7 (5%)	8 (2%)
Accidental overdose	9 (19%)	12 (17%)	15 (12%)	16 (5%)
Seriousness of AEs (% of n, % of E)				
SAE	11 (4%)	12 (2%)	7 (2%)	10 (1%)
Non-SAE	173 (62%)	496 (98%)	221(78%)	819 (99%)
AEs leading to discontinuation (% of n, % of E)				
Yes	8 (3%)	10 (2%)	25 (9%)	46 (6%)
No	171 (62%)	498 (98%)	213 (76%)	783 (94%)
Action taken (% of n, % of E)				
None	168 (61%)	461 (91%)	206 (73%)	705 (85%)
Temp. int	23 (8%)	37 (7%)	47 (17%)	78 (9%)
IMP disc.	8 (3%)	10 (2%)	25 (9%)	46 (6%)
Outcome (% of n, % of E)				
Recovered	171 (62%)	479 (94%)	217(77%)	802 (97%)
Rec. seql.	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)
Not rec	22 (8%)	26 (5%)	20 (7%)	24 (3%)
Unknown	2 (<1%)	2 (<1%)	3 (1%)	3 (<1%)

n: number of subjects with events, %n: % of subjects in treatment group of analysis set with events, E: number of events, %E: % of all events in treatment group, AE: adverse event, SAE: serious AE, Temp.int.: IMP temporarily interrupted, IMP disc.: IMP discontinued, Rec.seql.: recovered with sequelae, not rec.: subject not recovered at the end of trial

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	MT-04			
	Placebo, n=277		12 SQ-HDM, n=282	
	n (%)	E (%)	n (%)	E (%)
Abbreviations: SQ, standardised quality; HDM, house dust mite; AE, adverse event; IMP, investigational medicinal product; SAE, serious adverse event; TRAE, treatment-related adverse event.				

Treatment-related AEs (TRAE) were reported in 17% of subjects (n=48) from the placebo group, 39% (n=107) from the 6 SQ-HDM group, and 46% (n=130) from the 12 SQ-HDM group. The 3 most frequently reported TRAEs were oral pruritus, mouth oedema, and throat irritation. The most common AEs had a median onset time 1 or 2 days after start of the treatment. The median onset in minutes on Day 1 was 1 to 2 minutes. The median number of days from start of the AE until the event no longer occurred was 4.5 days for oral pruritus, 7 days for throat irritation, and 23 days for mouth oedema.

The most frequently experienced AEs with 12 SQ-HDM treatment were mild transient local application site reactions, with the majority related to treatment administration. Only 6 patients in the 12 SQ-HDM group and 3 patients in the placebo group experienced AEs that were assessed as severe (i.e., causing considerable interference with the subject's daily activities and considered unacceptable).

The number of patients who experienced a serious AE (SAE) with 12 SQ-HDM treatment was low and less than placebo: 7 patients and 11 patients, respectively. Only 5 SAEs were assessed as treatment-related: 2 in the placebo group, 2 in the 6 SQ-HDM group and 1 in the 12 SQ-HDM group.

Most of the AEs (85% in the 12 SQ-HDM group, and 91% in the placebo group) did not lead to any specific action, while treatment was temporarily interrupted in 9% and 7% of events in the 12 SQ-HDM and placebo group, respectively. Treatment was discontinued due to AEs in 25 (9%) patients in the 12 SQ-HDM group and in 8 (3%) patients in the placebo group.

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No deaths occurred during the trial, and no AEs were reported as systemic allergic reaction in either of the groups. Only 22 patients in the placebo group and 20 patients in the 12 SQ-HDM group had not recovered from AEs at the end of the trial. There was no dose response trend in the outcome of AEs.

There were no reports of anaphylactic reactions (including anaphylactic shocks) or AEs requiring treatment with adrenaline.

B.2.10.2 MT-06

Overall, 579 (58%) patients in the MT-06 trial reported AEs. The number of subjects reporting AEs was higher in the 12 SQ-HDM treatment group (213, 67%) compared with the placebo group (154, 46%)[34, 48]. An overview of these AEs is presented in Table 59.

Table 59: Summary of adverse events in the MT-06 trial[34, 48]

	MT-06			
	Placebo, n=338		12 SQ-HDM, n=318	
	n (%)	E (%)	n (%)	E (%)
All AEs	154 (46%)	327 (100%)	213 (67%)	681 (100%)
All TRAEs	50 (15%)	96 (29%)	167 (53%)	457 (67%)
Severity of all AEs (% of n, % of E)				
Mild	119 (35%)	235 (72%)	184 (58%)	505 (74%)
Moderate	56 (17%)	82 (25%)	78 (25%)	168 (25%)
Severe	10 (3%)	10 (3%)	7 (2%)	8 (1%)
Most common TRAEs (occurring in ≥2% of patients) (% of nTRAE, % of ETRAE)				
Throat irritation	12 (24%)	14 (15%)	47 (28%)	61 (13%)
Oral pruritis	8 (16%)	8 (8%)	66 (40%)	89 (19%)
Tongue pruritis	5 (10%)	5 (5%)	17 (10%)	20 (4%)
Oedema mouth	1 (2%)	1 (1%)	29 (17%)	34 (7%)
Oral paraesthesia	2 (4%)	2 (2%)	23 (14%)	31 (7%)
Lip swelling	0 (0%)	0 (0%)	7 (4%)	10 (2%)
Ear pruritis	1 (2%)	2 (2%)	16 (10%)	21 (5%)
Glossodynia	1 (2%)	1 (1%)	10 (6%)	13 (3%)
Lip oedema	2 (4%)	2 (2%)	7 (4%)	9 (2%)
Pharyngeal oedema	0 (0%)	0 (0%)	7 (4%)	8 (2%)
Oral discomfort	0 (0%)	0 (0%)	9 (5%)	10 (2%)
Tongue oedema	0 (0%)	0 (0%)	7 (4%)	9 (2%)
Eye pruritus	3 (6%)	3 (3%)	7 (4%)	7 (2%)
Seriousness of AEs (% of n, % of E)				

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	MT-06			
	Placebo, n=338		12 SQ-HDM, n=318	
	n (%)	E (%)	n (%)	E (%)
SAE	8 (2%)	8 (2%)	0 (0%)	0 (0%)
Non-SAE	151 (45%)	319 (98%)	213 (67%)	681 (100%)
AEs leading to discontinuation (% of n, % of E)				
Yes	7 (2%)	8 (2%)	13 (4%)	28 (4%)
No	151 (45%)	319 (98%)	207 (65%)	653 (96%)
Action taken (% of n, % of E)				
None	135 (40%)	277 (85%)	195 (61%)	595 (87%)
Temp. int	29 (9%)	42 (13%)	38 (12%)	59 (9%)
IMP disc.	7 (2%)	8 (2%)	13(4%)	27 (4%)
Outcome				
Recovered	150 (44%)	308 (94%)	211 (66%)	671 (99)
Rec. seql.	1(<1%)	1 (<1%)	0 (0%)	0 (0%)
Not rec	13 (4%)	15 (5%)	6 (2%)	8 (1%)
Unknown	3(<1%)	3 (<1%)	2 (<1%)	2 (<1%)

n: number of subjects with events, %n: % of subjects in treatment group of analysis set with events, E:number of events, %E: % of all events in treatment group, AE: adverse event, SAE: serious AE, Temp.int.: IMP temporarily interrupted, IMP disc.: IMP discontinued, Rec. seql.: recovered with sequelae, not rec.: subject not recovered at the end of trial

Abbreviations: SQ, standardised quality; HDM, house dust mite; AE, adverse event; IMP, investigational medicinal product; SAE, serious adverse event; TRAE, treatment-related adverse event.

TRAEs were reported in 15% of subjects (n=50) from the placebo group and 53% (n=167) from the 12 SQ-HDM group. The 3 most frequently reported TRAEs were oral pruritus, throat irritation, and mouth oedema. The most common adverse events had a median onset time 1 or 2 days after start of the treatment, with very few new AEs starting at a later time point. The majority of the most frequent TRAEs had a median onset within 1 to 15 minutes.

The majority of all TRAEs were mild or moderate in severity with no dose response trend in the outcome of TRAEs. Only 9 out of the 30 reported severe AEs were assessed as treatment-related. These 9 treatment-related severe AEs were reported in 3 patients receiving 6 SQ-HDM and 5 patients receiving 12 SQ-HDM. No severe TRAEs were reported in the placebo group.

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12 (1%) subjects in the overall trial population reported a total of 12 SAEs: 8 subjects from the placebo group and 4 subjects from the 6 SQ-HDM group. No SAEs were reported in the 12 SQ-HDM group.

Most of the AEs (87% in the 12 SQ-HDM group, and 85% in the placebo group) did not lead to any specific action; treatment was temporarily interrupted in 9% and 13% of events in the 12 SQ-HDM and placebo group, respectively. Treatment was discontinued due to AEs in 13 (4%) patients in the 12 SQ-HDM group and in 7 (2%) patients in the placebo group.

No deaths occurred during the trial, and no AEs were reported as systemic allergic reaction in either of the groups. Only one subject from the 12 SQ-HDM group received adrenaline after the first IMP intake due to mild laryngeal oedema (no vital risk). The subject subsequently continued the trial and completed the trial without any other AEs except for mild oral pruritus.

B.2.10.3 P001

As previously stated, the P001 trial actively solicited local AEs from subjects. A total of 1481 treated subjects (743 with 12 SQ-HDM; 738 with placebo) were included in the safety analyses. 3 cross-treated subjects were originally randomised to placebo but received 12 SQ-HDM for a period of time during the trial. Therefore, for the safety analysis, the number of subjects in the 12 SQ-HDM group increased and the number of subjects in the placebo group decreased by 3 subjects.

Overall, 1,215 (82%) patients in the P001 trial reported AEs. The number of subjects reporting AEs was higher in the 12 SQ-HDM group (676, 91%) compared with the placebo group (539, 73%) [35, 49]. An overview of AEs is presented in Table 60.

Table 60: Summary of adverse events in the P001 trial [35, 49]

	P001	
	Placebo, n=738	**12 SQ-HDM, n=743**
	n (%)	**n (%)**
All AEs	539 (73%)	676 (91%)
All TRAEs	301 (41%)	624 (84%)
Severity of all AEs		
Mild	-	-
Moderate	-	-

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	P001	
	Placebo, n=738	12 SQ-HDM, n=743
	n (%)	n (%)
Severe	-	-
Most common TRAEs (occurring in ≥2% of patients) (% of n)		
Throat irritation	162 (54%)	498 (80%)
Oral pruritis	105 (35%)	463 (74%)
Tongue pruritis	7 (2%)	35 (6%)
Oral paraesthesia	21 (7%)	68 (11%)
Lip swelling	16 (5%)	133 (21%)
Ear pruritis	84 (28%)	378 (61%)
Glossodynia	25 (8%)	114 (18%)
Nausea	33 (11%)	98 (16%)
Lip oedema	1 (%)	12 (2%)
Pharyngeal oedema	20 (7%)	106 (17%)
Swollen tongue	16 (5%)	119 (19%)
Diarrhoea	13 (4%)	34 (5%)
Oral pain	5 (2%)	22 (4%)
Upper abdominal pain	31 (10%)	82 (13%)
Mouth ulceration	19 (6%)	76 (12%)
Tongue ulceration	16 (5%)	94 (15%)
Dysgeusia	27 (9%)	67 (11%)
Seriousness of AEs (% of n)		
SAE	7 (1%)	11 (2%)
Non-SAE	-	-
AEs leading to discontinuation (% of n)		
Yes	19 (3%)	73 (10%)
No	-	-
Action taken (% of n)		
None	-	-
Temp. int	-	-
IMP disc.	-	-
Outcome (% of n)		
Recovered	-	-
Rec. seql.	-	-
Not rec	-	-
Unknown	-	-

N: number of subjects (safety set), n: number of subjects with events, %n: % of subjects in treatment group of analysis set with events, EAE: adverse event, SAE: serious AE, Temp.int.: IMP temporarily interrupted, IMP disc.: IMP discontinued, Rec.seql.: recovered with sequelae, not rec.: subject not recovered at the end of trial

Abbreviations: SQ, standardised quality; HDM, house dust mite; AE, adverse event; IMP, investigational medicinal product; SAE, serious adverse event; TRAE, treatment-related adverse event.

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TRAEs were reported in 41% of subjects (n=301) from the placebo group, and 84% (n=624) from the SQ-HDM group. The most frequently reported TRAEs were throat irritation, oral pruritus, and ear pruritus; each of these were more frequently reported in the 12 SQ-HDM group than in the placebo group. The majority of initial TRAEs in both treatment groups occurred within 7 days of the first dose of study drug.

The majority of TRAEs were assessed by the investigators as mild or moderate in intensity. A total of 15 subjects (1.0%) had at least 1 severe AE during the trial: 13 subjects in the 12 SQ-HDM group and 2 subjects in the placebo group. None of the severe TRAEs were serious.

A total of 18 (1.2%) subjects in the overall trial population reported with one or more SAEs: 7 (<1%) in the placebo group and 11 (2%) in the 12 SQ-HDM group.

A total of 92 (6.2%) subjects experienced an AE resulting in discontinuation from study drug: 73 (9.8%) in the 12 SQ-HDM group and 19 (2.6%) in the placebo group.

No deaths occurred during the trial, and no AEs were reported as systemic allergic reaction in either of the groups.

No major differences were found in the incidence of AEs between subjects aged 12 to 18 years and those aged at least 18 years (see Table 61). Please note, the small number of subjects within the subgroups limits the interpretation of these data [35, 49].

Table 61: Summary of adverse events in the P001 trial by age[35, 49]

	P001					
	12 to 18 n (%)		18 to 50 n (%)		50+ n (%)	
	Placebo n=95	12 SQ-HDM n=94	Placebo n=524	12 SQ-HDM n=530	Placebo n=119	12 SQ-HDM n=119
All AEs	75 (79%)	89 (95%)	373 (71%)	485 (92%)	91 (77%)	102 (86%)
All TRAEs	45 (48%)	87 (93%)	211 (40%)	446 (84%)	45 (38%)	91 (77%)
AEs leading to discontinuation (% of N)						
AE, Yes	1 (1%)	9 (10%)	16 (3%)	59 (11%)	2 (2%)	6 (5%)
TRAE, Yes	0 (0%)	9 (10%)	5 (1%)	49 (9%)	1 (1%)	4 (3%)

Abbreviations: SQ, standardised quality; HDM, house dust mite; AE, adverse event; TRAE, treatment-related adverse event.

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B.2.10.4 TO-203-31

Overall, 766 (93%) patients in the TO-203-31 trial reported AEs. The number of subjects reporting AEs was higher in the 12 SQ-HDM treatment group (266, 96%) than the placebo group (246, 89%)[37, 50]. An overview of these AEs is presented in Table 62.

Table 62: Summary of adverse events in the TO-203-31 trial[37, 50]

	TO-203-31			
	Placebo, n=274		12 SQ-HDM, n=276	
	n (%)	E (%)	n (%)	E (%)
All AEs	246 (89%)	1091 (100%)	266 (96%)	1495 (100%)
All TRAEs	72 (26%)	138 (13%)	185 (67%)	413 (28%)
Severity of all AEs (% of n, % of E)				
Mild	168 (61%)	964 (88%)	175 (63%)	1334 (89%)
Moderate	73 (27%)	123 (11%)	87 (32%)	154 (10%)
Severe	2 (<1%)	4 (<1%)	4 (1%)	7 (<1%)
Most common TRAEs (occurring in ≥2% of patients) (% of nTRAE, % of ETRAE)				
Throat irritation	2 (3%)	2 (1%)	33 (18%)	35 (8%)
Oral pruritis	5 (7%)	5 (4%)	37 (20%)	39 (9%)
Oedema mouth	3 (4%)	3 (2%)	40 (22%)	46 (11%)
Oral paraesthesia	2 (3%)	2 (1%)	28 (15%)	29 (7%)
Lip swelling	0 (0%)	0 (0%)	8 (4%)	9 (2%)
Ear pruritis	1 (1%)	1 (1%)	25 (14%)	26 (6%)
Swollen tongue	0 (0%)	0 (0%)	9 (5%)	10 (2%)
Lip pruritis	0 (0%)	0 (0%)	6 (3%)	6 (1%)
Oral discomfort	11 (15%)	11 (8%)	57 (31%)	66 (16%)
Stomatitis	7 (10%)	10 (7%)	5 (3%)	6 (1%)
Abdominal discomfort	0 (0%)	0 (0%)	5 (3%)	5 (1%)
Oropharyngeal discomfort	11 (15%)	11 (8%)	28 (15%)	34 (8%)
Seriousness of AEs (% of n, % of E)				
SAE	11 (4%)	13 (1%)	10 (4%)	13 (1%)
Non—SAE	-	1078 (99%)	-	1482 (99%)
AEs leading to discontinuation (% of n, % of E)				
Yes	7 (3%)	11 (1%)	14 (5%)	28 (2%)
No	-	1080 (99%)	-	1467 (98%)
Action taken (% of n, % of E)				
None	-	-	-	-
Temp. int	8 (3%)	13 (1%)	5 (%2%)	11 (1%)
IMP disc.	7 (3%)	11 (1%)	14 (5%)	28 (2%)
Outcome				

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	TO-203-31			
	Placebo, n=274		12 SQ-HDM, n=276	
	n (%)	E (%)	n (%)	E (%)
Recovered	-	-	-	-
Rec. seql.	-	-	-	-
Not rec	-	-	-	-
Unknown	-	-	-	-

n: number of subjects with events, %n: % of subjects in treatment group of analysis set with events, E:number of events, %E: % of all events in treatment group, AE: adverse event, SAE: serious AE, Temp.int.: IMP temporarily interrupted, IMP disc.: IMP discontinued, Rec. seql.: recovered with sequelae, not rec.: subject not recovered at the end of trial
Abbreviations: SQ, standardised quality; HDM, house dust mite; AE, adverse event; IMP, investigational medicinal product; SAE, serious adverse event; TRAE, treatment-related adverse event.

TRAEs were reported in 26% of subjects (n=72) from the placebo group and 67% (n=185) from the 12 SQ-HDM group. The 3 most frequently reported TRAEs were oral discomfort, mouth oedema, and oral pruritis. Of the TRAEs, 52.1% (480/922 events) occurred within 2 weeks after the start of study treatment and 66.3% (611/922 events) occurred within 4 weeks. The median time to the first onset of common TRAEs related to oral findings was 0.0 to 35.0 days. The median duration of these TRAEs was 4.0 to 99.5 days.

No severe TRAEs occurred in the active group. Of the TRAEs in the study, 95.3% were mild. A causal relationship to IMP was ruled out for all SAEs except for 3 events in 1 subject in the placebo group. No deaths occurred in the study.

Treatment was discontinued due to AEs in 14 (5%) patients in the 12 SQ-HDM group and in 7 (3%) patients in the placebo group.

B.2.10.5 TO-203-32

Overall, 820 (86.7%) patients in the TO-203-32 trial reported AEs. The number of subjects reporting AEs was higher in the 12 SQ-HDM treatment group (284; 94%) than the placebo group (256’ 80%) [38, 51]. An overview of these AEs is presented in Table 63.

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Table 63: Summary of adverse events in the TO-203-32 trial[38, 51]

	TO-203-32			
	Placebo, n=319		12 SQ-HDM, n=314	
	n (%)	E (%)	n (%)	E (%)
All AEs	256 (80%)	789 (100%)	284 (94%)	1196 (100%)
All TRAEs	54 (17%)	87 (11%)	200 (64%)	447 (37%)
Severity of all AEs (% of n, % of E)				
Mild	232 (73%)	759 (96%)	254 (81%)	1156 (97%)
Moderate	24 (8%)	30 (4%)	30 (10%)	40 (3%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Most common TRAEs (occurring in ≥2% of patients) (% of nTRAE, % of ETRAE)				
Throat irritation	3 (6%)	3 (3%)	37 (19%)	42 (9%)
Oral pruritis	4 (7%)	4 (5%)	55 (28%)	65 (15%)
Oedema mouth	0 (%)	0 (%)	47 (24%)	61 (14%)
Oral paraesthesia	4 (7%)	4 (5%)	33 (17%)	34 (8%)
Ear pruritis	1 (2%)	1 (1%)	27 (14%)	28 (6%)
Oral discomfort	3 (6%)	3 (3%)	31 (16%)	35 (8%)
Stomatitis	7 (13%)	11 (13%)	9 (5%)	15 (3%)
Glossitis	0 (0%)	0 (0%)	7 (4%)	7 (2%)
Abdominal discomfort	0 (0%)	0 (0%)	7 (4%)	7 (2%)
Oropharyngeal discomfort	4 (7%)	4 (5%)	34 (17%)	34 (8%)
Oropharyngeal pain	2 (4%)	2 (2%)	7 (4%)	8 (2%)
Seriousness of AEs (% of n, % of E)				
SAE	3 (<1%)	4 (1%)	5 (2%)	5 (<1%)
Non—SAE	-	785 (99%)	-	1191 (100%)
AEs leading to discontinuation (% of n, % of E)				
Yes	6 (2%)	6 (1%)	4 (1%)	6 (1%)
No	-	783 (99%)	-	1190 (99%)
Action taken (% of n, % of E)				
None	-	-	-	-
Temp. int	5 (2%)	9 (1%)	14 (5%)	22 (2%)
IMP disc.	6 (2%)	6 (1%)	4 (1%)	6 (1%)
Outcome				
Recovered	-	-	-	-
Rec. seql.	-	-	-	-
Not rec	-	-	-	-
Unknown	-	-	-	-

n: number of subjects with events, %n: % of subjects in treatment group of analysis set with events, E:number of events, %E: % of all events in treatment group, AE: adverse event, SAE: serious AE, Temp.int.: IMP temporarily interrupted, IMP disc.: IMP discontinued, Rec. seql.: recovered with sequelae, not rec.: subject not recovered at the end of trial

Abbreviations: SQ, standardised quality; HDM, house dust mite; AE, adverse event; IMP, investigational medicinal product; SAE, serious adverse event; TRAE, treatment-related adverse event.

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TRAEs were reported in 17% of subjects (n=54) from the placebo group and 64% (n=200) from the 12 SQ-HDM group. The 3 most frequently reported TRAEs were mouth oedema, oral pruritis, and throat irritation. 53.2% (500/939 events) of ADRs occurred within 2 weeks after the start of study treatment and 72.8% (684/939 events) within 4 weeks. The median time to the first onset was 44 days for stomatitis; for other common ADRs related to oral findings, this time ranged from 1-18.5 days. The median duration of these events was 2 days for lip swelling, 8 days for stomatitis, and 56-80 days for other events.

No severe TRAEs occurred. Of all TRAEs reported in the trial, 97.3% (914/939 events) were mild. No deaths occurred in the study. A causal relationship to IMP was ruled out for all SAEs. One anaphylactic reaction occurred in 1 subject (0.3%) in the placebo group.

4 (1%) patients in the 12 SQ-HDM group and 6 (2%) patients in the placebo group discontinued their treatment due to AEs.

No major differences were found in the incidence of common TRAEs between subjects aged younger than 18 years and those aged at least 18 years[38, 51].

B2.11 Ongoing studies

Not applicable.

B2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Key findings on the clinical efficacy of 12 SQ-HDM

A reduction in symptoms (and correspondingly medication use) for AA and AR patients constitutes the pivotal aim of treatment, as allergy symptoms impose a significant burden of patient's HRQoL. The value of 12 SQ-HDM in improving patient symptomology and concomitant medication use has been demonstrated through a robust clinical trial programme including five Phase 3, placebo-controlled, RCTs conducted in diverse patient populations. This clinical evidence strongly supports the efficacy and safety of 12 SQ-HDM in the treatment of AR and AA patients:

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Treatment with 12 SQ-HDM is associated with a significant increase in the time to the first moderate or severe asthma exacerbation in AR and AA patients [36, 37, 47, 50].

As shown in MT-04, 12 SQ-HDM was associated with a statistically significant and clinically meaningful increase in the time to a first moderate or severe asthma exacerbation compared with placebo. This was measured by a 34% risk reduction (HR: 0.66 [95% CI, 0.47-0.93], p=0.02) of the probability of a moderate-to-severe asthma exacerbation in FAS population with 12 SQ-HDM treatment compared to placebo.

In the FAS population, there was a statistically significant treatment effect of 12 SQ-HDM over placebo for all three predefined analyses of the components of a moderate asthma exacerbation: deterioration in asthma symptoms (HR: 0.64 [95% CI 0.42,0.96], p= 0.03), increased SABA use (HR: 0.52 [95% CI 0.29,0.94], p=0.03), and deterioration in lung function (HR: 0.58 [95% CI 0.36,0.93] p=0.02).

In a subgroup analysis of the TO-201-31 study for the subgroup of subjects who required SABA during the baseline period, 12 SQ-HDM was associated with a reduction in the risk of a moderate or severe asthma exacerbation compared with placebo (HR: 0.71 [95% CI,0.49,1.02], p=0.061), This subgroup analysis reported by Tanaka et al., 2020 is more applicable and representative of the target population in this submission.

Treatment with 12 SQ-HDM is associated with a significant reduction in AR medication use and symptoms in AR patients compared with placebo, as measured by TCRS, TCS, DSS, and DMS scores in TO-203-32, MT-06 and P001 [34, 35, 38, 48, 49, 51].

12 SQ-HDM was associated with a significant reduction in AR medication use and symptoms in AR patients, as demonstrated by a significant reduction in the TCRS compared with placebo of 18% in the MT-06 trial, 19% in the T0-203-32, and 17% in the P001 trial.

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Further evidencing the impact on AR medication use and AR symptoms in AR patients, treatment with 12 SQ-HDM in the MT-06 trial was shown to result in a significant improvement in both DSS (FAS-MI absolute difference: 0.47 [95% CI 0.11,0.82], p=0.001) and DMS (FAS-MI absolute difference: 0.54 [95% CI 0.01,1.07], p=0.045) compared with placebo. These results are further supported by data from P001 showing a statistically significant and lower average rhinitis DSS in the 12 SQ-HDM group when compared with the placebo group during the final 8 weeks of treatment (Hodges-Lehmann estimate of shift, median: -0.60 [95% CI -1.00,-0.30], p<0.001). Additionally, in the TO-203-32 trial, the adjusted mean of rhinitis DSS in patients receiving 12 SQ-HDM was reduced compared with patients receiving placebo with an adjusted MD of -0.87 (p=0.0001) and a ratio of the adjusted mean of 0.82 [95% CI: 0.73,0.90], indicating a 18% relative reduction.

The average rhinitis DMS in the P001 trial was numerically lower in the 12 SQ-HDM group than in the placebo group (Hodges-Lehmann estimate of shift, mean: -0.15 [95% CI -0.35,0.05], p=0.154). However, the treatment difference was not statistically significant compared to placebo. This impact was similar in the TO-203-32 trial, where although the adjusted mean in 12 SQ-HDM group was reduced compared with that in the placebo group, no significant differences were found in analyses of the 12 SQ-HDM versus placebo (p=0.1244).

In the P001 and TO-203-32 trials, adults and adolescents both demonstrated a significant improvement in TCRS compared with placebo, regardless of age group, suggesting similar efficacy across the two groups. In P001, for adults, a 19.2% reduction in TCRS was shown for 12 SQ-HDM compared with placebo (Hodges-Lehmann estimate of shift: -0.9 [95% CI -1.30, -0.40]). For adolescents, a 22.4% reduction in TCRS was shown for 12 SQ-HDM compared with placebo (Hodges-Lehmann estimate of shift: -1.0 [95% CI -2.00,-0.10])[35, 49]. The TO-203-32 study reports that a relative difference of 17% (adjusted MD: -0.88), 16% (adjusted MD: -0.77), and 22% (adjusted MD: -1.11) for 12 SQ-HDM compared to placebo can be observed in the 12-18, 18-30, and 30-40 age subgroups, respectively.

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Treatment with 12 SQ-HDM is associated with a significant improvement in the quality of life of AR patients with or without AA, as measured by RQLQ, VAS scores, AQLQ, and JRQLQ in MT-06, P001, MT-04, and TO-203-32 [34-36, 38, 47-49, 51].

As shown in MT-06, 12 SQ-HDM is associated with a significant improvement in the QoL of AR patients compared with placebo when added to symptom-relieving medications, as measured through a reduction in patients' RQLQ score (AD: 0.19 [95% CI 0.02-0.37], p=0.031), with this improvement evident after 24 weeks (as shown in Figure 17). This significant difference in overall RQLQ score for AR patients treated with 12 SQ-HDM was also true for several RQLQ domains, with significant improvement versus placebo being demonstrated for nasal symptoms, non-nose/eye symptoms, practical problems, and sleep impairment.

In addition, subjects from the 12 SQ-HDM group in P001 reported fewer symptoms on the VAS compared to the placebo group. These results correspond with the reduction in the DSS also observed in the 12 SQ-HDM-treated subjects. Treatment with 12 SQ-HDM was associated with a significant improvement ($p<0.001$) in patient QoL (as measured by average AR/ARC VAS scores). However, the result cannot be considered confirmatory due to the prespecified multiplicity control strategy for this trial.

For the analysis of asthma QoL in the MT-04 trial, more subjects in the 12 SQ-HDM group had a clinically relevant improvement in AQLQ(S) score than in placebo at Visit 13 (55% for 12 SQ-HDM and 47% for placebo) (12 SQ-HDM OR: 0.97 [95% CI, 0.61-1.53]). Notably, in the analysis which controlled for change from baseline in ICS, there were no statistically significant differences between the groups in the proportion of subjects with improvement.

In TO-203-32, the mean JRQLQ No.1 score was lower in the 12 SQ-HDM group compared with the placebo group in 6 categories, with significant differences in scores in 4 of the categories (daily life [p=0.0147], outdoor [p=-.0251], sleep [p=0.005], and body [p=0.0223]).

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Treatment with 12 SQ-HDM is associated with elevated Dermatophagoides pteronyssinus and Dermatophagoides farinae IgG4 levels across the 5 pivotal trials [34-38, 47-51].

The presence of antibodies against the immunoglobulin IgG4 is associated with prolonged elevated IgG-associated IgE- antibody blocking activity, a marker of long-term tolerance after discontinuation of immunotherapy. From baseline after treatment with 12 SQ-HDM across the MT-04, MT-06, P001, TO-203-31, and TO-203-32 trials, there were almost no changes from baseline in the placebo groups over the trial durations in specific IgG4 levels, and significant increases in the levels of both measured HDM species, Dermatophagoides pteronyssinus and Dermatophagoides farinae. The difference between 12 SQ-HDM and placebo was statistically significant at all visits after initiation of treatment for the MT-06 trial, and after 4 weeks of treatment in the MT-04 trial.

B.2.12.2 Key findings on the clinical safety of 12 SQ-HDM

As shown in all 5 key clinical studies, 12 SQ-HDM is well-tolerated, with minimal TEAEs, SAEs and AE-related discontinuation [34-38, 47-51].

Across all five pivotal trials, the number of subjects reporting AEs was higher in the 12 SQ-HDM group compared with the placebo group (MT-04: 79% vs 63%; MT-06: 67% vs 46%; P001: 91% vs. 73%; TO-203-31: 96.4% vs 88.7%; TO-203-32: 90.4% vs 80.3%). The most commonly experienced AEs with 12 SQ-HDM treatment were mild, transient local application site reactions, with the majority related to treatment administration.

12 SQ-HDM TRAEs were minimal. There was a higher number of TRAEs reported in the 12 SQ-HDM groups than in placebo (MT-04: 46% vs 17%; MT-06: 67% vs 29%; P001: 84% vs 40.8%; TO-203-31: 67% vs 26%; TO-203-32: 64% vs 17%).

In MT-04, the number of patients who experienced SAEs with 12 SQ-HDM treatment was low (2 for placebo and 1 for 12 SQ-HDM). In MT-06, no patients experienced SAEs with 12 SQ-HDM treatment, compared with 8 patients in the placebo group. In P001, TRAEs occurred in 84% of 12 SQ-HDM treated patients compared with 40.8% of patients from the placebo group. A total of 18 (1.2%) subjects in the overall trial

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population reported with one or more SAEs; 7 (<1%) in the placebo group, and 11 (2%) in the 12 SQ-HDM group. In TO-203-31, no severe TRAEs occurred in the 12 SQ-HDM group. A causal relationship to IMP was ruled out for all SAEs except for 3 events in 1 subject in the placebo group. In TO-203-32, no severe TRAEs occurred.

Treatment with 12 SQ-HDM was discontinued due to AEs in 9% of patients in the MT-04 trial, 4% of patients in the MT-06 trial, 10% in the P001 trial, 5% of patients in the TO-203-31 trial, and 1% of patients in the TO-203-32 trial. In addition, no deaths or systemic allergic reaction events were observed during the trials.

B.2.12.3 Strengths and limitations of the clinical evidence base for 12 SQ-HDM

The efficacy of 12 SQ-HDM has been established in the robust MT-04, MT-06, TO-203, and P001 studies, which were all randomised, multicentre, parallel-group, double-blind, placebo-controlled Phase 3 trials [34-38, 47-51].

The MT-04, MT-06, TO-203 and P001 trials were large confirmatory studies which generated robust data on both adolescent and adult ARD populations, with minimal risk of bias from randomisation. These studies can be categorised as in-field trials, having been in a relevant clinical setting. Further, these studies provide data for clinically relevant endpoints, such as time to first asthma exacerbation and the risk for a moderate-to-severe asthma exacerbation, as a measure of patient asthma control and future risk.

Throughout the MT-04, MT-06, TO-203, and P001 trials there was adequate concealment of treatment allocation and successful blinding, wherein patients, investigators, study staff, and the sponsor were blinded to the study drug assignment, only breaking the blind in cases of medical emergency. In MT-04, all analyses defined after unblinding of the trial were considered exploratory post-hoc analyses.

A statistically significant difference was found with 12 SQ-HDM treatment compared to placebo for the primary endpoints across all four trials. The MT-04 trial was not sufficiently powered to investigate its secondary endpoints: the QoL as measured by AQLQ and the time to a moderate or severe asthma exacerbation. The MT-06, TO-

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203-32, and P001 trials found a significant reduction in their primary endpoint. The exploratory endpoint, the change in IgE and IgG4 levels, was also found in both P001 and MT-06 to have a significant increase on 12 SQ-HDM treatment compared to placebo.

In terms of limitations of the clinical evidence base, the current 12 SQ-HDM trials do not assess the full 3 years of treatment as recommended in clinical guidelines or provide follow-up data after treatment cessation. Real-world evidence for AITs is provided by the CARIOCA study [52], Reiber et al., 2021 [53], Sidenius et al., 2021 [54], and the REACT study [55], although these studies face limitations with regards to lack of comparator treatment arms and use of AIT products for other sensitisations.

One of the main limitations of MT-04 was an operational definition of a moderate asthma exacerbation that appears to have been used for the first time. Although being applicable to a trial setting, the establishment of a baseline and the twice daily diary recordings will have limited usability in clinical practice. Additionally, the trial was not powered for comparative assessment of AEs [36, 47]. A second limitation is the multiple imputation strategy used in MT-04 and MT-06 to analyse the primary endpoint, TCRS. Missing data in all treatment groups was replaced with the observed data of the TCRS randomly selected in the placebo group (i.e., it is assumed that all patients with missing data of the primary endpoint have no treatment effect). This represents a conservative approach for statistical analysis that introduces an inherent dilution of the treatment effect [34, 48] .

The P001 study actively solicited AEs, making a comparative assessment of the safety outcomes with the European and Japanese trials, which used recorded unsolicited AEs, limited [35, 49].

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B.3 Cost effectiveness

B3.1 Published cost-effectiveness studies

An SLR was undertaken in March-April 2023 to identify published health economic evaluation studies associated with HDM-induced AA and/or AR. Full details of the SLR search strategy, study selection process, and results are presented in Appendix G. MEDLINE, Embase, Cochrane Library ALL EBM Reviews, and Econlit were searched, in addition to searching of the CEA registry and the NICE website. Records were eligible for inclusion if they reported an economic evaluation or included summary cost and health outcomes in an adult or adolescent population with HDM-induced AA and/or AR. Studies published as abstracts or conference presentations were not included, as they rarely provide adequate data.

The SLR retrieved a total of 507 records, of which, 15 studies met the inclusion criteria after full-text screening [61-75]. 8 studies conducted a cost-effectiveness analysis [62, 64-66, 68, 69, 72, 74], 3 studies conducted a cost-minimisation analysis [61, 63, 71], 1 study conducted a cost-benefit analysis[70], and 3 studies conducted other economic analyses [67, 73, 75]. Of the 8 cost-effectiveness analyses, 5 studies [61, 64-66, 69] conducted a cost-utility analysis; these are summarised in Table 64.

The evaluations reported by Hahn-Pederson et al., 2016 [66], Green et al., 2017 [64], and Green et al., 2019 [65] evaluated the cost-effectiveness of 12 SQ-HDM in patients with AA and/or AR using data from the MT-04 and MT-06 trials. These analyses were funded and developed by ALK. A separate model was commissioned by ALK, which has been developed to address the decision problem of the current appraisal.

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Table 64: Summary list of published cost-effectiveness studies

Study	Country	Summary of model (model structure)	Patient population	QALYs	Costs	ICER (per QALY gained)
Bjorstad et al., 2017 [61]	Sweden	Cost-minimisation analysis. 3-year time horizon Decision tree model	SLIT vs SCIT HDM AR with or without AA, or HDM AR+AA	N/A	3-year total costs €5,129 for SLIT €11,933 for SCIT	Cost saving equal to €6,804 over 3 years
Green et al., 2017 [64]	Germany	Cost-effectiveness analysis. 9-year time horizon Markov model	MT-06 12 SQ-HDM vs placebo HDM AR	Intervention = 6.96 QALYs Comparator = 6.65 QALYs	Intervention = €3,598 Comparator = €1,301	€7,519/QALY
Green et al., 2019 [65]	Poland, Czech Republic, and Slovakia	Cost-effectiveness analysis. 5-year time horizon Markov model	MT-04 12 SQ-HDM vs placebo HDM AA+AR	Inc QALYs: Czech Republic = 0.37 Poland = 0.36 Slovakia = 0.34	Inc costs: Czech Republic = €2.722 Poland = €2,675 Slovakia = €3,013	Czech Republic = €7,455/QALY Poland = €7,492/QALY Slovakia = €8,814/QALY
Hahn-Pedersen et al., 2016 [66]	Germany	Cost-effectiveness analysis. 9-year time horizon Markov model	MT-04 12 SQ-HDM vs placebo HDM AA+AR	Intervention = 6.16 QALYs Comparator = 5.50 QALYs	Intervention = €5,658 Comparator = €2,985	€4,041/QALY
Parra-Padilla et al., 2021 [69]	Columbia	Cost-effectiveness analysis. 10-year time horizon Markov model	SCIT vs ICS HDM AR with or without AA, or HDM AR+AA	Inc QALYs = 0.37	Inc. costs = $828	Avert 847 exacerbations per 1,000 patients

Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; HDM, house dust mite; AR, allergic rhinitis; AA, allergic asthma; SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy; ICS, inhaled corticosteroid.

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B3.2 Economic analysis

A *de novo* economic model was developed to assess the cost-effectiveness of 12 SQ-HDM compared with established clinical management for treating HDM-induced AA and/or AR. As described above, the modelling approach and model structures of other previously published cost-effectiveness model were considered during the development of the model for this appraisal. The key features of the economic analysis and their justifications are presented in Table 65.

Table 65: Key features of the economic analysis

Factor	Chosen values	Justification
Model structure	3-state Markov model for both AA+AR and AR only population	Cohort Markov models have been used in previously published cost-effectiveness analyses (see Table 64). The mutually exclusive health states appropriately capture the heterogeneity of HRQoL and healthcare costs incurred in different AA and AR severity states.
Time horizon	Lifetime	NICE reference case [76]. Considered to reflect that AA and AR is chronic and expected to continue for the duration of patients' lifetime.
Comparator	Established clinical management, referred to as SOC AA+AR and SOC AR	NICE final scope. Considered as treatments for AR and AA are bundled and aimed at managing symptoms. There are currently no NICE guidelines for treating HDM AR. NICE guideline [NG80] recommends a stepwise approach for treating asthma, with the aim of achieving disease control. Further detail on comparators is discussed below.
Source of utilities	Post-hoc analysis of key trial data	In line with NICE reference case, post-hoc analysis of EQ-5D data (MT-06) and SF-36 data (MT-04) collected during the trials is used.
Source of costs	NHS and personal social services (PSS) perspective; sourced from national databases including British National Formulary, National Cost Collection, and Personal Social	NICE reference case [76]

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	Services Research Unit (PSSRU)	
Discounting	3.5% per year for costs, QALYs, and life years	NICE reference case [76]
Half-cycle correction	Applied in each model cycle (annual cycles)	NICE reference case [76].
Abbreviations: NHS, National Health Service; NICE, National Institute for Health And Care Excellence; CKD-aP, chronic kidney disease-associated pruritus; QALY, quality-adjusted life year; PSS, personal social services; PSSRU, Personal Social Services Research Unit; SOC, standard of care.		

B.3.2.1 Perspective

In accordance with current NICE guidance [76], a cost-utility analysis considering lifetime quality-adjusted life years (QALYs) and costs from a current UK NHS and PSS perspective was undertaken. Costs and QALYs were discounted at a rate of 3.5% per year.

B.3.2.2 Patient population

As detailed in Section B.1, 12 SQ-HDM is licensed for the treatment of patients aged 12 to 65 years (adolescents and adults) with a confirmed diagnosis of persistent moderate-to-severe HDM AR despite the use of symptom-relieving medication, and patients aged 18 to 65 years (adults) with a confirmed diagnosis of HDM AA not well-controlled by ICS and associated with mild-to-severe HDM AR. For the purposes of this evaluation, and in accordance with the NICE final scope, these two distinct populations have been modelled independently.

The clinical evidence supporting the use of 12 SQ-HDM in the AR population is provided by the MT-06, P001, and TO-203-32 trials. For all three trials, the efficacy results evidence a reduction in the burden of AR, as demonstrated by a significant reduction in the TCRS compared with placebo of 18% in the MT-06 trial, 19% in the T0-203-32, and 17% in the P001 trial.

The clinical evidence supporting the use of 12 SQ-HDM in the AA+AR population is provided by the MT-04 and TO-203-31 trials. In the MT-04 trial, the efficacy results evidence a reduction in the burden of AA, as demonstrated by a statistically significant 31% risk reduction (HR: 0.69 [95% CI, 0.50-0.96], p=0.03) of the

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probability of a moderate-to-severe asthma exacerbation compared to placebo. The TO-203-31 trial did not demonstrate a reduction in exacerbations versus placebo. However, due to differences in Japanese guidelines (12) for asthma, the inclusion of subjects considered to have sufficiently controlled asthma according to GINA criteria (used in the UK and Europe) may be the reason the TO-203-31 trial did not meet this endpoint (11,14). Tanaka et al., 2020 conducted a subgroup analysis on the primary endpoint for the subgroup of subjects who required SABA during the baseline period to align with European guidelines more closely. In this subgroup, 12 SQ-HDM was associated with a reduction in the risk of a moderate or severe asthma exacerbation compared with placebo (HR: 0.71 [95% CI, 0.49-1.02], p=0.061), similar to the results in the European MT-04 trial.

The starting cohort age and proportion by sex are used as inputs in the model to account for variations in costs and health outcomes due to demographic factors. To be consistent with the efficacy data used in the model, these inputs are informed by the MT-04 and MT-06 trial populations. There were no meaningful differences in the mean age and proportion by sex across the AA+AR trials or the AR trials, and neither age or sex is anticipated to be prognostic of health outcomes. The baseline characteristics applied in the model and across the key trials are summarised in Table 66.

Table 66: Baseline characteristics applied in the model

	AA+AR population		AR population		
	MT-04*	**TO-203-31**	**MT-06***	**TO-203-32**	**P001**
Mean age (years)	33.4	38.2	32.3	27.0	35.1
Proportion male	51.7%	51.1%	49.8%	45.9%	41.0%

* Used as model baseline characteristic
Abbreviations: AA, allergic asthma; AR, allergic rhinitis.

B.3.2.3 Intervention and comparator

The proposed intervention is 12 SQ-HDM administered sublingually as a tablet daily. 12 SQ-HDM does not require any special storage conditions and is suitable for at-home sublingual administration following administration of the first tablet under

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physician supervision (to enable discussion and possible treatment of any immediate side effects). It is proposed that 12 SQ-HDM be used as an adjunct to current established clinical management. Onset of the clinical effect of 12 SQ-HDM is to be expected 8–14 weeks after initiation. International treatment guidelines and consensus statements refer to a treatment period of 3 years for AIT to achieve disease modification after its cessation [3, 4]. If no improvement is observed during the first year of treatment with 12 SQ-HDM, there is no indication for continuing treatment.

The proposed comparator is established clinical management without 12 SQ-HDM. For the purposes of this analysis, established clinical management has been defined for two distinct populations: adults with AA+AR, and adolescents and adults with AR.

The NICE Clinical Knowledge Summary on AR [28] incorporates recommendations from the BSACI [29] and the ARIA international guidelines (2016 revision) [9] for the diagnosis and management of patients with AR. For patients with mild-to-moderate intermittent or mild persistent symptoms, oral or intranasal antihistamines are the first line of therapy. For patients with moderate-to-severe persistent symptoms, or those for whom initial treatment is ineffective, intranasal corticosteroids are recommended. If symptoms continue to persist despite these treatments, combination therapies can be explored, including combinations of oral antihistamines and intranasal corticosteroids, or combined preparations of intranasal corticosteroids and intranasal antihistamines [9, 28].

The GINA guidelines are used for the diagnosis and management of AA and are based on the concept of control-based management [31]. The NICE guideline (NG80) recommends a similar stepwise approach for treatment and management of asthma. The BTS and Scottish Intercollegiate Guidelines Network (SIGN) [77] guideline provides recommendations based on current evidence for best practice management of asthma. A joint NICE/BTS/SIGN guideline for the diagnosis, monitoring, and management of chronic asthma is due to be released in July 2024. Pharmacotherapies for asthma are typically classified as controller medication for control of symptoms, reliever/rescue medication for short-term symptom relief, and add-on therapies for difficult-to-treat asthma. Controller and add-on therapies can

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include long-acting beta-2 agonist (LABA), ICSs, and leukotriene antagonists. For severe asthma, biologics may be considered, but this is outside the scope of this appraisal. A summary of the recommended treatment options for adults and adolescents with asthma from the GINA, BTS/SIGN, and NICE guidelines is provided in Table 67. The GINA guidelines recommend treatment with HDM SLIT (12 SQ-HDM) as an other controller option under treatment Steps 2, 3, and 4. The BTS/SIGN guidelines do not recommend SLIT for the treatment of asthma in children or adults.

In the model, established clinical management has been bundled for the AA+AR and AR populations, using existing guidelines and input and validation from clinical experts elicited from an advisory board conducted in September 2023 [78].

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Table 67: Overview of asthma treatment guideline (GINA, BTS/SIGN, and NICE)

<table>
<tr><th></th><th>Severity definitions</th><th colspan="2">Recommended treatment options and steps for adult and adolescents†</th></tr>
<tr><td rowspan="2">GINA
2022</td><td rowspan="2">Mild asthma is currently defined as asthma that is well-controlled with as-needed ICS-formoterol, or with low dose ICE plus as-needed SABA
Moderate asthma is currently defined as asthma that is well-controlled with Step 3 or Step 4 treatment. E.g. with low or medium dose ICS-LABA in either treatment track
Severe asthma is defined as asthma that remains uncontrolled despite optimised treatment with high dose ICS-LABA</td><td>Reliever: ICS-formoterol as needed
1. Steps 1-2: as-needed low dose ICS-formoterol
2. Step 3: low dose maintenance ICS-formoterol
3. Step 4: medium dose maintenance ICS-formoterol
4. Step 5: add-on LAMA, consider high dose maintenance ICS-formoterol, consider anti-IgE, anti-IL5/5R/4R, anti-TSLP</td><td>Reliever: SABA as needed
1. Step 1: ICS whenever SABA taken
2. Step 2: low dose ICS
3. Step 3: low dose maintenance ICS-LABA
4. Step 4: medium/high dose maintenance ICS-LABA
5. Step 5: add-on LAMA, consider high dose maintenance ICS-LABA, consider anti-IgE, anti-IL5/5R/4R, anti-TSLP</td></tr>
<tr><td colspan="2">HDM SLIT can be considered as a controller option at Steps 2, 3, and 4 for the treatment of suboptimally controlled asthma with allergic rhinitis.</td></tr>
<tr><td>BTS/SIGN
2019</td><td>Mild asthma: no definition provided.
Moderate asthma: no definition provided.
Annex 3 notes PEF>50-75% of best or predicted.
Severe asthma defined as more than two asthma attacks a year or persistent symptoms with SABA use more than twice a week despite specialist-level therapy. Annex 3 notes PEF>33-50% of best or predicted.</td><td colspan="2">Reliever: SABA as needed
1. Regular preventative therapy: low dose ICS
2. Initial add-on therapy: low dose ICS-LABA
3. Additional therapy: medium dose ICS-LABA, consider adding LTRA
4. Specialist therapy: high dose ICS/LABA, consider adding LTRA, LAMA, and a theophylline.
5. Biologic therapy may be considered in eligible patients with high oral corticosteroid burden. NICE guidance on Omalizumab, Mepolizumab, Reslizumab, and Benralizumab to be considered.</td></tr>
<tr><td>NICE
2017</td><td>No definitions of mild, moderate, or severe asthma provided.</td><td colspan="2">Reliever: SABA as needed
1. First-line therapy: low dose ICS
2. Second-line therapy: low dose ICS plus LTRA
3. Next step therapy: low dose ICS-LABA with or without LTRA
4. Next step therapy: medium dose ICS-LABA with or without LTRA
5. Next step therapy: consider high dose ICS-LABA with or without LTRA, OR consider medium dose ICS-LABA with or without LTRA plus LAMA or theophylline
6. No commentary on specialist therapies including biologics and immunotherapies.</td></tr>
<tr><td colspan="4">NICE/BTS/SIGN joint guideline for the Diagnosis, Monitoring and Management of Chronic Asthma to be released July 2024
† Not all treatment options are available for adolescents.
Abbreviations: ICS, inhaled corticosteroids; SABA, short-acting β 2-agonist; LABA, long-acting beta agonist; NICE, national institute for health and care excellence; BTS, British thoracic society; SIGN, Scottish intercollegiate guidelines network; HDM, house dust mite; SLIT, sublingual immunotherapy; LTRA, leukotriene receptor antagonists; LAMA, long-acting muscarinic antagonists; TSLP, thymic stromal lymphopoietin; IL, interleukin; IgE, immunoglobulin E.</td></tr>
</table>

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B.3.2.4 Model structure

Two Markov models were constructed to calculate lifetime costs and QALYs for treatment with 12 SQ-HDM compared with established clinical management: one for the AA+AR population and one for the AR population. In a Markov model, a set of mutually exclusive health states are defined to describe what can happen to the population of interest over time. Possible transitions are defined between each of the health states, and the probability of each transition occurring within a defined period of time (a cycle) is assigned to each possible transition.

Both models comprise 3 core health states reflecting disease severity, from which patients can transition to a dead health state (absorbing state). Figure 25 and Figure 26 illustrate the model structure and the possible transitions between health states for the AR and AA+AR model, respectively.

For the AR population, the 3 health states are defined according to a modified version of the ARIA classification. In the original ARIA classification, disease severity was classified as either mild AR, or moderate/severe AR, and is defined on the basis of the presence or absence of impairment in any of the four HRQoL items: sleep, daily activities/sport, work/school, and troublesome symptoms [3]. This definition was used in the inclusion criteria for the MT-06 trial with subjects' clinical history to be consistent with moderate/severe persistent AR.

Valero et al., 2007 developed a modified version of the ARIA classification that discriminates moderate from severe AR [11]. Based on the items in the ARIA severity classification, patients with mild AR have no affected items, patients with moderate AR have 1 to 3 affected items, and patients with severe AR have all 4 affected items. At baseline and during the last 2 weeks of the efficacy assessment period in the MT-06 trial, subjects were asked about the presence of 3 ARIA QoL items (sleep disturbance, impairment of daily activities/sport, and impairment of work or school). To complete the 4th item of the ARIA classification (troublesome symptoms), the DSS was used, as recorded in the MT-06 trial. This is discussed further in Section B.3.4.

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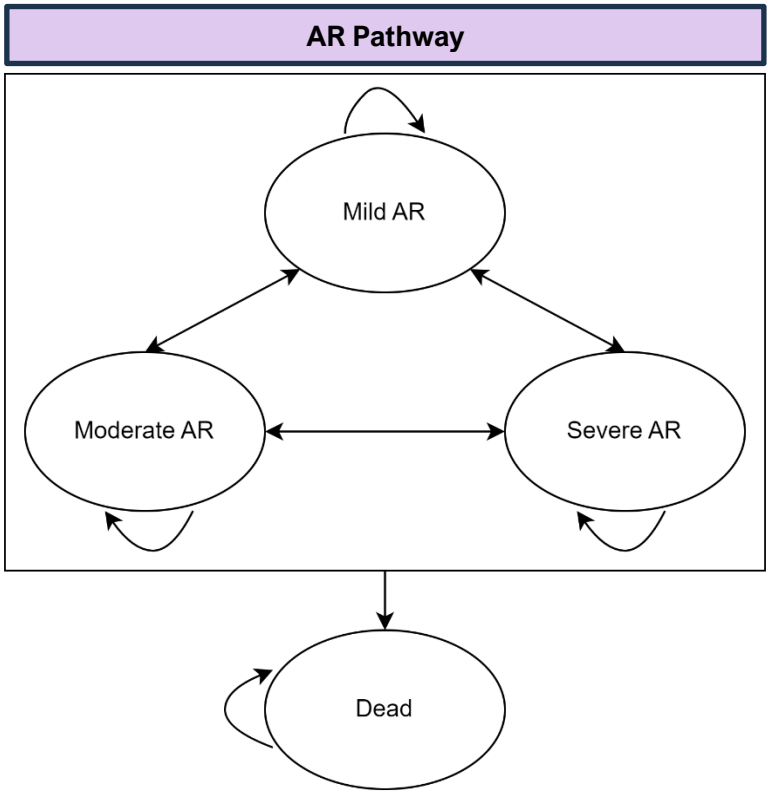
Figure 25: AR model schematic



For the AA+AR population, the 3 health states were defined to reflect asthma control according to the GINA guidelines. According to the guidelines, asthma management involves a continual cycle involving assessment, adjustment of treatment, and review. First, patients should be assessed based on their symptom control, as well as for future risk of exacerbations, decline in lung function, medication adverse effects including inhaler compliance and technique, and any comorbidities. Treatment strategies are adjusted based on this assessment, including treatment of comorbidities, non-pharmacologic strategies, and adjustment of asthma medication. The long-term goals of asthma management are to achieve good symptom control and maintain normal activity levels, as well as to minimise the future risk of exacerbations, persistent airflow limitation, and side effects of treatment [31]. The GINA guidelines define asthma control as well-controlled, partly controlled, or uncontrolled on the basis of answers to 4 questions relating to the presence of daytime asthma symptoms more than twice per week, night waking due to asthma, need for reliever/rescue treatment, and activity limitation due to asthma. In MT-04 trial, the level of asthma control was classified in GINA levels of control by

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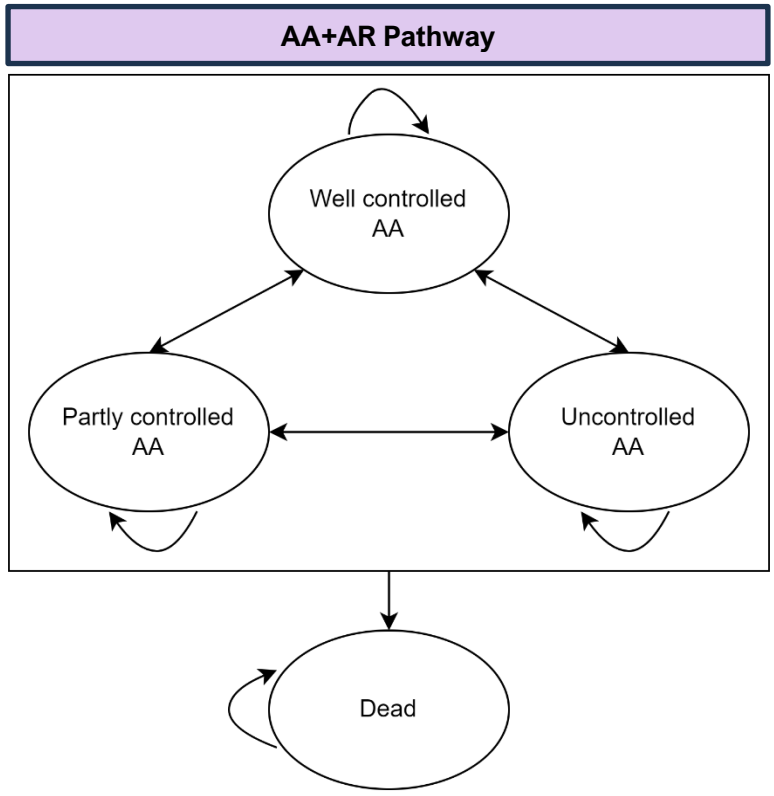
transforming results from the ACQ. Results from the ACQ were recorded throughout the trial, consisting of 5 questions related to symptoms (nocturnal wakening, morning symptoms, activity limitation, short of breath, wheeze), 1 question related to SABA use, and 1 question related to lung function (percentage of predicted FEV1). This is discussed further in Section B.3.4.

Figure 26: AA+AR model schematic



The model structures are designed to reflect current UK clinical practice in the management of AR and AA. Although international treatment guidelines refer to a treatment period of 3 years for AIT to achieve disease modification, during the key trials evidencing 12 SQ-HDM, patients discontinued treatment due to AEs and other reasons. In the models, patients who discontinue treatment with 12 SQ-HDM continue to receive established clinical management. As demonstrated in the Phase 2 P003 trial, statistically significant improvements in efficacy could be observed as early as 8 weeks following initiation of 12 SQ-HDM [42, 43]. Furthermore, during an advisory board, it was noted that patients who discontinue AIT treatment early may still receive treatment benefit. To reflect this, the models allow for a proportion of

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patients to continue receiving the benefit associated with 12 SQ-HDM depending on the year in which treatment with 12 SQ-HDM is discontinued.

In each model cycle, people accrue costs and QALY benefits associated with the relevant health state and treatment arm. In the base case, the model estimates total lifetime costs and QALYs for each treatment arm, with the summary measure presented as an ICER. A half-cycle correction is applied in the model for all model cycles.

The cycle length of the model was 1 year. A shorter cycle length was considered as it could be expected that asthma control and rhinitis severity may fluctuate on a more frequent basis. However, given the uncertainty in long-term effectiveness, variation in the transition of patients through shorter cycles and beyond Year 1 could be compounded and lead to unreliable estimates of disease control and severity in the long run. This is a noted limitation of the model: by assuming an average level of disease control or severity throughout the year, health care costs and HRQoL impact may be underestimated as patients may fluctuate between state of control or severity throughout the year. However, it is expected that the overall proportion of people in each health state will be more appropriate, and it is not anticipated to result in any overall net bias as patients on average will spend correct time in each health state.

B3.3 Clinical parameters and variables

B.3.3.1 Efficacy, disease control

The data informing estimate of treatment efficacy in the model has been derived from the MT-04 trial for the AA+AR population, and the MT-06 trial for the AR population. As noted, the model structures were designed to be generalisable to UK clinical practice. In doing so, for the AR population, a structure using the ARIA classification was designed. To estimate treatment-specific transition probabilities to match the ARIA classifications, data was required on the presence or absence of impairment in the four HRQoL items – sleep, daily activities/sport, work/school, and troublesome symptoms – at baseline and trial end. The primary endpoint of the 3 AR trials (MT-06, P001, and TO-203-32) was the average TCRS score during the efficacy assessment period. Although data on the DSS (which forms part of the

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TCRS score) could be used to estimate the troublesome symptoms HRQoL item for all trials, only the MT-06 trial collected data on the remaining 3 HRQoL items.

Similarly, for the AA population, the model structure was designed to reflect asthma control as defined in the GINA guidelines. The primary endpoint of the MT-04 trial and TO-203-31 trial was the time to first moderate or severe asthma exacerbation. The MT-04 trial also reported the GINA asthma control level at baseline and at trial end by transforming data from the ACQ results. This additional analysis on asthma control was not conducted in the TO-203-31 trial.

In both populations, the efficacy for the comparator, established clinical management without 12 SQ-HDM is represented by the placebo arms of the clinical trials. In the AA+AR and AR models, the comparators are termed SOC AA+AR and SOC AR, respectively.

B3.3.1.1 Effectiveness in Year 1 (Cycle 1)

AR population (MT-06 trial)

As stated previously, in the MT-06 trial, subjects were asked about the presence of impairment of 3 ARIA HRQoL items (sleep disturbance, impairment of daily activities/sport, and impairment of work or school) at baseline and during the last 2 weeks of the efficacy assessment period. To estimate patients ARIA severity classification, patients' rhinitis DSS was used to estimate the presence of troublesome symptoms.

The proportion of people in each health state at baseline and at Year 1 (first cycle) was determined by the proportion of patients in each health state at the start and end of the MT-06 trial. To estimate these proportions, a post-hoc patient-level data analysis of the MT-06 trial was conducted using data on patients' rhinitis DSS, and 3 ARIA HRQoL components. Figure 27 summarises the number of observations included in the full dataset and the number of observations used to populate results in the model. Of the 992 patients included in the full data set, only 914 had 3 valid ARIA assessment values indicated with either a 'Yes' or 'No' response for presence of the HRQoL item. Of those, 871 patients had a reported rhinitis DSS. Of the 871,

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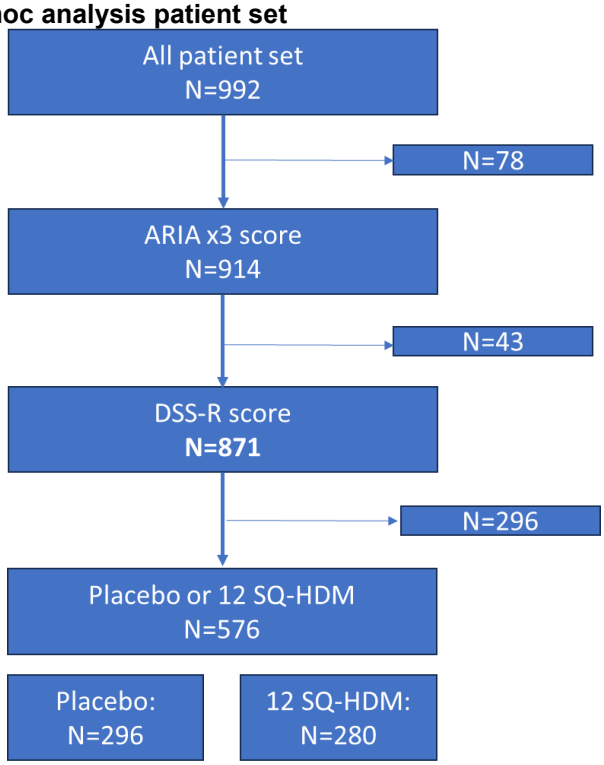
576 patients were treated with either placebo (n=296) or 12 SQ-HDM (n=280), with the remaining 296 patients having received 6 SQ-HDM.

Figure 27: MT-06 post-hoc analysis patient set



The total rhinitis DSS was the total of 4 rhinitis symptom scores (runny nose, blocked nose, sneezing, and itchy nose), which were measured on a 4-point scale from 0 (no symptoms) to 3 (severe symptoms) and ranged from 0-12. Two approaches were considered in estimating the cut-off for the presence of ‘troublesome symptoms’ item. In the model base case, whether or not the cut-off for the 'troublesome symptoms' item was impaired was determined by whether patients had an average rhinitis DSS score of 4. This means that if a subject scored at least 1 on all 4 rhinitis symptoms or had a severe symptom (score of 3) and a mild symptom (score of 1), it was determined that the 'troublesome symptom' item was affected.

As a model scenario, a rhinitis DSS score of at least 6 or a score of at least 5 with one symptom being severe was used. To reach a rhinitis score of 6, subjects had to score at least 2 symptoms as being moderate (i.e. definite awareness of symptom that is bothersome but tolerable). A score of at least 5 with one symptom being severe means that the subject had a least 1 symptom that was hard to tolerate (i.e.

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causes interference with activities of daily living and/or sleeping). This definition was used as the criteria for trial inclusion, whereby only subjects who had experienced an appropriate minimum level of rhinitis symptoms despite treatment with symptomatic medications could be enrolled in the MT-06 trial. The proportion of patients at baseline and end of treatment using the model base case and scenario is presented in Table 68 and Table 69.

Table 68: Distribution of patients at MT-06 baseline and trial end (model base case)

Base case	Placebo (n=296)	12 SQ-HDM (n=280)	All (N=576)
Baseline			
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	176 (59.5%)	162 (57.9%)	338 (58.7%)
Severe	120 (40.5%)	118 (42.1%)	238 (41.3%)
End of trial			
Mild	127 (42.9%)	153 (54.6%)	-
Moderate	157 (53.0%)	119 (42.5%)	-
Severe	12 (4.1%)	8 (2.9%)	-
Abbreviations: SQ, standardised quality; HDM, house dust mite.			

Table 69: Distribution of patients at MT-06 baseline and trial end (model scenario)

Scenario	Placebo (n=296)	12 SQ-HDM (n=280)	All (N=576)
Baseline			
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	185 (62.5%)	171 (61.1%)	356 (61.8%)
Severe	111 (37.5%)	109 (38.9%)	220 (38.2%)
End of trial			
Mild	182 (61.5%)	186 (66.4%)	-
Moderate	108 (36.5%)	93 (33.2%)	-
Severe	6 (2.0%)	1 (0.4%)	-
Abbreviations: SQ, standardised quality; HDM, house dust mite.			

AA+AR population (MT-04 trial)

In the MT-04 trial, the level of asthma control was classified in GINA levels of control by transforming results from the ACQ. The ACQ was recorded throughout the trial and consists of 5 questions related to symptoms (nocturnal wakening, morning

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symptoms, activity limitation, short of breath, wheeze), 1 question related to SABA use, and 1 question related to about lung function (percentage of predicted FEV1). Table 70 provides the classification of asthma control according to GINA 2010 criteria as used in the MT-04 trial.

It is relevant to note that at the time of the trial, the ACQ scores were translated to GINA control levels as defined in the 2010 guidelines. In the updated GINA guidelines (2022) lung function is no longer part of the criteria for asthma control. For reference, during the MT-04 trial the means of FEV1 (% or predicted value) were between 90-100% for all groups at all visits, with minor changes from baseline. During the trial, only 44 placebo subjects and 36 12 SQ-HDM subjects had at least one FEV1 (% of predicted value) <70% after randomisation.

Table 70: GINA 2010 criteria for asthma control

GINA 2010 criteria	Controlled	Partially controlled	Uncontrolled
Daytime symptoms	Twice or less per week	More than twice per week	If 3 or more features of partly controlled asthma are present
Limitations for activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	Twice or less per week	More than twice per week	
Lung function*	Normal, predicted FEV1 ≥80%	Predicted FEV1 <80%	

*At the time of the trial, the ACQ scores were translated to GINA control levels as defined in the 2010 guidelines. Lung function is no longer part of the criteria for asthma control in the updated GINA guidelines (2022).
Abbreviations: GINA, global initiate for asthma; FEV, forced expiratory volume.

The proportion of people in each health state at baseline and at Year 1 (first cycle) was determined by the proportion of patients in each health state at the start and end of the MT-04 trial. The results of the MT-04 trial showed that for the placebo and 12 SQ-HDM treatment arms, 71.6% of subjects had partly controlled asthma and 28.4% of subjects had uncontrolled asthma at baseline**.** Table 71 provides the proportion of patients in each health state at trial baseline and end of trial (Visit 13).

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Table 71: Asthma control: MT-04 baseline and trial end (model base case)

	Placebo (N=277)	12 SQ-HDM (N=282)	All (N=559)
Baseline			
Well-controlled asthma	0 (0.0%)	0 (0.0%)	0 (0.0%)
Partly controlled asthma	200 (72.2%)	200 (70.9%)	400 (71.6%)
Uncontrolled asthma	77 (27.8%)	82 (29.1%)	159 (28.4%)
End of trial			
Well-controlled asthma	54 (26.0%)	64 (31.5%)	-
Partly controlled asthma	110 (52.9%)	100 (49.3%)	-
Uncontrolled asthma	44 (21.2%)	39 (19.2%)	-

Abbreviations: SQ, standardised quality; HDM, house dust mite.

Although more subjects receiving 12 SQ-HDM achieved a clinically relevant improvement in ACQ score compared with subjects receiving placebo at the end of trial (50% versus 43%), there was no statistically significant difference between the groups (OR: 1.31 [95% CI, 0.85-2.01], p=0.2147). However, as the trial was not powered to estimate differences in asthma control, the results of the MT-04 trial are still appropriate to include in this appraisal.

As detailed in Section B.2.2.2, three non-interventional studies were considered relevant to this submission and provide data on asthma control. The CARIOCA study [52], and the studies by Reiber et al., 2021 [53] and Sidenius et al., 2021 [54] assessed the benefit, safety, and tolerability of 12 SQ-HDM in a real-life setting across France, Germany, Sweden, and Denmark. All three studies report safety outcomes and asthma symptom control status as assessed according to the GINA criteria. As these studies were non-comparative, asthma control levels at baseline are assumed to be reflective of established clinical management without 12 SQ-HDM. The results of these studies are provided in scenario analysis.

The CARIOCA study [52] collected data on asthma control at the initiation of 12 SQ-HDM and at the end of the 12-month trial. Data were collected on a total of 1,483 participants, with 984 patients with AR only and 499 patients with AA+AR. The results of this trial showed a benefit in the levels of asthma control achieved following

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treatment with 12 SQ-HDM, as shown in Table 72. Results were available for 494 AA+AR patients at baseline and 228 AA+AR patients at Year 1.

Table 72: Asthma control: CARIOCA study baseline and Year 1 (model scenario)

Asthma control status	Baseline n=494	Year 1 N=228
Well-controlled asthma	266 (53.8%)	184 (80.7%)
Partly controlled asthma	138 (27.9%)	33 (14.5%)
Uncontrolled asthma	90 (18.2%)	11 (4.8%)

Reiber et al., 2021 [53] collected data on asthma control at the initiation of 12 SQ-HDM, first follow-up after 1 to 3 months, and subsequent follow-up every 3 months for up to 1 year. Data were collected on a total of 1,525 participants, with 1,096 patients with AR only, 424 patients with AA+AR, and 5 patients with AA only. The results of this trial showed a benefit in the levels of asthma control achieved following treatment with 12 SQ-HDM, as shown in Table 73. The probabilities reported by Reiber et al., 2021 were rounded and did not sum to 100%. As such, the values reported in Table 73 have been adjusted for appropriate use in the model.

Table 73: Asthma control: Reiber et al., 2021 baseline and Year 1 (model scenario)

Asthma control status	Baseline n=369	Year 1 n=369
Well-controlled asthma	36.86%	78.38%
Partly controlled asthma	41.16%	15.42%
Uncontrolled asthma	21.98%	6.21%

Sidenius et al., 2021 [54] collected data on asthma control at the initiation of 12 SQ-HDM (Visit 1), first follow-up after 1 month (Visit 2), and the second follow-up after 12 months (Visit 3). For patients discontinuing treatment before 12 months, the final visit was conducted at the time of discontinuation. Data were collected on a total of 198 participants, with 115 patients with AR only, and 83 patients with AA+AR. The results of this trial showed a benefit in the levels of asthma control achieved following treatment with 12 SQ-HDM, as shown in Table 74.

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Table 74: Asthma control - Sidenius et al., 2021 baseline and Year 1 (model scenario)

Asthma control status	Baseline N=82	Year 1 N=67
Well-controlled asthma	43 (52.4%)	42 (62.7%)
Partly controlled asthma	21 (25.6%)	17 (25.4%)
Uncontrolled asthma	18 (22.0%)	8 (11.9%)

B3.3.1.2 Long-term effectiveness (Cycle 2 onwards)

Assessment of the long-term effectiveness of 12 SQ-HDM beyond 12 months has not been conducted in a controlled trial format, and the current key clinical studies do not assess full 3-years of treatment as recommended in clinical guidelines, or data after treatment cessation follow-up. To address this data limitation, there are 3 factors considered in the cost-effectiveness models for both the AR and AA+AR.

Firstly, the possible transitions of patients across health states are determined by an annual rate of change across 4 time periods. As there is no data available that can be used to inform these transition probabilities, the annual rate of change was simplified so as not to overcomplicate the model. The 4 time periods are Year 2 to Year 5, Year 5 to Year 10, Year 10 to Year 20, and Year 20 onwards. Patients' health can remain stable (i.e., remain in the same health state), decline (i.e., move to a worse health state), or improve (i.e., move to a better health state). This is applied in the model as a probability of moving from well to partly controlled, and partly to uncontrolled for both the 12 SQ-HDM and the established clinical management treatment arms in both models. Table 75 and Table 76 provide the probability of moving between states for the AA+AR and AR models.

In a modified Delphi advisory panel, conducted with 8 secondary care allergy specialists across Ireland, it was agreed that after cessation of 12 SQ-HDM, treatment effectiveness is likely to have a sustained and clinically significant effect for at least 10 years with potential waning over the subsequent decade, with treatment effectiveness unlikely to completely disappear for HDM-sensitised AA patients. These results were presented in a second advisory board conducted with 12 clinical experts across the UK who similarly agreed that treatment effectiveness is likely to have a sustained and clinically significant effect for at least 10 years with potential waning over the subsequent decade.

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As such, in the base case for both the AA+AR and AR models, for the 12 SQ-HDM treatment arm it was assumed that patients would improve by 5% each year from Year 2 to Year 5, reduced to a 2.5% improvement from Year 5 to Year 10, followed by a period of waning of 2.5% each year to Year 20. After Year 20, it is assumed that patients remain stable in their state. It is assumed that patients receiving established clinical management will remain stable during all years following Year 1.

Table 75: AA+AR population - long-term treatment effectiveness

Annual rate of change	12 SQ-HDM		SOC AA+AR	
	Well to partly controlled	**Partly to uncontrolled**	**Well to partly controlled**	**Partly to uncontrolled**
Year 2 to Year 5	-5.00%	-5.00%	0.00%	0.00%
Year 5 to Year 10	-2.50%	-2.50%	0.00%	0.00%
Year 10 to Year 20	2.50%	2.50%	0.00%	0.00%
Year 20 onwards	0.00%	0.00%	0.00%	0.00%
A negative probability indicates an improvement in health (backwards transition) **Abbreviations:** SQ, standardised quality; HDM, house dust mite; SOC, standard of care; AA, allergic asthma; AR, allergic rhinitis.				

Table 76: AR population - long-term treatment effectiveness

Annual rate of change	12 SQ-HDM		SOC AR	
	Mild-to-moderate	**Moderate-to-severe**	**Mild-to-moderate**	**Moderate-to-severe**
Year 2 to Year 5	-5.00%	-5.00%	0.00%	0.00%
Year 5 to Year 10	-2.50%	-2.50%	0.00%	0.00%
Year 10 to Year 20	2.50%	2.50%	0.00%	0.00%
Year 20 onwards	0.00%	0.00%	0.00%	0.00%
A negative probability indicates an improvement in health (backwards transition) **Abbreviations:** SQ, standardised quality; HDM, house dust mite; SOC, standard of care; AR, allergic rhinitis.				

The second consideration of the model is the functionality to ensure that patients in 12 SQ-HDM treatment arm cannot decline to a state which is worse than patients receiving established clinical management alone. This is accounted for in the model by assuming that the proportion of patients in either the well-controlled or uncontrolled health states in the 12 SQ-HDM treatment arm will be equal to the established clinical management arm if there is a lower proportion in the well-controlled or greater proportion in the uncontrolled health state. In these instances,

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patients will move from the partly controlled health state to adjust for the differences. If there are both a lower proportion of less well-controlled and a greater proportion of uncontrolled patients, the proportions of patients in all three health states are assumed to be equal for the 12 SQ-HDM arm, and the established clinical management arm.

Thirdly, as an additional means to modelling any potential waning associated with 12 SQ-HDM, a proportion of patients in the intervention arm can be set to wane to the comparator arm distribution at a user specified time point. This effect is cancelled out if the patients are already set to match the comparator arm, as accounted for previously. In alignment with the previously discussed results from 2 clinical advisory boards which agreed that treatment effectiveness is unlikely to disappear for all patients, in the model base case, it is assumed that treatment waning will start in Year 15, and by Year 20, 80% of patients in the 12 SQ-HDM treatment arm will be set to match the distribution of patients in the established clinical management arm. This waning effect impacts patients' health state movements, exacerbation rates (AA+AR model only), primary care and secondary care costs, and QALYs.

Additional evidence supporting long-term effectiveness

The international consensus on allergy immunotherapy, which supplemented the recommendation for a 3-year treatment period [4], referenced a prospective study of SLIT with HDM extract in patient with AR which demonstrated remissions lasting 7 years with 3 years of active treatment [79].

As detailed in Section 2.2.2, the REACT study assessed the long-term effectiveness of AIT for the treatment of AR and asthma in a real-world setting. AIT-treated subjects were propensity score match 1:1 with control subjects (not treated with AIT), using characteristic and potential confounding variables. Control subjects who received AIT at a later timepoint were censored when they were prescribed the AIT alongside the matched subject in the AIT group. Outcomes were analysed as within (pre- vs post-AIT) and between (AIT vs control) group differences across 9 years of follow-up. Although the results are not specific to the type of allergen, allergen product, or route of administration, compared to the pre-index year, AIT was consistently associated with greater reductions compared to control subjects in

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asthma prescriptions and in AR prescriptions, which was sustained for 9 years. Additionally, the AIT group had a significantly greater likelihood of stepping down asthma treatment ($p<0.0001$). In the AIT-treated pre-existing asthma cohort, the study demonstrated sustained, long-term reductions in the number of severe asthma exacerbations ($p<0.05$). The results of the REACT study evidence a treatment benefit with AIT, with no evidence of treatment waning over the 9 years of follow-up.

B.3.3.2 Efficacy, asthma exacerbations

For the AA+AR population, the model considers the results on the number of patients experiencing an exacerbation in the MT-04 trial during the efficacy assessment phase. The number of exacerbations experienced in both arms of the MT-04 trial are presented in Table 77. The exacerbation rates collected over the 180-day trial period were converted to annual probabilities for use in the model.

Table 77: AA+AR - modelled exacerbation rates from MT-04

Exacerbation severity	12 SQ-HDM			
	N	Events	Probability (180 days)	Annual probability
Any	248	59	-	-
Moderate	-	49	19.76%	36.02%
Severe	-	10	4.03%	8.01%

Exacerbation severity	Placebo			
	N	Events	Probability (180 days)	Annual probability
Any	257	83	-	-
Moderate	-	65	25.29%	44.66%
Severe	-	18	7.00%	13.70%

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

As noted in Briggs et al., 2021 [80], the total number of exacerbations in the MT-04 trial may be considered small. However, this is a result of the MT-04 trial design, whereby patients were able to discontinue after the experience of the first asthma exacerbation or continue on an increased ICS dose.

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B.3.3.3 Discontinuation

Patients receiving 12 SQ-HDM within the model have a per-cycle probability of discontinuing treatment with 12 SQ-HDM due to AEs and other reasons, based on the rates of treatment discontinuation observed in the MT-04 and MT-06 trial.

No treatment discontinuation was modelling the established clinical management arm of either the AA+AR or AR model.

B3.3.3.1 AE-related discontinuation

The modelled rate of AE treatment discontinuation was derived from the MT-04 and MT-06 trials for the AA+AR and AR population, respectively, and is applied to all patients receiving treatment with 12 SQ-HDM. In the MT-04 and MT-06, the majority of all adverse events were reported as mild or moderate, and over 98% of subjects experiencing an AE had recovered by the end of the trials. Furthermore, the most common AEs had a median onset time of 1 or 2 days after start of treatment, and a median resolution time of 1 to 23 days the most common TRAEs. As such, all AEs, and their associated costs and QALY loss, occur in the first model cycle only. Similarly, the probability of discontinuation due to AEs is applied in the first model cycle only. The probability of discontinuation due to AEs is informed by the number of patients who discontinued treatment as a result of IMP-related AEs, and is 8.87% in the AA+AR model and 4.09% in the AR model.

All patients who discontinue treatment with 12 SQ-HDM incur 1 month’s cost of treatment with 12 SQ-HDM to account for any previous time on treatment prior to discontinuation. Although a likely overestimate of the time on treatment, as 12 SQ-HDM is provided in a pack of 30 tablets, this cost most appropriately reflects the cost to the health care system.

Patients who discontinue treatment with 12 SQ-HDM are modelled as placebo treatment patients, and experience the same transition probabilities, health care costs, and HRQoL as patients receiving established clinical management alone for the duration of the model.

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B3.3.3.2 Discontinuation due to other reasons

The modelled rate of treatment discontinuation due to other reasons was derived from the MT-04 and MT-06 trials for the AA+AR and AR population, respectively, and is applied to all patients receiving treatment with 12 SQ-HDM. The probability of discontinuation due to other reasons is applied in the first 3 model cycles, reflecting the treatment schedule with 12 SQ-HDM.

In the AA+AR population, the probability of discontinuation due to other reasons is informed by the number of patients who discontinued treatment due to lack of efficacy, lost to follow-up, withdrawal of consent, and 19.75% of other reasons in the MT-04 trial. Of those labelled as other reasons, 65 of 81 (80.25%) were due to asthma exacerbations during period 3 of the MT-04 trial. Because patients who experienced more than 3 exacerbations during Period 3A or any exacerbation during Period 3B of the MT-04 trial were required to discontinue treatment, only 16 patients (19.75%) were considered to be discontinuations generalisable to the modelled rate. The probability of discontinuation due to other reasons in the AA+AR population was estimated as 8.49% for the first model cycle. In the absence of additional data on the discontinuation of 12 SQ-HDM beyond 12 months, a rate of 8.49% was assumed in Cycles 2 and 3.

In the AR population, the probability of discontinuation due to other reasons is informed by the number of patients who discontinued treatment due to lack of efficacy, loss to follow-up, withdrawal of consent, and other reasons, in the MT-06 trial. The probability of discontinuation due to other reasons in the AR population was estimated as 5.03% for the first model cycle. In the absence of additional data on the discontinuation of 12 SQ-HDM beyond 12 months, a rate of 5.03% was assumed in Cycles 2 and 3.

In the model, it is assumed that patients would not re-initiate treatment with 12 SQ-HDM. However, as demonstrated in the Phase 2 P003 trial, statistically significant improvements in efficacy could be observed as early as 8 weeks following initiation of 12 SQ-HDM [42, 43]. Additionally, during an advisory board, it was noted that patients who discontinue AIT treatment early may still receive treatment benefit. Two out of three clinicians said that half of patients who discontinue may still receive benefits,

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while one clinician said this would be a small number of patients. To account for any potential treatment benefit achieved prior to discontinuation and sustained post discontinuation, a proportion of patients are modelled as 12 SQ-HDM patients and experience the same transition probabilities, health care costs, and HRQoL as patients receiving 12 SQ-HDM for the duration of the model. In the base case for the AA+AR and AR population, the proportion of patients who discontinue treatment with 12 SQ-HDM but continue to be modelled as 12 SQ-HDM patients is 50% for Cycles 1, 2, and 3. This has been tested in sensitivity and scenario analyses.

All patients who discontinue treatment with 12 SQ-HDM incur the cost of 6 months' treatment with 12 SQ-HDM, to account for any previous time on treatment prior to discontinuation.

B.3.3.4 Mortality

The modelled mortality rate is assumed to follow age-adjusted all-cause mortality using rates obtained from UK life tables. A weighted age-dependent mortality probability was calculated using the proportion of male patients in the model.

There is no considered impact of AA+AR or AR on mortality as no deaths were reported in the key trials. However, this approach may be considered conservative in the AA+AR population, as results of a systematic literature review on asthma-related mortality conducted in the NICE technology appraisal of omalizumab for treatment severe persistent AA (TA278) report an increased mortality risk associated with severe exacerbations.

B.3.3.5 Adverse events

The AEs considered in the model are based on the common TRAEs from the MT-04 trial for the AA+AR population, and the MT-06 trial for the AR population.

B3.3.5.1 AA+AR population (MT-04)

In the MT-04 trial, the most commonly reported TEAEs occurring in either treatment group with ≥2% incidence were throat irritation, oral pruritis, tongue pruritis, mouth oedema, oral paraesthesia, lip swelling, and ear pruritus. The number of events, duration of event (days), and annual probability of AEs used in the model are summarised in Table 78.

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Table 78: AA+AR - incidence and annual probability of AEs used in model

Most common TRAEs	Number of events		Annual probability		Duration of event (days)
	12 SQ-HDM	Placebo			
	n=282	n=277	12 SQ-HDM	SOC AA+AR	
Throat irritation	32	4	11.35%	1.44%	7.00
Oral pruritis	78	8	27.66%	2.89%	4.50
Tongue pruritis	15	1	5.32%	0.36%	1.00
Oedema mouth	35	0	12.41%	0.00%	23.00
Oral paraesthesia	15	0	5.32%	0.00%	11.00
Lip swelling	7	0	2.48%	0.00%	1.00
Ear pruritis	2	2	0.71%	0.72%	1.00

Abbreviations: SQ, standardised quality; HDM, house dust mite; SOC, standard of care; AA, allergic asthma; AR, allergic rhinitis; TRAE, treatment-related adverse event; AE, adverse event.

In the MT-04 trial, the majority of adverse events were reported as mild (67%) or moderate (31%); 99% of subjects experiencing an AE had recovered by the end of the trial. Furthermore, the most common AEs had a median onset time on 1 or 2 days after start of treatment. There was a median resolution time of 4.5 days, 7 days, and 23 days for the 3 most common AEs. As such, the model assumes that all AEs, and their associated costs and QALY loss, occur in the first model cycle only.

B3.3.5.2 AR population (MT-06)

In the MT-06 trial, the TEAEs occurring in either treatment group with ≥2% incidence were throat irritation, oral pruritis, tongue pruritis, mouth oedema, oral paraesthesia, lip swelling, ear pruritus, and glossodynia. The number of events, duration of event (days), and annual probability of AEs used in the model are summarised in Table 79.

Table 79: AR - incidence and annual probability of AEs used in model

Most common TRAEs	Number of events		Annual probability		Duration of event (days)
	12 SQ-HDM	Placebo			
	n=318	n=338	12 SQ-HDM	SOC AR	
Throat irritation	61	14	19.18%	4.14%	2.50
Oral pruritis	89	8	27.99%	2.37%	8.00
Tongue pruritis	20	5	6.29%	1.48%	1.00
Oedema mouth	34	1	10.69%	0.30%	21.00
Oral paraesthesia	31	2	9.75%	0.59%	1.00
Lip swelling	10	0	3.14%	0.00%	5.00

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Most common TRAEs	Number of events		Annual probability		Duration of event (days)
	12 SQ-HDM	Placebo			
	n=318	n=338	12 SQ-HDM	SOC AR	
Ear pruritis	21	2	6.60%	0.59%	14.50
Abbreviations: SQ, standardised quality; HDM, house dust mite; SOC, standard of care; AR, allergic rhinitis; TRAE, treatment-related adverse event; AE, adverse event.					

In the MT-06 trial, the majority of adverse events were reported as mild (72%) or moderate (24%); 98% of subjects experiencing an AE had recovered by the end of the trial. Furthermore, the majority of the most frequent TEAEs had a median onset within 1 to 15 minutes, with very few new AEs starting at a later timepoint. As such, the model assumes that all AEs, and their associated costs and QALY loss, occur in the first model cycle only.

B3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life studies

In 2015, ALK commissioned an SLR to identify utilities in HDM AR and/or HDM AA. To support the current appraisal, an SLR update was undertaken in March-April 2023 to identify and synthesise the evidence on the HRQoL of patients with HDM AA and AR from 2015 to 2023. Full details of the SLR search strategy, study selection process, and results are presented in Appendix H.

In total, 37 studies reporting HRQoL data were identified: 19 studies (in 21 reports) in the original SLR, and 18 studies (in 21 reports) in the updated SLR.

In the original SLR, 2 studies report EQ-5D data and 5 studies report SF-36 data. However, only the 2 EQ-5D studies report utility values appropriate for modelling. Petersen et al., 2013 [81] report utility values from a prospective study in patients with grass pollen and/or HDM-induced ARC and/or AA receiving SCIT. Canonica, Poulsen, and Vetenbaek, 2007 [82] report utility values collected alongside a Phase 3 randomised trial assessing the efficacy of grass pollen SIT (GRAZAX®).

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Additionally, 13 studies reported RQLQ data and 2 studies reported AQLQ outcomes.

In the updated SLR, 4 reports from 2 studies reported utility values. Green et al., 2019 [65], Briggs et al., 2021 [80], and Hahn-Pedersen et al., 2016 [66] report utility values from the MT-04 trial. Green et al., 2017 [64] report utility values from the MT-06 trial.

Additionally, 14 reports reported RQLQ outcome data, 2 reports reported AQLQ outcome data, 1 report reported Juniper Quality of Life Questionnaire outcome data, 1 study reported ESPRINT-15 outcome data, and 1 study reported Routine Assessment of Patient Progress (RAPP) outcome data.

Of the HRQoL data identified in the original and updated SLR, only the utility values provided in Green et al., 2019 [65], Briggs et al., 2021 [80], Hahn-Pedersen et al.[66], and Green et al., 2017 [64] report utility values suitable for consideration in this appraisal. As highlighted, Green et al., 2019 [65], Hahn-Pedersen et al., 2016 [66], and Green et al., 2017 [64] report utility values from the MT-04 and MT-06 trials, which are discussed further in Section B.3.4.2.

In a post-hoc analysis of the MT-04 trial data, Briggs et al., 2021 [80] mapped AQLQ to EQ-5D-3L to estimate the disutility of moving from ‘well-controlled asthma’ to the other four health states: ‘partially controlled asthma’, ‘uncontrolled asthma’, ‘moderate exacerbation’, and ‘severe exacerbation’. The results of Briggs et al., 2021 are discussed further in Section B.3.4.3.

An additional study by Doz et al., 2013 (EUCOAST study) [83], which assessed utilisation of healthcare resources, costs, and HRQoL in adult patients with asthma in a real-life setting in France and Spain according to the level of asthma control, was referenced in the original SLR. The study was primarily conducted in an asthma population (not specific to AA) which had a high prevalence of AR (72.5%) as a comorbidity. This paper was highlighted as an additional paper of interest due to the investigation of costs and utilities (measured using the EQ-5D-3L) related to asthma control, something which is not provided in the other studies. The EUCOAST study was an observation study conducted in primary care setting which enrolled 2,371 patients (1,154 in France and 1,517 in Spain). Data were collected retrospectively

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(over the previous 3 months) during a single study visit by participating GPs, with patients completing the EQ-5D-3L questionnaire at the time of inclusion. In both countries, the average utility scores were higher for patients with controlled asthma than patients with partly controlled or uncontrolled asthma (0.88 vs. 0.78 vs. 0.63 in France and 0.89 vs. 0.82 vs. 0.69 in Spain; p<0.0001). The results from the EUCOAST study are presented in the scenario analysis.

B.3.4.2 Health-related quality of life data from clinical trials

B3.4.2.1 AA+AR population (MT-04)

The MT-04 trial collected data on HRQoL using the AQLQ and the SF-36.

As detailed previously, the AQLQ is a disease-specific measure and contains 32 questions organised into four domains: symptoms, activity limitation, emotional function, and environmental stimuli. Each question is scored on a 7-point scale, with higher scores indicating better QoL and lower scores indicating a more negative impact of asthma on daily functioning and well-being. An improvement of 0.5 to 0.7 points in the AQLQ score is considered clinically meaningful for patients with asthma. More subjects in the 12 SQ-HDM group had a clinically relevant improvement in AQLQ score than in placebo (55% vs. 47%) at Visit 13. However, in the analysis controlled for change from baseline in ICS, there were no statistically significant differences between the groups in the proportion of subjects with improvement.

The SF-36 is a generic measure of QoL, with 36 questions yielding an 8-scale profile of functional health and well-being scores. Participants completed the SF-36 questionnaire at Visits 3, 6 ,9, 10, 11, 12, and 13. The resultant scores are not comparable across dimensions and are not based on individual preferences, meaning they cannot be used to generate QALYs [84]. The SF-6D preference-based algorithm was used to generate utility scores. Table 80 provides the results of the analysis.

Treatment-specific utility scores used in the model were derived from the mean utility scores estimated from the SF-36 results for the placebo and 12 SQ-HDM group at baseline (Visit 3), the end of the treatment maintenance period (Visit 9) and the end

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of trial (Visit 13) for patients with a utility score at all visits. For the treatment-specific utility scores used in the model, the data was corrected for baseline to determine the between-group differences at the end of the relevant period. The average baseline utility was calculated as a weighted average using utility scores from the full trial sample. Differences between the 12 SQ-HDM treatment group and the placebo treatment group were statistically significant in both the change from baseline to the end of the treatment maintenance period (p=0.032) and the change from baseline to the end of the trial (p=0.017).

Table 80: AA+AR - summary of utility values used in the model (MT-04)

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

† Change in utility of placebo versus 12 SQ-HDM statistically significant. Visit 3 to 9, p=0.032. Visit 3 to 13, p=0.017
‡ Average baseline utility was estimated using the full trial sample (placebo utility=0.7495 and N=267, 12 SQ-HDM utility=0.7233 and N=275)
Abbreviations: SQ, standardised quality; HDM, house dust mite; AA, allergic asthma; AR, allergic rhinitis.

B3.4.2.2 AR population (MT-06)

The MT-06 trial collected data on HRQoL using the RQLQ and the EQ-5D.

As stated previously, the RQLQ consists of 28 questions, each on a 7-point (0-6) scale, divided into 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional). All items within each domain are weighted equally. The weekly domain scores were calculated as the average of all items scores for each domain. The weekly overall RQLQ score was

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the average of all 28 item scores, with higher scores indicating worse rhinoconjunctivitis HRQoL. 12 SQ-HDM was associated with a significant improvement in the QoL, as demonstrated by an improvement in RQLQ score compared with placebo (absolute difference: 0.19 [95% CI 0.02,0.37], p=0.031) in the FAS population. The significant reduction in RQLQ score with 12 SQ-HDM compared to placebo was evident after 24 weeks of treatment and onwards to Week 52. The minimal clinically important difference (MCID) of 0.5 was reached by patients in both groups (i.e., within both groups). A MCID between groups has not been defined.

The EQ-5D is a generic preference-based measure, and NICE's preferred measure of HRQoL. A common characteristic of EQ-5D data is that many participants may be in perfect health (i.e. EQ-5D utility index of 1). As such, regression analysis was used to correct for skewed data that occurred because of this fact. As reported in Green et al., 2017, a two-stage approach was adopted for the regression analysis. This approach was adopted because it was shown to be a less biased regression method for analysing utility data, and was similar to that reported by Poole et al., 2014 [85]. During the first stage, a binomial model was used to estimate the proportion of EQ-5D observations in which the patient was in perfect health (61.4%). In this model, the EQ-5D index was modelled as a binary variable, indicating perfect health or imperfect health, with the inclusion of five predictor variables (asthma status, age, rhinitis DSS, rhinitis daily medication score, and smoking status). During the second stage, a generalised, mixed linear model was applied to the imperfect health observations (38.6%), to estimate the EQ-5D index scores for 12 SQ-HDM and placebo patients.

Using this approach, treatment-specific and health state specific (using ARIA criteria) utility values were estimated. Table 81 and Table 82 provides the results of this analysis.

Table 81: AR: Summary of treatment-specific utility values used in the model (MT-06)

	Treatment-specific mean utility score	
	12 SQ-HDM n=301	**Placebo n=326**
Visit 3	0.891	0.884

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Visit 8	0.926	0.916
Mean change in utility Visit 3 to 8†	0.029	0.014
Utility score used in model		
Average utility Visit 3 to 8	0.919	0.898
† Change in utility of placebo versus 12 SQ-HDM statistically significant. Visit 3 to 8 equal to 0.0145 p=0.0.175 **Abbreviations:** SQ, standardised quality; HDM, house dust mite; AR, allergic rhinitis.		

Table 82: AR - Summary of disease-specific utility values used in the model (MT-06)

	12 SQ-HDM n (mean utility)	Placebo n (mean utility)	Combined n (mean utility)
Visit 1 to 2			
Mild	0 (0.000)	0 (0.000)	0 (0.000)
Moderate	175 (0.888)	188 (0.886)	363 (0.887)
Severe	125 (0.897)	138 (0.881)	263 (0.888)
Visit 7 to 8			
Mild	153 (0.956)	127 (0.950)	280 (0.953)
Moderate	132 (0.898)	169 (0.901)	301 (0.899)
Severe	15 (0.861)	29 (0.856)	44 (0.858)
			Weighted n (mean utility)
Mild	-	-	280 (0.953)
Moderate	-	-	664 (0.892)
Severe	-	-	307 (0.884)
Abbreviations: SQ, standardised quality; HDM, house dust mite; AR, allergic rhinitis.			

B.3.4.3 Mapping

Briggs et al., 2021 estimated the duration of moderate and severe exacerbations in patients with HDM AA and the impact on patients' QoL in a post-hoc analysis of the MT-04 trial data. The first post-hoc analysis investigated the duration of exacerbations through an analysis of patients' electronic diaries (e-diaries). The second analysis derived utilities (patients' preferences) for five mutually exclusive asthma health states (well-controlled, partially controlled, uncontrolled, moderate, and severe exacerbation), derived from the AQLQ data through a stepwise approach, in order to measure the impact of asthma control and exacerbations on patients' HRQoL.

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To estimate the duration of exacerbations, baseline-adjusted mean scores for e-diary data for the 4 weeks before and after the patients' first exacerbation were compared to the final 8 weeks of data for patients who did not experience exacerbations. The last 8 weeks of trial data for patients who did not experience an exacerbation were expected to be the most appropriate control group, as this was the complete ICS withdrawal phase (Period 3B) of the MT-04 trial.

To estimate utilities at each visit for 5 mutually exclusive asthma health states, AQLQ data were mapped using the definition of asthma exacerbations used in the trial and GINA asthma control status. If patients had an exacerbation within a given number of days after a visit, the AQLQ data was categorised as a moderate or severe exacerbation at that visit. All remaining AQLQ data points were grouped according to the GINA asthma control status of the patient. Categorisation of control status was done by mapping ACQ data to the GINA asthma control categories, as discussed in Section B.3.3.1. Observation periods of 7, 14, 21 and 28 days from an asthma exacerbation were used to include AQLQ data, in order to explore how long the impact of an asthma exacerbation on patients' utility lasts. Utility values were obtained by mapping from AQLQ to EQ-5D-3L and the Asthma Quality of Life Questionnaire (AQL-5D) using two previously developed algorithms [86]. Using a mixed effects regression model, a predicted utility for the 'well-controlled' asthma state was estimated, alongside the predicted disutility of moving from the 'well-controlled' state to either of the remaining 4 health states (partly controlled, uncontrolled, moderate exacerbation, and severe exacerbation) [80]. Table 83 presents the mapped EQ-5D-3L utility scores.

Table 83: Mapped utility scores used in the model from Briggs et al., 2021

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

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* p<0.001
** Difference is measure from the 'controlled' asthma state
Abbreviations: EQ-5D-3L, European quality of life 5 dimensions 3 level.

During the efficacy assessment period of the MT-04 trial, 204 patients experienced a moderate or severe exacerbation (59 in the 12 SQ-HDM group, 62 in the 6 SQ-HDM group, and 83 in the placebo group). As shown in Figure 28, moderate and severe exacerbations were associated with a significant reduction in lung function, and increases in asthma symptoms, SABA use, and the frequency of nocturnal awakening over a 28-day period.

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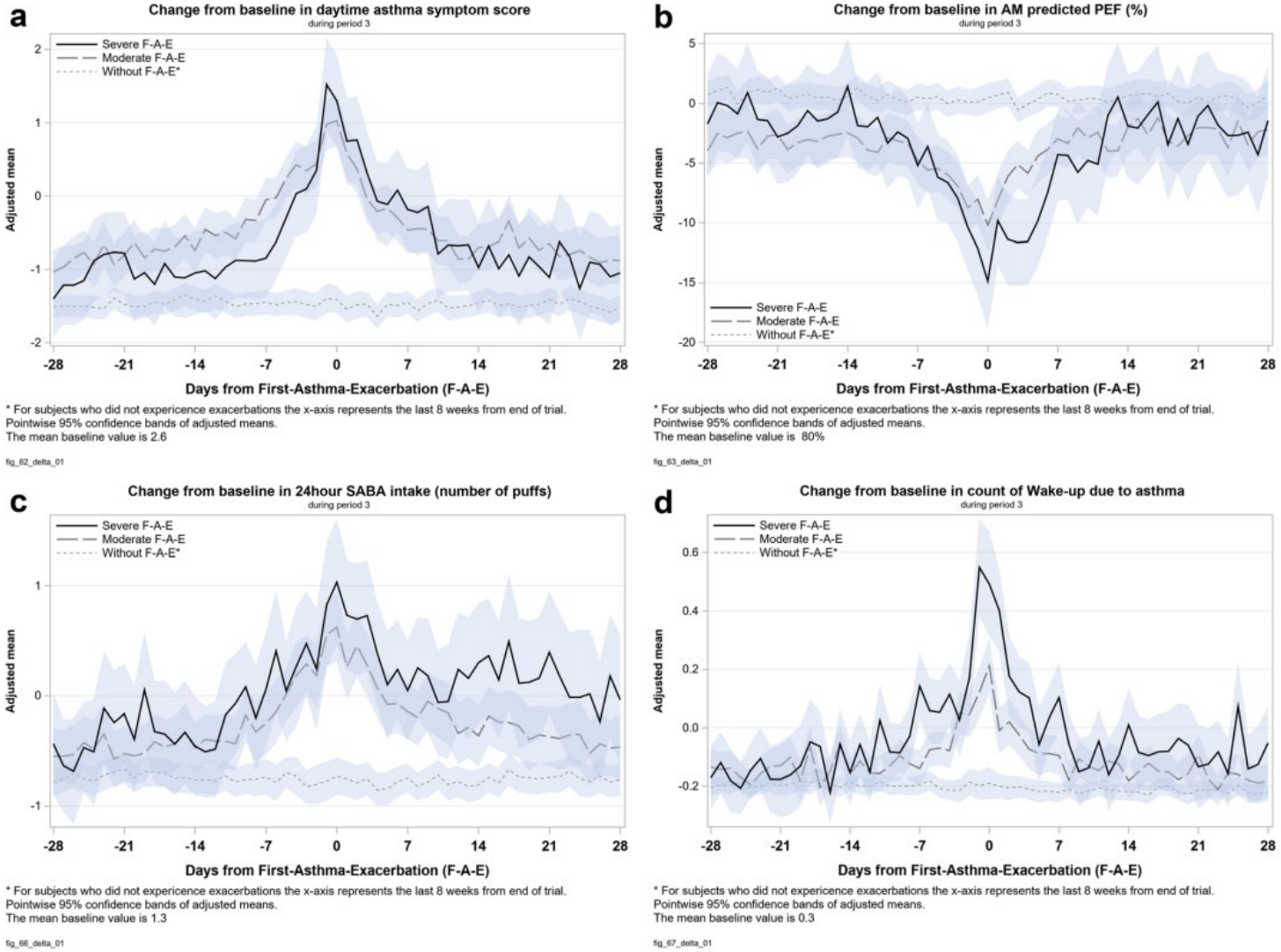
Figure 28: Duration and impact of asthma exacerbation (as reported in Briggs et al., 2021)



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B.3.4.4 Adverse reactions

The AEs considered in the model are based on the common TRAEs from the MT-04 trial for the AA+AR population and the MT-06 trial for the AR population.

As stated previously, in the MT-04 trial, the majority of AEs were reported as mild (67%) or moderate (31%). Of the 7 TRAEs modelled, 6 had a median duration of under 11 days, with mouth oedema having a median duration of 23 days. In the MT-06 trial, the majority of AEs were reported as mild (72%) or moderate (24%). Of the 8 TRAEs modelled, 7 had a median duration of under 15 days, with mouth oedema having a median duration of 21 days.

The SLR on the HRQoL of patients with HDM AA and AR did not identify any utility values for the AEs associated with SLIT. In the model base case, no AE-related utility decrements were applied to the modelled AEs in either the AA+AR or AR population. Given the reported severity and duration of the reported TRAEs, the exclusion of specific utility decrements is not anticipated to have any material impact on the cost-effectiveness of 12 SQ-HDM.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The utility values used in the model are summarised in Table 84. In the model base case, the treatment-specific utilities captured during the MT-04 and MT-06 trial are used to inform the QALY gain in the AA+AR and AR populations, respectively. For the AA+AR population, treatment-specific utilities derived from the full study period are used (Visit 3 to 13).

Table 84: Summary of utility values for cost-effectiveness analysis

Health state-specific utilities			
AA+AR population	**Well-controlled**	**Partly controlled**	**Uncontrolled**
MT-04, mapped (Briggs et al., 2021)	0.923	0.898	0.860
EUCOAST, Spain	0.890	0.820	0.690
EUCOAST, France	0.880	0.780	0.630
AR population	**Mild**	**Moderate**	**Severe**

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MT-06, weighted	0.953	0.892	0.884
Treatment-specific utilities			
	12 SQ-HDM	**SOC AA+AR**	**SOC AR**
MT-04, Visit 3 to 9	0.768	0.742	-
MT-04, Visit 3 to 13	0.785	0.753	-
MT-06, Visit 3 to 8 (Green et al., 2017)	0.919	-	0.898
Exacerbation disutility			
Moderate exacerbation (28 days)	-0.0834		
Severe exacerbation (28 days)	-0.115		
Abbreviations: SQ, standardised quality; HDM, house dust mite; AR, allergic rhinitis; AA, allergic asthma; SOC, standard of care; EUCOAST, European cost of asthma treatment.			

In both, the AR model, and the AA+AR model, utilities are applied in a multiplicative manner to appropriately adjust for the natural decline in QoL associated with age. As reported in Ara and Brazier, 2010 [87], the following regression equation for individuals from the general population was used to estimate an age-adjusted baseline set of utilities:

*EQ-5D = 0.9508566 + 0.0212126*male - 0.0002587*age - 0.0000332*age^2*

The primary health states ('well-controlled' state in the AA+AR model) and the (‘mild’ state in the AR model) are modelled as the reference states and applied as a multiplier to correct for age and sex- adjusted general population utilities. This is calculated as the mean cohort utility divided by the age and sex-adjusted general population utility, with the multiplier capped at a max of 1 (i.e. a person cannot have a utility greater than the equivalent age general population utility). The secondary and tertiary states are applied as a disutility relative to the reference state utility. This assumes that the disutility associated with the secondary and tertiary states is an average disutility.

The disutility associated with an asthma exacerbation is not age-adjusted and is applied in the model as a utility decrement (or QALY loss).

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As noted in Section B3.3.1.2, in the model base case, it is assumed that treatment waning will start in Year 15, and by Year 20, 80% of patients in the 12 SQ-HDM treatment arm will be set to match the distribution of patients in the established clinical management arm. This waning effect is applied to utilities when the treatment-specific utility approach is selected. A linear waning effect is modelled, whereby the proportion of patients to whom waning is applied is divided by the difference between the waning start year and the waning end year.

B3.5 Cost and healthcare resource use identification, measurement and valuation

In 2015, ALK commissioned an SLR to identify cost and resource use in HDM AR and/or HDM AA. To support the current appraisal, an SLR update was undertaken in March-April 2023 to identify and synthesise the evidence on the cost and resource use of patients with HDM AA and AR from 2015 to 2023. Full details of the SLR search strategy, study selection process, and results are presented in Appendix I.

In total, 10 studies reporting cost and resource use data were identified: 3 studies (in 4 reports) in the original SLR, and 7 studies (in 7 reports) in the updated SLR.

Ariano et al. 2009 [88] report costs for SLIT-drops (Staloral 300) plus symptomatic drugs and symptomatic drugs only for patients with HDM AA. The prospective study randomised, and enrolled 50 patients treated with SLIT, and 20 patients treated with symptomatic treatment only. The study was conducted in Italy between January 2002 and December 2006. Data was collected every 6 months for 3 years of SLIT treatment, and 2 years post-treatment. The total cost per patient at Year 5 were €3,881 for those treated with SLIT, which represented a 22.7% saving compared to the total cost per patient at Year 5 of €5.020 for those treated with symptomatic medication only. The savings increased with disease severity, reaching a relative total cost reduction of 33.8% for severe asthmatic patients. No data on health care resource use was reported.

Bachert et al. 2004 [89] and Rogkakou et al. 2011 [90] report the results of the XPERT trial; a 6-month randomised controlled trial comparing levocetirizine (an antihistamine) to placebo in adults with HDM or grass pollen-AR in Belgium, France,

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Germany, Italy, and Spain in 2001. Direct medical costs for persistent AR were €16.81 for levocetirizine and €5.32 for placebo per patient per month. No hospitalisations were reported in the XPERT study. Neither study reported data on health care resource use, or total costs split by allergen (grass pollen versus HDM). The XPERT trial did not consider treatment with immunotherapy.

Omnes et al. 2007 [91] calculated the direct costs of current symptomatic treatment, SCIT (Alustal) and SLIT-drops (Staloral 300), to inform its decision tree model for AR and AA plus AR populations in France in 2003. Costs were sourced from French Nomenclature Générale des Actes des Praticiens (NGAP) tariffs. In adults, the incremental costs per asthma case avoided with SCIT were €393 and €1,327 for HDM and pollen allergy, respectively, over a 6-year period. For SLIT-drops, the costs per asthma case avoided were €3,158 and €1,708 for HDM and pollen allergy, respectively. No data on health care resource use was reported and limited information was provided regarding the decision tree model used to estimate costs and symptom endpoints.

Ronborg et al., 2016 [71] report the results of a cost-minimisation analysis of SLIT (12 SQ-HDM, ACARIZAX) versus SCIT (Alutard SQ) for HDM ARD in Denmark. Data on resource use in terms of medication use, physician visits, and patient time was based on information from clinical trials and treatment guidelines in Denmark. Where information was limited, medical expert opinion was acquired. Unit costs were obtained from the Danish Medical Association and the Danish Health Data Agency. For SLIT, it was assumed that there were two follow-up visits in Years 2 and 3: these were performed by general practitioners (40%), outpatient hospitalisations (5%) and specialists in a private clinic (55%). The study only included treatment cost estimates, costs of administration, and patient costs related to treatment administration. As such, the analysis does not provide information on disease-related costs.

Robaina, Sanchez, and Perez, 2016 [92], report the results of an observational, retrospective study in 419 adult patients with HDM AR and/or bronchial asthma in Spain in 2013, with the aim to quantify the cost difference between symptomatic treatment and SCIT (Acaroid®). Results were modelled up to 6 years using the

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results of the study during the first year of immunotherapy treatment (assuming 3 years of active treatment). Data on urgent care visits, hospital days, diagnostic tests, allergist visits, and medication use were reported pre and post-treatment with SCIT. After a year of treatment, the need for unscheduled medical assistance decreased from the months before commencement of treatment. During the months pre-treatment with SCIT, 16.3% of patients required urgent care, 14.6% saw an allergist, and 7.7% missed work or school. After a year of treatment with SCIT, these percentages dropped to 4.5%, 3.7%, and 1.2%, respectively. At baseline, 85.4% of patients had at least one drug scheduled for daily use, reducing to 52.1% after a year of treatment. There was also a significant decrease in the use of rescue medication compared to its use in the months before the start of the treatment. This was associated with a reduction of 64% in direct health care costs (unscheduled medical care, tests, and medication), and 94% in indirect costs (days of sick leave).

Green et al., 2017 [64] report the results of a cost-effectiveness analysis based on the results of the MT-06 trial from a German perspective. In the MT-06 trial, data were collected on four resources: doctors' visits, desloratadine (5 mg) intake, budesonide (64 µg) intake, and azelastine (0.05%) intake. Data on medication use from the MT-06 trial is reported in detail in Section B.3.5.1. The mean annual number doctor visits were 0.098 visits and 0.1037 visits in the 12 SQ-HDM group and placebo group, respectively.

Demoly et al., 2016 [93] report the results of an observational study conducted in France, Italy, and Spain in adults with a severe, poorly controlled, HDM ARD. Survey data was collected, and patients were followed-up with fortnightly telephone interview between May 2012 and July 2013 to gather data on patients' symptoms, QoL, medication use, and medical consultations (primary and secondary care visits). Of the 313 patients included in the study, the poorly controlled allergy population had an average of 3.5 GP visits and 1.7 allergist visits each year.

Hahn-Pedersen et al., 2016, [66] report the results of a cost-effectiveness analysis based on the results of the MT-04 trial from a German perspective. Within MT-04, patients recorded medication use using electronic diaries during the last 4 weeks of the treatment maintenance period. Physician and emergency room visits were also

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recorded by trial investigators at each visit. Data on medication use from the MT-04 trial are reported in detail in Section B.3.5.1. The mean annual number of GP visits reported in Hahn-Pedersen et al., 2016 were 0.175 visits and 0.105 visits in the 12 SQ-HDM group and placebo group, respectively. The mean annual number of emergency room visits reported were 0.010 visits and 0.025 visits in the 12 SQ-HDM group and placebo group, respectively. However, using the MT-04 clinical trial data, the company could not replicate the data on the annual number of GP visits and emergency room visits reported by Hahn-Pedersen et al., 2016. As data were available from the clinical trial reports, the values from Hahn-Pedersen et al., 2016 are not considered further in this analysis.

El-Qutob et al., 2016 [94] report the healthcare and rescue medication use for patients treated with SCIT (Acaroid®) with HDM AA and/or AR collected in an observational, retrospective study in Spain. Data on use of rescue medication, scheduled or unscheduled emergency health care resources, and work/school abstenteesim were collected at baseline (pre-treatment) and after 9 months of treatment (post-treatment). Of the 281 patients with disease symptoms at baseline, 78.3%, 84.5%, and 72.6% of patients reported an improvement in ocular, nasal, and bronchial symptoms, respectively. There was a significant decrease in the number of patients on rescue medications following immunotherapy. 38.2% (n=160/419) of patients who used bronchodilators dropped to 30.4% (n=122/401) after immunotherapy (reduction of use, p<0.0001), eye drops 11.5% to 5.2% (p<0.0001), nasal steroids 41.3% to 26.7% (p<0.0001) and oral antihistamines 64.7% to 60.8% (p<0.0487). A significant reduction was noted for visits at an emergency department (75.4% reduction; p<0.0001) and for unscheduled specialist outpatient visits (73.5% reduction; p<0.0001). Hospital admissions were also significantly reduced (from 1.2% to 0%: p=0.0253); and work/school absenteeism showed a significant decline (84.4% reduction; p<0.0001).

Bjorstad et al., 2017 [61] report the results of a cost-minimisation analysis comparing SLIT to SCIT for the treatment of HDM AA and AR in Sweden. Data on health care resource use was based on clinical practice and treatment regimens described in the SmPC's for the relevant products. The total cost over 3 years for SLIT-tablets was estimated to be €8,804, compared to €19,562 for SCIT. This included direct medical

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costs, drug costs, and healthcare visit costs. Similar to the study by Ronborg et al., 2016, the study only included treatment cost estimates, costs of administration, and patient' costs related to treatment administration. As such, the analysis does not provide information on disease-related costs.

As detailed in Section B.3.4.1, an additional study by Doz et al., 2013 (EUCOAST study) [83] which assessed utilisation of healthcare resources, costs, and HRQoL in adult patients with asthma in a real-life setting in France and Spain according to the level of asthma control, was referenced in the original SLR. The average asthma-related total health care costs over a three-month period were €85.4, €314.4, and €537.9 in France and €152.6, €241.2, and €556.8 in Spain for patients with controlled, partially controlled, and uncontrolled asthma, respectively.

B.3.5.1 Intervention and comparators' costs and resource use

B3.5.1.1 12 SQ-HDM treatment costs

12 SQ-HDM should be initiated by physicians with experience in the treatment of allergic diseases. Following this, patients can self-administer at home. 12 SQ-HDM is provided as an oral lyophilisate. The recommended dose for adults and adolescents (12-17 years) is one oral lyophilisate (12 SQ-HDM) daily. The onset of the clinical effect is expected 8-14 weeks after treatment initiation. If no improvement is observed during the first year of treatment with 12 SQ-HDM, there is no indication for continuing treatment.

The list price of 12 SQ-HDM is £80.12 per pack of 30 tablets of 12 SQ-HDM. The average annual cost of 12 SQ-HDM treatment is £975.46 per patient. In the model, the cost of treatment is applied to all patients receiving treatment with 12 SQ-HDM for the first 3 model cycles (to reflect 3 years of treatment). The cost of treatment for patients who discontinue treatment due to AEs and other reasons is discussed in Section B.3.4.3.

The cost of a non-admitted face-to-face attendance with a respiratory specialist (£262.25, National schedule of NHS costs, WF01B) is included in the administration costs of treatment. Additionally, in line with the NICE final scope, to account for a requirement of a positive test for HDM sensitisation, the cost of a diagnostic blood

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test is included in the administration costs of treatment (£2.96, National schedule of NHS costs, DAPS05). In the model, administration costs are applied to all patients in the intervention arm in Cycle 0 only.

B3.5.1.2 Established clinical management treatment costs

The proposed comparator is established clinical management without 12 SQ-HDM. As treatment with 12 SQ-HDM is additive, the background established management costs are added to the 12 SQ-HDM treatment costs for the intervention arms of the AA+AR and AR models.

AR established clinical management costs

Established clinical management costs for the AR population were estimated based on data collected on medication use throughout the MT-06 trial. As stated previously, symptomatic medications were permitted in the MT-06 trial and provided at randomisation as predefined, open-labelled medication used in addition to the IMP. For rhinitis symptoms, participants were provided with:

- Oral antihistamine tablets (desloratadine tablets, 5mg)
- Nasal corticosteroid spray (budesonide 64 µg/dose)

For the conjunctivitis symptoms, participants were provided with:

- Antihistamine eye drops (azelastine 0.05% or lodoxamide tromethamine 0.1% (in Croatia only)). In Serbia, oral antihistamine tablets were provided instead of eye drops for conjunctivitis symptoms.

Data on symptomatic use by visit and AR severity (based on the modified ARIA) was reported. Table 85 provides the average daily doses from the treatment maintenance phase to the end of the MT-06 trial (Visit 3 to Visit 8).

Table 85: MT-06 symptomatic medication use

Daily dose	12 SQ-HDM			SOC AR		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Desloratadine	0.51	0.59	0.61	0.54	0.65	0.63
Budesonide	0.16	0.29	0.27	0.21	0.29	0.42
Azelastine	0.06	0.12	0.09	0.06	0.11	0.12

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Daily dose	12 SQ-HDM			SOC AR		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Abbreviations: SQ, standardised quality; HDM, house dust mite; AR, allergic rhinitis; SOC, standard of care.						

Appendix Q provides a summary of the unit costs, dose, pack size, and data source used to estimate all established clinical management treatment costs used in the AA+AR and AR models.

The total AR annual treatment costs for the 12 SQ-HDM and SOC AR model treatment arms are detailed in Table 86.

Table 86: AR model - established clinical management treatment costs

AR health state	Total cost	
	12 SQ-HDM	SOC AR
Mild	£12.15	£15.24
Moderate	£21.03	£21.57
Severe	£19.86	£30.86
Abbreviations: SQ, standardised quality; HDM, house dust mite; AR, allergic rhinitis; SOC, standard of care.		

AA+AR established clinical management costs

The model allows for two methods of estimating established clinical management costs in the AA+AR population.

In the first instance, established clinical management costs have been estimated using data collected on symptomatic medication use in the MT-04 trial. As stated previously, symptomatic medications were allowed to be used as needed in addition to the IMP to which the patients had been randomised. ICS was provided as budesonide powder for inhalation in strengths of 100 or 200 µg per dose, and was used as daily controller treatment of asthma until Period 3B (ICS complete withdrawal), or throughout the trial for patients who had an asthma exacerbation in Period 3A (ICS 50% reduction) and continued the trial. Throughout the trial, SABA was provided as salbutamol for inhalation in a strength of 200 µg/dose, for use as needed to control asthma symptoms. Oral steroids were provided as prednisone or prednisolone tablets in strength of 5, 10, or 20 mg/tablet depending on the availability in each country. Oral steroids were used in accordance with the individual

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asthma action plan: only to treat acute severe asthma symptoms, acute deterioration of asthma symptoms, or acute deterioration in lung function in cases where the subject could not get in contact with the investigator [47].

Table 87 provides the average daily dose of ICS across the treatment maintenance phase of the MT-04 trial (Visit 4 to Visit 8), and the annual intake of SABA, estimated by taking the average total intake between Visit 9 to Visit 13 (representing the average total intake over 6 weeks over the efficacy assessment phase of the MT-04 trial) and extrapolating for 52 weeks.

Table 87: MT-04 symptomatic medication use

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

Abbreviations: SQ, standardised quality; HDM, house dust mite; AR, allergic rhinitis; AA, allergic asthma; SOC, standard of care.

The total AA+AR annual treatment costs for the 12 SQ-HDM and SOC AR model treatment arms are detailed in Table 88.

Table 88: AA+AR model - established clinical management treatment costs (MT-04)

AA+AR health state	Total cost	
	12 SQ-HDM	SOC AR
Well-controlled	£90.50	£90.22
Partially controlled	£99.42	£96.27
Uncontrolled	£123.40	£127.38

Abbreviations: SQ, standardised quality; HDM, house dust mite; AR, allergic rhinitis; AA, allergic asthma; SOC, standard of care.

In the second instance, health state costs are calculated as a weighted cost based on bundled treatment costs using treatment guidelines reflecting five levels of treatment steps with an estimated proportion of patients at each treatment step (termed the microcosting approach). As previously stated, the GINA guidelines are used for the diagnosis and management of AA and are based on the concept of control-based management [31]. The NICE guideline (NG80) recommends a similar

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stepwise approach for treatment and management of asthma. The BTS and Scottish Intercollegiate Guidelines Network (SIGN) [77] guideline provides recommendations based on current evidence for best practice management of asthma. Using the relevant treatment guidelines, Table 89 provides a summary of the established clinical management treatments used across the five treatment steps.

Table 89: AA+AR population – guideline treatment recommendations

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

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

The CARIOCA study [52] and the study by Reiber et al., 2021 [53], provide estimates for the distribution of patients across the five GINA treatment steps (see Table 90). In the base case, the distribution from the CARIOCA study was used to estimate a weighted cost for the well-controlled health state.

Table 90: Distribution of patients across 5 treatment steps as defined by GINA guidelines

Asthma guidelines	Proportion of patients	
	CARIOCA study	Reiber et al., 2021
Step 1	30.96%	34.08%
Step 2	14.23%	41.43%
Step 3	44.14%	22.16%
Step 4	10.25%	2.12%
Step 5	0.42%	0.22%

Abbreviations: GINA, global initiate for asthma.

Using the proportional split of patients from the CARIOCA study, the annual bundled weighted treatment cost for the 'well-controlled' AA+AR health state is £303.09.

As validated in an advisory board [8], people who have partially controlled or uncontrolled asthma will have an increased use of reliever and maintenance therapy compared with people who have controlled asthma. To reflect the increase in the use

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of reliever and maintenance therapy, the model applies a proportional increase to the costs in the 'partially controlled' and 'uncontrolled' health states, as informed by the relative increase in ICS use between the AA+AR health states as collected in the MT-04. The proportional increase in ICS use between the 'partially controlled' and 'uncontrolled' health states is 105.46% and 130.44%, respectively, resulting in a cost of £319.65 in the 'partially controlled' state and £395.35 in the 'uncontrolled' state.

In addition, in the advisory board it was highlighted that SLIT therapy may result in a reduced likelihood of mild-to-moderate AA patients progressing to a state of severe asthma. Although not considered a comparator treatment, biologics are predominantly used to treat severe and difficult-to-treat asthma (~50-60% of use), as recommended in the BTS/SIGN and GINA guidelines. As such, it is clinically plausible that a patient receiving AIT with mild or moderate AA may be less likely to progress to severe AA when compared to a patient who does not receive AIT, SLIT treatment could reduce the overall use of biologics. To reflect this, the model includes functionality to apply a relative reduction to the proportion of people in Step 5 in the 12 SQ-HDM treatment arm. Clinical experts from the advisory board suggested an average reduction in biologics of 22.5%.

As the MT-04 trial only included ICS and SABA treatments, with a 50% and 100% reduction in ICS applied in the efficacy assessment phase of the MT-04 trial, a microcosting approach is used to inform AA+AR health state cost in the model base case (see Table 91).

Table 91: AA+AR model - established clinical management treatment costs (microcosting)

AA+AR health state	Cost weighting	Weighted total cost	
		12 SQ-HDM	SOC AA+AR
Well-controlled	100.00%	£285.14	£303.09
Partially controlled	105.46%	£300.72	£319.65
Uncontrolled	130.44%	£371.94	£395.35

Abbreviations: SQ, standardised quality; HDM, house dust mite; AR, allergic rhinitis; AA, allergic asthma; SOC, standard of care.

Furthermore, to include the relevant rhinitis management costs for the AA+AR model population, the cost of the AR health states (see Table 86) are added to the AA+AR established clinical management costs.

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B.3.5.2 Health-state unit costs and resource use

As detailed in Section B.3.6, of the 10 studies identified across the original and updated cost and resource use SLR, five studies were considered appropriate for this submission. Green et al., 2017 [64] and Hahn-Pedersen et al., 2016 [66] report the results of the MT-04 and MT-06 trials, respectively. Robaina, Sanchez and Perez, 2016, As detailed in Section B.3.6, of the 10 studies identified across the original and updated cost and resource use SLR, 5 studies were considered appropriate for this submission. Green et al., 2017 [64] and Hahn-Pedersen et al., 2016 [66] report the results of the MT-04 and MT-06 trials, respectively. Robaina, Sanchez, and Perez, 2016 [92], and El-Qutob et al, 2016, [94] report the results of two separate observational studies conducted in Spain assessing the healthcare and rescue medication use for patients treated with SCIT (Acaroid®). Demoly et al., 2016 [93] report resource use data from an observational study conducted in France, Italy, and Spain in adults with severe, poorly controlled HDM ARD. The outcomes with respect to the relevant healthcare resource use are reported in Table 92.

Table 92: Summary results of cost and resource use SLR

Study	Country and study	Patient group	Healthcare resource use outcomes
Green et al., 2017 [64] (Analysis on MT-06)	Cost-effectiveness analysis from German perspective	AR with or without AA	Healthcare resource use values (annual mean) from MT-06 trial: 0.098 doctor visits vs 0.1037 doctor visits in the SLIT vs pharmacotherapy groups (5.8% reduction)
Hahn-Pedersen et al., 2016 [66] (Analysis on MT-04)†	Cost-effectiveness analysis from German perspective	AA with AR	Healthcare resource use values (annual mean) from MT-04 trial: 0.175 vs 0.105 GP visits, and 0.010 vs 0.025 emergency room visits in the SLIT vs pharmacotherapy groups
Robaina, Sanchez, and Perez. 2016 [92]	Observational study in Spain	AR and/or AA	Pre-treatment vs post-treatment with SCIT there was a 79% reduction in urgent care visits, 100% reduction in hospitalisation days, 82% reduction in allergist visits
El-Qutob et al., 2016 [94]	Observational study in Spain	AA and/or AR	A significant reduction after immunotherapy in use of scheduled medication from 358 [85.4%] to 209 [52.1%]. A significant reduction, both for visits at emergency department (75.4% reduction) and for unscheduled specialist outpatient visits (73.5% reduction)

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Study	Country and study	Patient group	Healthcare resource use outcomes
Demoly et al., 2016 [93]	Observational study in France, Italy, and Spain	AA and AR	On average, the poorly controlled allergy population had 3.5 GP visits and 1.7 allergist visits each year

† The company could not replicate the data on the annual number of GP visits and emergency room visits reported by Hahn-Pedersen et al., 2016. As data were available from the clinical trial reports, the values from Hahn-Pedersen et al., 2016 are not considered further in this analysis.
Abbreviations: AA, allergic asthma; AR, allergic rhinitis; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SLR, systematic literature review; GP, general practitioner.

For the AR population, data from the MT-06 study revealed 4.9% reduction in doctor visits from randomisation to the end of trial, as reported in Green et al., 2017 [64].

For the AA+AR population, data from the MT-04 study revealed a 18.7% reduction in GP visits during the treatment maintenance phase (Visit 4 to Visit 8), a 38.8% reduction during the final 4 weeks of the treatment maintenance phase, and a 25.8% reduction for all trial visits (Visit 3 to Visit 13). Data from the MT-04 study also revealed a 60.3% reduction, 79.9% reduction and 54.6% reduction in emergency room (ER) visits during the same assessment periods.

For mixed populations assessed in observational studies, Robaina, Sachez, and Perez, 2016 [92], report a significant reduction of 79% ($p<0.0001$) in urgent care visits and a significant 82% reduction in allergist visits ($p<0.0001$). El-Qutob et al., 2016 [94] report a significant reduction of 75.4% in emergency visits ($p<0.001$) and a significant 73.5% reduction in outpatient visits ($p<0.001$).

In their assessment of the burden of AA and AR, Demoly et al., 2016 [93] report that the poorly controlled allergy population had an average of 3.5 GP visits and 1.7 Allergist visits each year.

In addition to the SLR on cost and resource use, the company commissioned an assessment of the HES to identify the average number of episodes per patient for each hospital setting (elective day case, elective inpatient, emergency, outpatient) and by financial year with corresponding standard deviations, for the overall allergy patient cohort at a national level. Detail on the analysis and identification of the

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patient cohort is reported in Appendix R. The average number of outpatient appointments from 2016 to 2021 was 2.66.

The company conducted a primary care Delphi panel in April 2023 to develop a better understanding of the burden of ARD in primary care in the UK. During the Delphi panel, 7 GPs who treat patients with ARD were asked about the distribution of ARD severity and the frequency of GP visits in patients with AA+AR and AR alone. The average results of survey data completed by the panellists is reported in Table 93. On average, AA+AR patients have 2.7 GP visits per year, and AR patients have 1.7 GP visits per year.

Table 93: Survey results from primary care Delphi panel (April 2023)

Disease severity	Distribution of patients		Annual GP visits	
	AA+AR	AR	AA+AR	AR
Mild	54.09%	64.25%	1.42	0.96
Moderate	33.75%	26.47%	3.50	2.42
Severe	12.16%	9.28%	6.17	4.75
Abbreviations: AA, allergic asthma; AR, allergic rhinitis; GP, general practitioner.				

The company conducted a study which included a) caregivers of children aged 5 to 17 years with parent-reported symptomatic, moderate-to-severe AR according to the ARIA classification and at least one parent-reported perennial allergy, and b) a matched control group of caregivers of children without any parent-reported allergies. The aim of the study was to investigate the differences in HRQoL between children aged 5 to 17 years with AR and those without allergies in the UK and Canada. It excluded caregivers of children with any food allergy, as well as children who are receiving or have received allergy immunotherapy. The survey was distributed through email panels. The results of the study for the UK population identified that children with AR visited a GP 3.8 times per year compared with 1.4 times per year in children without allergies [95].

Table 94 provides a summary of the sources of data and the relevant number of primary care and secondary care visits identified in the SLR.

Table 94: Summary of primary and secondary care visits

Study	GP visits per year	

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	Established clinical management	12 SQ-HDM	GP reduction associated with AIT
MT-04 [36]	0.2345	0.1741	-25.76%
MT-06 [34]	0.1037	0.0986	-4.92%
Demoly et al., (2016) [93]	3.5	-	-
Primary care Delphi [8]	2.2	-	-
Romano et al., (2023) [95]	3.8	-	-
	Pre-treatment with AIT (Num. patients)	**Post-treatment with AIT (Num. patients)**	
Robaina, Sanchez, and Perez (2016) [92]	-	-	-
El-Qutob et al., (2016) [94]	-	-	-

Study	Hospital/ED/Allergist visits per year		Outpatient reduction associated with AIT
	Established clinical management	12 SQ-HDM	
MT-04	0.0273	0.0124	-54.58%
MT-06	-	-	-
Demoly et al., (2016)	1.70	-	-
HES data analysis	2.66	-	-
	Pre-treatment with AIT (Num. patients)	**Post-treatment with AIT (Num. patients)**	
Robaina, Sanchez, and Perez (2016)	91	16	-82.42% (p<0.0001)
El-Qutob et al., (2016)	68	18	-73.53% (p<0.0001)

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

In the model base case, the number of GP visits is informed by the results of the primary care Delphi and the number of secondary care visits is informed by the HES data analysis, as this was expected to best reflect UK clinical practice. The results of the MT-04 and MT-06 trials for the relative reduction in GP visits associated with 12 SQ-HDM is used. The results of the MT-04 trial and the study by El-Qutob et al., 2016, [94] are used to inform the relative reduction in secondary care visits for the AA+AR population, and the AR population, respectively.

As noted in Section B3.3.1.2, in the model base case, it is assumed that treatment waning will start in Year 15, and by Year 20, 80% of patients in the 12 SQ-HDM

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treatment arm will be set to match the distribution of patients in the established clinical management arm. This waning effect is applied to management costs. A linear waning effect is modelled, whereby the proportion of patients to whom waning is applied is divided by the difference between the waning start year and the waning end year.

B3.5.2.1 Exacerbation costs

The costs associated with moderate and severe exacerbations were considered in the analysis. The costs of moderate and severe exacerbations include both primary and secondary care visits, and additional medication costs as informed by the GINA guidelines and a publication by Lane et al., 2006[96]. The corresponding estimates for a moderate and severe exacerbation are presented in Table 95 and Table 96. These figures were validated during an advisory board, in which 12.5% of respiratory specialists noted that these costs may not reflect the current management of exacerbation in the UK. However, no alternative figures or data sources were provided.

Table 95: Moderate exacerbation - resource use

Type of Care	Resource	Resource Frequency/Dose	Source
Primary Care (70%)	GP consultation	70% of patients will visit the GP	GINA Guidelines 2023 [31]
	SABA use	4-10 puffs every 20 mins for 1 hour	
	Prednisolone	40-50 mg the day of, followed by 40-50 mg taken for 5-7 days after	
Secondary Care (30%)	Emergency Department	30% of patients with moderate exacerbations are assumed to seek treatment in secondary care.	Assumption

Abbreviations: GINA, global initiative for asthma; SABA, short-acting β 2-agonist; GP, general practitioner.

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Table 96: Severe exacerbation - resource use

Type of Care	Resource	Resource Frequency/Dose	Source
Primary Care (70%)	GP consultation	70% of patients will visit the GP	GINA Guidelines 2023 [31]
	SABA	4-10 puffs every 20 mins for 1 hour	
	Prednisolone	40-50 mg the day of, followed by 40-50 mg taken for 5-7 days after	
Secondary Care	ED	90% of patients with severe exacerbations are treated in emergency departments	Lane et al., (2006)[96]
	Respiratory ward	38% of patients referred onto secondary care are hospitalised	
	Intensive Care Unit (ICU)	3% of patients with severe exacerbations are admitted to an ICU for a duration of 2 days	

Abbreviations: GINA, global initiative for asthma; SABA, short-acting β 2-agonist; GP, general practitioner; ED, emergency department; ICU, intensive care unit.

It was assumed that only 30% of patients with a moderate exacerbation would require secondary care (equal to an emergency department visit). The remaining 70% of patients are assumed to be treated within a primary care setting. Patients experiencing a severe exacerbation are assumed to experience the same primary care resources as moderate exacerbations. However, these patients are subsequently hospitalised, using the resource breakdown outlined in Lane et al., 2006 [96].

In the base case, the cost of a moderate exacerbation is equal to £111.95, and the cost of a severe exacerbation is equal to £464.90. For reference, the cost of a exacerbations used in the NICE submission for omalizumab (TA278), was £87.70 for non-severe exacerbations and £124.32 for severe exacerbations. However, it was noted that these costs may be underestimated, referencing previous submissions using costs of £785 and £304.51 for exacerbation costs.

B.3.5.3 Adverse reaction unit costs and resource use

The costs associated with AEs in the AA+AR population and the AR population are considered in the model.

The AE and probability of events occurring in the model has been previously discussed. Of the events in the MT-04 trial, only 14.96% and 9.25% required specific action in the 12 SQ-HDM and placebo groups, respectively. Similarly, of the events

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in the MT-06 trial, only 12.63% and 15.29% required specific action in the 12 SQ-HDM and placebo groups, respectively.

As the majority of adverse events were reported as mild or moderate, and because no relevant or appropriate costs for AEs were identified in the SLR, in the base case analysis AEs were costed as a single GP appointment (£41.00; PSSRU 2022) and weighted by the proportion requiring management.

B3.6 Severity

The technology is not expected to meet the criteria for a severity weight.

B3.7 Summary of base-case analysis inputs and assumptions

B.3.7.1 Summary of base-case analysis inputs

A summary of the base case cost-effectiveness analysis inputs is provided in Table 97.

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Table 97: Summary of base case cost-effectiveness parameters

Parameter	Values fixed order	Input	SE	Distribution	Sheet name
Section B3.2 Economic analysis perspective					
Mean age (AA+AR)	N/A	33.40	0.41	*Normal*	Set-up
Mean age (AR)		32.30	0.35	*Normal*	Set-up
Sex (%M, AA+AR)		51.68%	5.17%	*Beta*	Set-up
Sex (%M, AR)		49.80%	4.98%	*Beta*	Set-up
Section B3.5 Cost and healthcare resource use					
12 SQ-HDM treatment cost	N/A	£975.46	£97.55	*Gamma*	Treatment costs
12 SQ-HDM initiation cost		£262.25	£26.23	*Gamma*	Treatment costs
12 SQ-HDM diagnostic test cost		£2.96	£0.30	*Gamma*	Treatment costs
12 SQ-HDM health state cost, Well-controlled	3	£310.23	£31.02	*Gamma*	Treatment costs
12 SQ-HDM health state cost, Partially controlled	2	£326.34	£32.63	*Gamma*	Treatment costs
12 SQ-HDM health state cost, Uncontrolled	1	£400.03	£40.00	*Gamma*	Treatment costs
SOC AA+AR health state cost, Well-controlled	3	£321.45	£32.15	*Gamma*	Treatment costs
SOC AA+AR health state cost, Partially controlled	2	£338.01	£33.80	*Gamma*	Treatment costs
SOC AA+AR health state cost, Uncontrolled	1	£413.71	£41.37	*Gamma*	Treatment costs
12 SQ-HDM health state cost, Mild	3	£12.15	£1.21	*Gamma*	Treatment costs
12 SQ-HDM health state cost, Moderate	2	£21.03	£2.10	*Gamma*	Treatment costs
12 SQ-HDM health state cost, Severe	1	£19.86	£1.99	*Gamma*	Treatment costs
SOC AR health state cost, Mild	3	£15.24	£1.52	*Gamma*	Treatment costs
SOC AR health state cost, Moderate	2	£21.57	£2.16	*Gamma*	Treatment costs
SOC AR health state cost, Severe	1	£30.86	£3.09	*Gamma*	Treatment costs
AA+AR, Annual GP visits, mild	3	1.42	0.30	*Gamma*	Management costs

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Parameter	Values fixed order	Input	SE	Distribution	Sheet name
AA+AR, Annual GP visits, moderate	2	3.50	0.55	*Gamma*	Management costs
AA+AR, Annual GP visits, severe	1	6.17	1.26	*Gamma*	Management costs
AR, Annual GP visits, mild	3	0.96	0.40	*Gamma*	Management costs
AR, Annual GP visits, moderate	2	2.42	0.90	*Gamma*	Management costs
AR, Annual GP visits, severe	1	4.75	1.65	*Gamma*	Management costs
Relative reduction, AA+AR GP visits	N/A	25.76%	2.58%	*Beta*	Management costs
Relative reduction, AR GP visits		4.92%	0.49%	*Beta*	Management costs
AA+AR, Annual outpatient visits		2.66	0.00	*Gamma*	Management costs
AR, Annual outpatient visits		2.66	0.00	*Gamma*	Management costs
Relative reduction, AA+AR outpatient visits		54.58%	5.46%	*Beta*	Management costs
Relative reduction, AR outpatient visits		73.53%	7.35%	*Beta*	Management costs
Moderate exacerbation cost	2	£111.95	£11.20	*Gamma*	Management costs
Severe exacerbation cost	1	£464.90	£46.49	*Gamma*	Management costs
Relative reduction, biologics use	N/A	22.50%	2.25%	*Beta*	Set-up
Section B3.4 Health-related quality of life					
12 SQ-HDM health state utility, Well-controlled	1	0.785	0.079	*Beta*	HRQoL
12 SQ-HDM health state utility, Partially controlled	2	0.785	0.079	*Beta*	HRQoL
12 SQ-HDM health state utility, Uncontrolled	3	0.785	0.079	*Beta*	HRQoL
SOC AA+AR health state utility, Well-controlled	1	0.753	0.075	*Beta*	HRQoL
SOC AA+AR health state utility, Partially controlled	2	0.753	0.075	*Beta*	HRQoL
SOC AA+AR health state utility, Uncontrolled	3	0.753	0.075	*Beta*	HRQoL
Moderate exacerbation disutility	2	-0.083	-0.005	*Gamma*	HRQoL
Severe exacerbation disutility	1	-0.115	-0.009	*Gamma*	HRQoL

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Parameter	Values fixed order	Input	SE	Distribution	Sheet name
12 SQ-HDM health state utility, Mild	1	0.919	0.092	*Beta*	HRQoL
12 SQ-HDM health state utility, Moderate	2	0.919	0.092	*Beta*	HRQoL
12 SQ-HDM health state utility, Severe	3	0.919	0.092	*Beta*	HRQoL
SOC AR health state utility, Mild	1	0.898	0.090	*Beta*	HRQoL
SOC AR health state utility, Moderate	2	0.898	0.090	*Beta*	HRQoL
SOC AR health state utility, Severe	3	0.898	0.090	*Beta*	HRQoL
Section B3.3 Clinical parameters and variables					
AA+AR, AE time on treatment (ToT) prior to discon.	N/A	30.44	3.04	*Normal*	Adverse events
AR, AE ToT prior to discon.		30.44	3.04	*Normal*	Adverse events
AA+AR, Treatment dicontinuation Year 2	N/A	8.49%	0.85%	*Beta*	Effectiveness
AA+AR, Treatment dicontinuation Year 3		8.49%	0.85%	*Beta*	Effectiveness
AA+AR, Discontinuation benefit Year 1		50.00%	5.00%	*Beta*	Effectiveness
AA+AR, Discontinuation benefit Year 2		50.00%	5.00%	*Beta*	Effectiveness
AA+AR, Discontinuation benefit Year 3		50.00%	5.00%	*Beta*	Effectiveness
AA+AR, ToT prior to treat discon.		182.63	18.26	*Normal*	Effectiveness
AA+AR, time horizon to meet comparator arm, start of waning		15.00	1.50	*Normal*	Effectiveness
AA+AR, time horizon to meet comparator arm, end of waning		20.00	2.00	*Normal*	Effectiveness
AA+AR, proportion of patients to meet comparator arm		80.00%	8.00%	*Beta*	Effectiveness
AA+AR, 12 SQ-HDM moderate exacerbation rate		36.02%	3.60%	*Beta*	Effectiveness
AA+AR, 12 SQ-HDM severe exacerbation rate		8.01%	0.80%	*Beta*	Effectiveness
AA+AR, SOC AA+AR moderate exacerbation rate		44.66%	4.47%	*Beta*	Effectiveness

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Parameter	Values fixed order	Input	SE	Distribution	Sheet name
AA+AR, SOC AA+AR severe exacerbation rate		13.70%	1.37%	*Beta*	Effectiveness
AR, Treatment dicontinuation Year 2		5.03%	0.50%	*Beta*	Effectiveness
AR, Treatment dicontinuation Year 3		5.03%	0.50%	*Beta*	Effectiveness
AR, Discontinuation benefit Year 1		50.00%	5.00%	*Beta*	Effectiveness
AR, Discontinuation benefit Year 2		50.00%	5.00%	*Beta*	Effectiveness
AR, Discontinuation benefit Year 3		50.00%	5.00%	*Beta*	Effectiveness
AR, ToT prior to treat discon.		182.63	18.26	*Normal*	Effectiveness
AR, time horizon to meet comparator arm, start of waning		15.00	1.50	*Normal*	Effectiveness
AR, time horizon to meet comparator arm, end of waning		20.00	2.00	*Normal*	Effectiveness
AR, proportion of patients to meet comparator arm		80.00%	8.00%	*Beta*	Effectiveness

Abbreviations: GP, general practitioner; AR, allergic rhinitis; AA, allergic asthma; SQ, standardised quality; HDM, house dust mite; ToT, time on treatment; SOC, standard of care; SE, standard error.

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B.3.7.2 Assumptions

A list of the assumptions made in the base case analysis and their justifications is provided in Table 98. Where appropriate, the exploration of the potential impact of these assumptions is a scenario analysis is noted.

Table 98: Summary of assumptions used in the analysis

Model input	Description of assumption	Justification
Discontinuation	It is assumed that a proportion of people who discontinue treatment in Year 1, 2, or 3, may continue to receive the benefit associated with 12 SQ-HDM. In the base case, 50% of patients who discontinue treatment with 12 SQ-HDM may continue to receive treatment benefit.	The Phase 2 P003 trial demonstrated statistically significant improvements in efficacy could be observed as early as 8 weeks following initiation of 12 SQ-HDM [42, 43]. Additionally, during an advisory board, it was noted that patients who discontinue AIT treatment early may still receive treatment benefit.
Long-term treatment effectiveness	For the 12 SQ-HDM treatment arm it was assumed that patients would improve by 5% each year from Year 2 to Year 5, reduced to a 2.5% improvement from Year 5 to Year 10, followed by a period of waning of 2.5% each year to Year 20. After Year 20, it is assumed that patients remain stable in their state. It is assumed that patients receiving established clinical management will remain stable during all years following Year 1. Additionally, it is assumed that for the 12 SQ-HDM treatment arm, a proportion of the population will wane to meet the established clinical management treatment arm. This waning effect impacts patients' health state movements, exacerbation rates (AA+AR model only), primary care and secondary care costs, and QALYs. In the base case it is assumed that treatment waning will	In a modified Delphi advisory panel, conducted with 8 secondary care allergy specialists across Ireland, it was agreed that after cessation of 12 SQ-HDM, treatment effectiveness is likely to have a sustained and clinically significant effect for at least 10 years with potential waning over the subsequent decade, with treatment effectiveness unlikely to completely disappear for HDM-sensitised AA patients. These results were presented in a second advisory board conducted with 12 clinical experts across the UK who similarly agreed that treatment effectiveness is likely to have a sustained and clinically significant effect for at least 10 years with potential waning over the subsequent decade. Furthermore, the results of the REACT study evidence a treatment benefit with AIT, with no

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Model input	Description of assumption	Justification
	start in Year 15, and by Year 20, 80% of patients in the 12 SQ-HDM treatment arm will be set to match the distribution of patients in the established clinical management arm.	evidence of treatment waning over the 9 years of follow-up.
Utilities	It is assumed that any AE-related utility decrements are implicitly captured in the treatment-specific utilities used in the model base case.	The majority of AEs reported in the key Phase 3 clinical trials were considered mild or moderate with a median duration of 15 to 21 days. Health-related quality of life data in the MT-04 and MT-06 trial were collected from treatment initiation. As such, any utility decrements associated with AEs will be implicitly captured in the average treatment-specific utility values.
Established clinical management costs	A proportional increase in the use of asthma medication associated with asthma control is applied in the model base case.	As validated in an advisory board, people who have partially controlled or uncontrolled asthma will have an increased use of reliever and maintenance therapy compared with people who have controlled asthma. To reflect the increase in the use of reliever and maintenance therapy, the model applies a proportional increase to the costs in the 'partially controlled' and 'uncontrolled' health states, as informed by the relative increase in ICS use between the AA+AR health states as collected in the MT-04.
Established clinical management costs	It is assumed that the use of 12 SQ-HDM in patients with mild or moderate AA+AR may prevent the future use of biologics.	In the advisory board it was highlighted that SLIT therapy may result in a reduced likelihood of mild-to-moderate AA patients progressing to a state of severe asthma. Although not considered a comparator treatment, biologics are predominantly used to treat severe and difficult-to-treat asthma (~50-60% of use), as recommended in the BTS/SIGN and GINA guidelines. As such, it is clinically plausible that a patient receiving AIT with

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Model input	Description of assumption	Justification
		mild or moderate AA may be less likely to progress to severe AA when compared to a patient who does not receive AIT, SLIT treatment could reduce the overall use of biologics.
Exacerbation costs	It was assumed that only 30% of patients with a moderate exacerbation would require secondary care (equal to an emergency department visit). The remaining 70% of patients are assumed to be treated within a primary care setting. Patients experiencing a severe exacerbation are assumed to experience the same primary care resources as moderate exacerbations.	Limited information were available on the management of moderate and severe asthma exacerbations. The systematic literature review on cost and resource use did not identified any suitable sources of data. For reference, the cost of a exacerbations used in the NICE submission for omalizumab (TA278), was £87.70 for non-severe exacerbations and £124.32 for severe exacerbations. However, it was noted that these costs may be underestimated, referencing previous submissions using costs of £785 and £304.51 for exacerbation costs.

Abbreviations: NICE, national institute for health and care excellence; AIT, allergy immunotherapy; SLIT, sublingual immunotherapy; GINA, global initiative for asthma; AA, allergic asthma; AR, allergic rhinitis; AE, adverse event; SQ, standardised quality; HDM, house dust mite; BTS, British thoracic society SIGN, Scottish intercollegiate guideline network; ICS. Inhaled corticosteroid.

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B3.8 Base-case results

B.3.8.1 Base-case incremental cost-effectiveness analysis results

The deterministic base case cost-effectiveness analysis results of 12 SQ-HDM compared with established clinical management for the treatment of HDM AA+AR and HDM AR over a lifetime time horizon are summarised in Table 99 and Table 100, respectively.

In the AA+AR population, treatment with 12 SQ-HDM compared with established clinical management alone was associated with 0.37 increased QALYs at an incremental cost of -£2,094 at list price.

Table 99: AA+AR - base case deterministic results

AA+AR	12 SQ-HDM	SOC AA+AR	Incremental	ICER
Total costs (£)	£24,124	£26,217	-£2,094	12 SQ-HDM dominant
Total life years (LY)	22.55	22.55	0.00	
Total QALYs	16.10	15.73	0.37	
Abbreviations: SOC, standard of care; LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; HDM, house dust mite; AA, allergic asthma; AR, allergic rhinitis				

In the AR population, treatment with 12 SQ-HDM compared with established clinical management alone was associated with 0.26 increased QALYs at an incremental cost of -£2,731 at list price.

Table 100: AR - base case deterministic results

AR	12 SQ-HDM	SOC AR	Incremental	ICER
Total costs (£)	£11,562	£14,294	-£2,731	12 SQ-HDM dominant
Total LY	22.74	22.74	0.00	
Total QALYs	19.29	19.03	0.26	
Abbreviations: SOC, standard of care; LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; HDM, house dust mite; AA, allergic asthma; AR, allergic rhinitis				

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In both model populations, treatment with 12 SQ-HDM results in a dominant ICER, and as such, is cost-effective at a willingness-to-pay (WTP) threshold of £20,000/QALY. The net monetary benefit (NMB) at a WTP of £20,000/QALY is £9,561 and £8,008 for the AA+AR and AR populations, respectively.

Table 101 and Table 102 provide a summary of the disaggregated costs, QALYs, and LYs for the AA+AR and AR populations, respectively.

Table 101: AA+AR - disaggregated costs, LYs, and QALYs

	12 SQ-HDM	SOC AA+AR	Incremental
Treatment and administration	£2,683	£0	£2,683
SOC costs	£7,618	£7,890	-£272
Exacerbations	£2,141	£2,563	-£422
Primary care	£2,238	£2,600	-£362
Secondary care	£9,439	£13,164	-£3,725
Adverse events	£4	£0	£4
Total costs	**£24,124**	**£26,217**	**-£2,094**
Well-controlled	7.19	5.73	1.46
Partially controlled	10.94	12.01	-1.07
Uncontrolled	4.41	4.80	-0.39
Total LYs	**22.55**	**22.55**	**0.00**
Well-controlled	5.21	4.01	1.19
Partially controlled	7.83	8.44	-0.61
Uncontrolled	3.15	3.37	-0.22
Moderate exacerbation	-0.06	-0.06	0.01
Severe exacerbation	-0.02	-0.03	0.01
Adverse events	0.00	0.00	0.00
Total QALYs	**16.10**	**15.73**	**0.37**

Abbreviations: SOC, standard of care; LY: Life years; QALY: quality-adjusted life year; SQ, standardised quality; HDM, house dust mite; AA, allergic asthma; AR, allergic rhinitis.

Table 102: AR - disaggregated costs, LYs, and QALYs

	12 SQ-HDM	SOC AR	Incremental
Treatment and administration	£2,868	£0	£2,868
SOC costs	£379	£440	-£61
Exacerbations	£0	£0	£0
Primary care	£562	£579	-£17

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Secondary care	£7,750	£13,274	-£5,524
Adverse events	£4	£1	£4
Total costs	**£11,562**	**£14,294**	**-£2,731**
Well-controlled	11.58	9.55	2.04
Partially controlled	10.17	12.09	-1.92
Uncontrolled	0.98	1.10	-0.12
Total LYs	**22.74**	**22.74**	**0.00**
Well-controlled	9.90	7.98	1.92
Partially controlled	8.56	10.12	-1.56
Uncontrolled	0.84	0.93	-0.09
Moderate exacerbation	0.00	0.00	0.00
Severe exacerbation	0.00	0.00	0.00
Adverse events	0.00	0.00	0.00
Total QALYs	**19.29**	**19.03**	**0.26**
Abbreviations: SOC, standard of care; LY: Life years; QALY: quality-adjusted life year; SQ, standardised quality; HDM, house dust mite; AR, allergic rhinitis.			

B3.9 Exploring uncertainty

B.3.9.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to explore the effect of uncertainty associated with key model inputs. PSA results for 2,000 iterations are presented in Table 103 and Table 104. The mean incremental costs and QALYs of 12 SQ-HDM compared with established clinical management alone were calculated to estimate the probabilistic ICER.

Sampled values for health state costs and utilities, management costs, and exacerbation costs and utilities were ordered in groups so as to ensure that iterations could not draw from illogical values. For example, the utility score for moderate AR could not be greater than the utility score for mild AR. Equally, the utility score for severe AR could not be greater than the utility score for moderate AR. This functionality can be turned off in the parameters sheet.

Additionally, sampling of utilities were limited so that if treatment-specific utility values are used in the model, treatment with 12 SQ-HDM could not result in a lower utility score compared with treatment established clinical management alone. This

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limitation does not extend to the QALY loss associated with AEs, and is not applied if health state specific utilities are used.

Table 103: AA+AR - base case probabilistic results

AA+AR	12 SQ-HDM	SOC AA+AR	Incremental	ICER
Total costs (£)	£23,970	£26,310	-£2,340	12 SQ-HDM dominant
Total LY	22.47	22.47	0.00	
Total QALYs	16.35	15.65	0.70	
Abbreviations: SOC, standard of care; LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; HDM, house dust mite; AA, allergic asthma; AR, allergic rhinitis				

Table 104: AR - base case probabilistic results

AR	12 SQ-HDM	SOC AR	Incremental	ICER
Total costs (£)	£11,601	£14,400	-£2,799	12 SQ-HDM dominant
Total LY	22.69	22.69	0.00	
Total QALYs	19.34	19.23	0.11	
Abbreviations: SOC, standard of care; LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; HDM, house dust mite; AA, allergic asthma; AR, allergic rhinitis				

The incremental costs from the probabilistic analysis were comparable with the deterministic analysis. In the AA+AR population, the incremental QALYs in the probabilistic analysis were materially higher compared with the deterministic analysis (0.70 versus 0.37). The skewness in the incremental QALYs is likely associated with the limitation that, under the treatment-specific utility approach, the utility score for the 12 SQ-HDM treatment arm cannot be lower than the utility score for the established clinical management treatment arm. The opposite skewness is observed in the AR population, in which, the incremental QALYs in probabilistic analysis were lower compared with the deterministic analysis (0.11 versus 0.26). Here, the skewed lower incremental QALYs is likely associated with the application of age-adjustment to match general population utilities, whereby any utility score sampled above the equivalent age-adjusted general population utility will be capped. In the basecase,

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the mean AR 12 SQ-HDM utility is 0.919 compared with a mean age general population utility of 0.920.

The PSA scatter plots are shown in Figure 29 and Figure 30. The ICER in the probabilistic analysis remained cost-effective with a dominant ICER in the AA+AR and AR populations, with a probability of cost-effectiveness of 100% at a WTP threshold of £20,000/QALY.

Figure 29: Cost-effectiveness plane: AA+AR

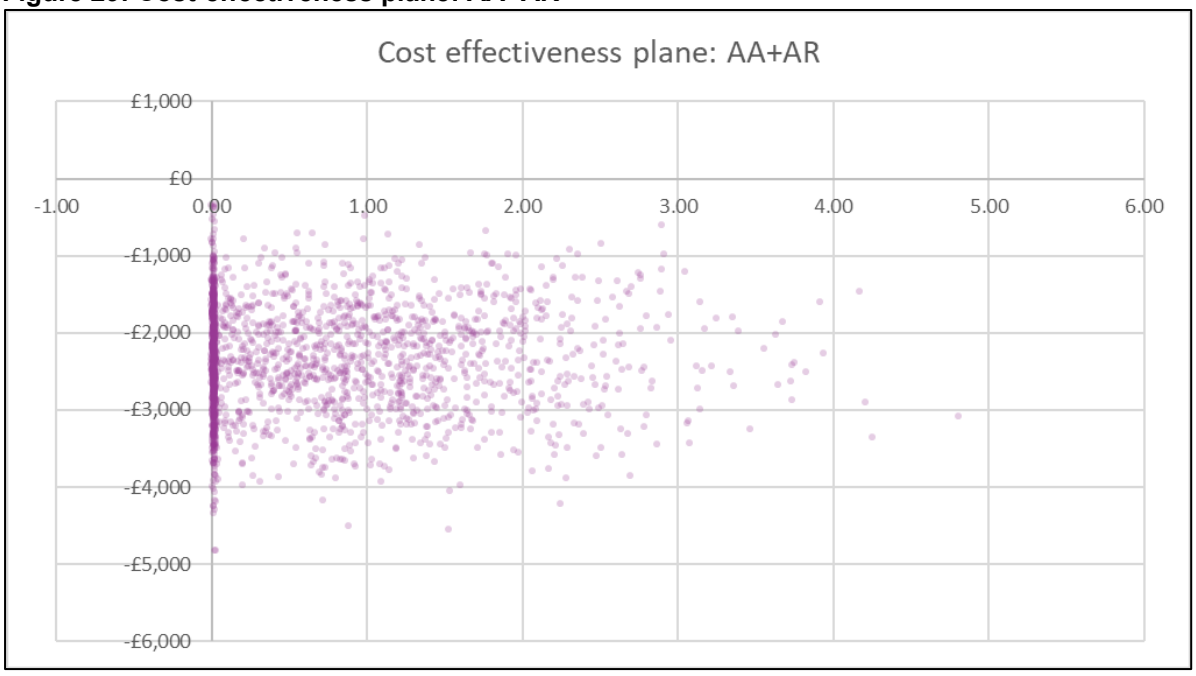

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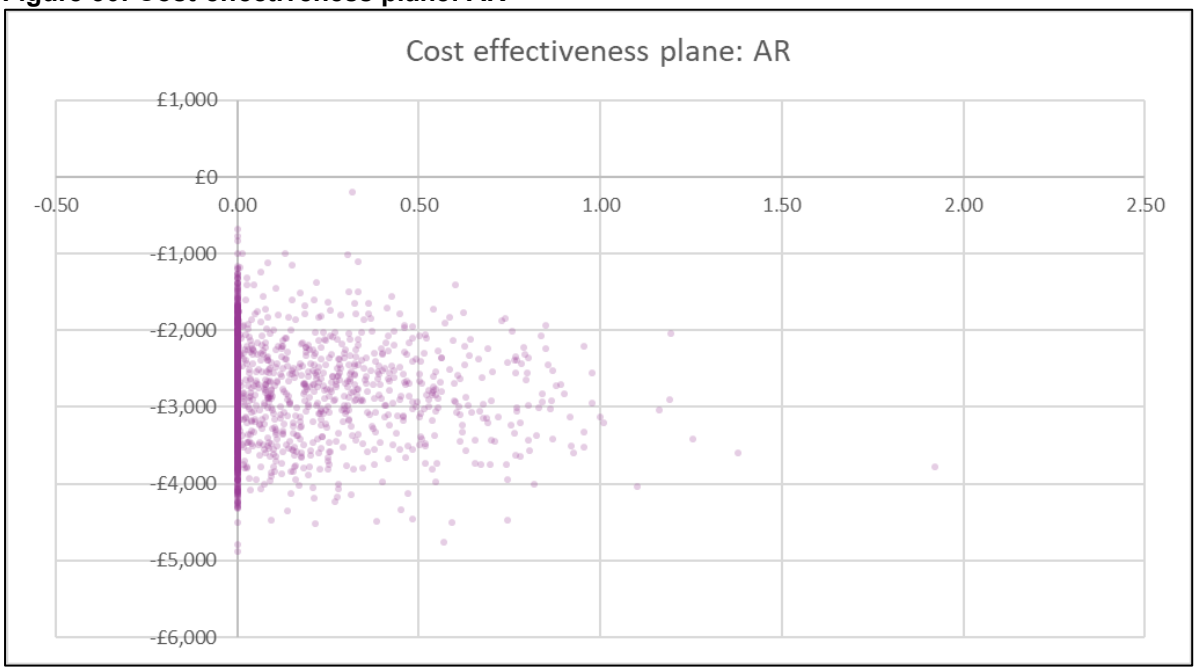
Figure 30: Cost-effectiveness plane: AR



B.3.9.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were performed to explore the effect of uncertainty associated with varying individual model inputs. The inputs with an impact on the NMB of ≥£1,000 are presented in descending order as a tornado plot in Figure 31 and Figure 32.

Similar to the PSA, sampling of utilities were limited so that if treatment-specific utility values are used in the model, treatment with 12 SQ-HDM could not result in a lower utility score compared with treatment established clinical management alone. This limitation does not extend to the QALY loss associated with AEs, and is not applied if health state specific utilities are used.

The cost-effectiveness of 12 SQ-HDM is most sensitive to changes in treatment-specific utilities. In none of the varied parameters did the ICER (or NMB) exceed a WTP threshold of £20,000/QALY.

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Figure 31: Tornado plot of DSA: AA+AR

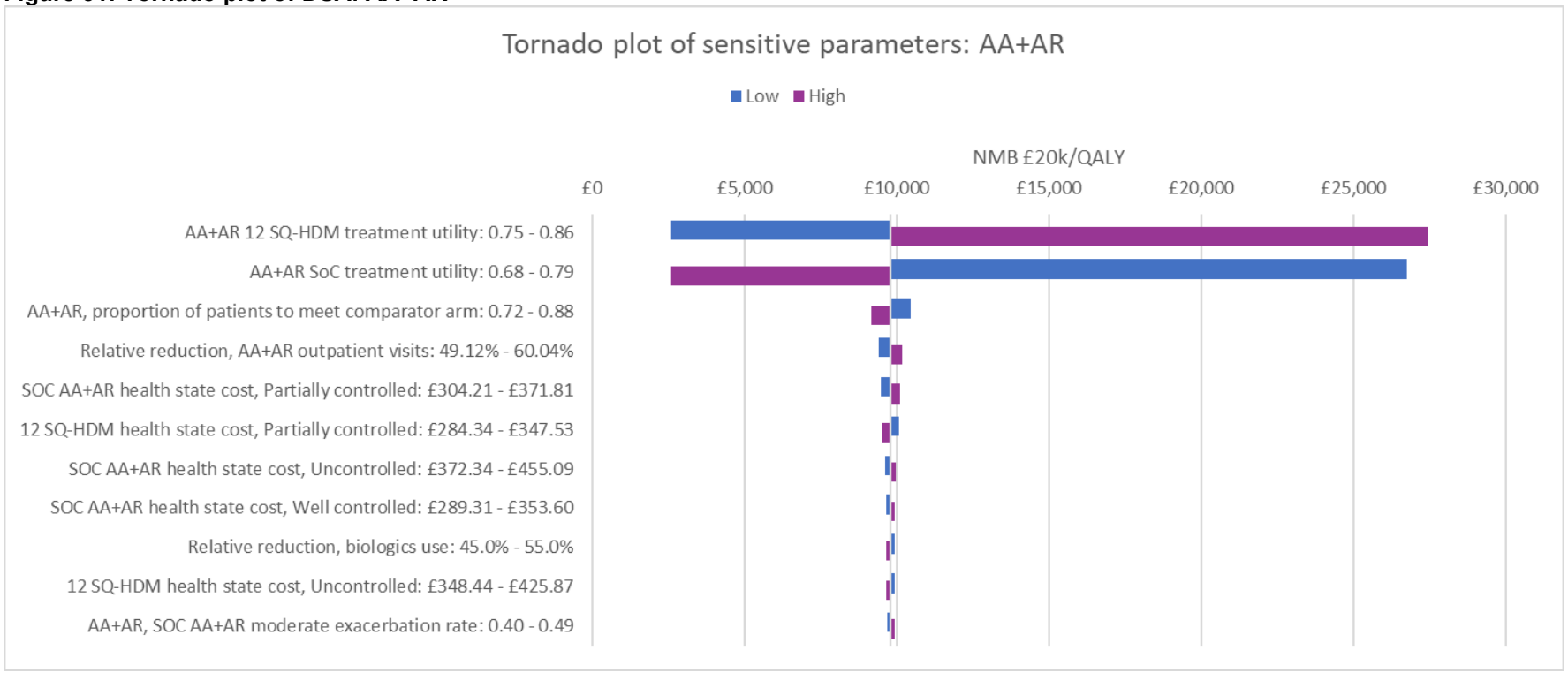

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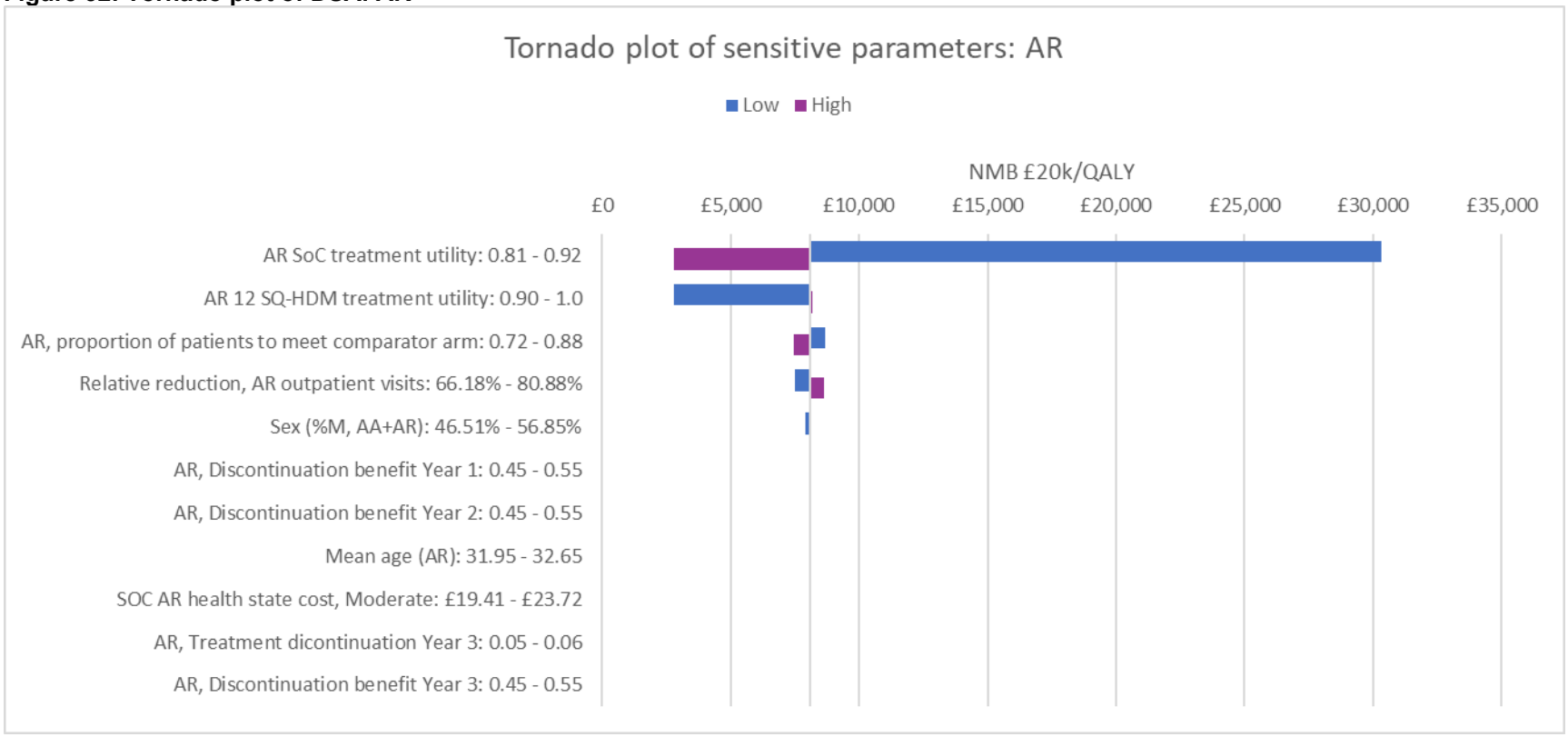
Figure 32: Tornado plot of DSA: AR



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B.3.9.3 Scenario analysis

A range of scenario analyses were conducted to test the robustness of the model to alternative model inputs and assumptions. The details of the undertaken analyses and the results of the scenario analyses, presented as the ICER of 12 SQ-HDM compared with established clinical management alone, are shown in Table 105.

In none of the 29 scenarios did the ICER (or NMB) exceed a WTP threshold of £20,000/QALY.

Table 105: Scenario analysis

Scenario	Description	NMB (£20k) AA+AR	NMB (£20k) AR
Base case deterministic results		**£9,561**	**£8,008**
1.	Asthma treatment step distribution at baseline In the base case, the CARIOCA study is used to inform the proportion of patients at each asthma treatment step. The results using data from Reiber et al., 2021 are presented here.		
1.a.	**Treatment step distributions: Reiber et al., 2021**	**£9,382**	**unchanged**
2.	Administration of 12 SQ-HDM in primary care In line with the marketing authorisation for 12 SQ-HDM, treatment should be initiated by physicians with experience in the treatment of allergic diseases. In the base case this is costed as a non-admitted face-to-face attendance with a respiratory specialist in secondary care. Following an improvement in the care pathway for ARD, it is reasonable to assume that 12 SQ-HDM could be administered in primary care.		
2.a.	**Administration cost equal to GP visit**	**£9,782**	**£8,229**
3.	12 SQ-HDM benefit following discontinuation To account for any potential treatment benefit achieved prior to discontinuation and sustained post discontinuation, a proportion of patients are modelled as 12 SQ-HDM patients and experience the same transition probabilities, health care costs, and HRQoL as patients receiving 12 SQ-HDM for the duration of the model. In the model basecase 50% of patients are assumed to experience benefits of 12 SQ-HDM following discontinuations. This scenario analysis presents alternative proportions following discontinuation in Cycles 1,2, and 3.		
3.a.	**Proportion to receive 12 SQ-HDM benefit: 0%**	**£8,112**	**£7,250**
3.b.	**Proportion to receive 12 SQ-HDM benefit: 100%**	**£11,003**	**£8,769**
4.	Discontinuation rates In the basecase, discontinuation rates are informed by the results of the MT-04 and MT-06 trials. In the non-interventional CARIOCA study, 40.3% of AR patients and 45.7% of AA patients discontinued treatment. This scenario analysis presents the results for discontinuation rates equal to those in the CARIOCA study for Cycles 1,2 and 3.		

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4.a.	**CARIOCA study discontinuation**	**£6,471**	**£5,323**
5.	Time horizon In the model base case, a lifetime time horizon is used to reflect that AA and AR are considered is chronic and expected to continue for the duration of patients' lifetime. Results are presented using alternative time horizons.		
5.a.	**Time horizon: 5 years**	**£1,345**	**£1,281**
5.b.	**Time horizon: 10 years**	**£4,555**	**£4,037**
5.c.	**Time horizon: 20 years**	**£8,171**	**£6,836**
6.	Treatment costing (MT-04) As the MT-04 trial only included ICS and SABA treatments, with a 50% and 100% reduction in ICS applied in the efficacy assessment phase of the MT-04 trial, a microcosting approach is used to inform AA+AR health state cost in the model base case. This scenario presents results using the costs collected during the MT-04 trial to inform established clinical management treatment costs.		
6.a	**MT-04 established clinical management costs**	**£9,395**	**unchanged**
7.	Annual number of GP visits In the model base case, the number of GP visits is informed by the results of the primary care Delphi. Results using alternative sources are presented. See Table 94 for detail on values used.		
7.a	**MT-04 and MT-06**	**£9,232**	**£7,989**
7.b	**Demoly et al., 2016**	**£9,692**	**£7,920**
7.c	**Romano et al., 2023**	**£9,734**	**£7,914**
8.	Annual number of hospitalisations In the model base case, the number of hospitalisations is informed by the results of the HES data analysis. Results using alternative sources are presented. See Table 94 for detail on values used.		
8.a	**MT-04**	**£5,875**	**unchanged**
8.b	**Demoly et al., 2016**	**£8,217**	**£6,014**
9.	Asthma control levels (non-interventional studies) As detailed in Section B.2.2.2, three non-interventional studies were considered relevant to this submission and provide data on asthma control. The CARIOCA study [52], and the studies by Reiber et al., 2021 [53] and Sidenius et al., 2021 [54] assessed the benefit, safety, and tolerability of 12 SQ-HDM in a real-life setting across France, Germany, Sweden, and Denmark. Results using the alternative sources of asthma control in Year 1 are presented below.		
9.a.	**CARIOCA study**	**£18,150**	**unchanged**
9.b.	**Reiber et al., 2021**	**£15,528**	**unchanged**

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9.c.	**Sidenius et al., 2021**	**£17,881**	**unchanged**
10.	MT-06 year 1 efficacy definition Two approaches were considered in estimating the cut-off for the presence of 'troublesome symptoms' item when estimating the proportion of people in each health state at baseline and at Year 1 for the AR population (See Section B3.3.1.1 for more detail).		
10.a.	**Alternative MT-06 efficacy at Year 1**	**unchanged**	**£8,009**
11.	Transitions from Year 2 to Year 20 in the base case for both the AA+AR and AR models, for the 12 SQ-HDM treatment arm it was assumed that patients would improve by 5% each year from Year 2 to Year 5, reduced to a 2.5% improvement from Year 5 to Year 10, followed by a period of waning of 2.5% each year to Year 20. After Year 20, it is assumed that patients remain stable in their state. This scenario presents the results whereby all patients remain stable in their state following Year 1. This scenario does not stop treatment waning to the SOC arm.		
11.a.	**No patient movement following Year 2.**	**£9,542**	**£8,016**
12.	Waning of 12 SQ-HDM to SOC arm To model any potential waning associated with 12 SQ-HDM, a proportion of patients in the intervention arm can be set to wane to the comparator arm distribution at a user specified time point. in the model base case, it is assumed that treatment waning will start in Year 15, and by Year 20, 80% of patients in the 12 SQ-HDM treatment arm will be set to match the distribution of patients in the established clinical management arm. This scenario explores alternative waning values.		
12.a.	**Waning: 15 to 20 at 100%**	**£7,959**	**£6,515**
12.b.	**Waning: 15 to 20 at 50%**	**£11,971**	**£10,251**
12.c.	**Waning: 10 to 20 at 100%**	**£6,714**	**£5,387**
12.d.	**Waning: 10 to 20 at 80%**	**£8,565**	**£7,105**
12.e.	**Waning: 10 to 20 at 50%**	**£11,348**	**£9,686**
13.	HRQoL, disease-specific In the model base case, the treatment-specific utilities captured during the MT-04 and MT-06 trial are used to inform the QALY gain in the AA+AR and AR populations, respectively. This scenario presents results using alternative sources for health state-specific utilities.		
13.a.	**MT-04 and MT-06 health state-specific**	**£3,379**	**£5,220**
13.b.	**EUCOAST Spain**	**£5,414**	**unchanged**
13.c.	**EUCOAST France**	**£6,450**	**unchanged**
14.	Asthma exacerbation costs In the base case, the cost of a moderate exacerbation is equal to £111.95, and the cost of a severe exacerbation is equal to £464.90. This scenario presents the results using costs from TA278 for omalizumab.		

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14.a	**Moderate = £87.70, Severe = £124.32**	**£9,310**	**unchanged**
14.b	**Moderate = £304.51, Severe = £785**	**£9,968**	**unchanged**

Abbreviations: SOC, standard of care; LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; SQ, standardised quality; HDM, house dust mite; AA, allergic asthma; AR, allergic rhinitis; EUCOAST, European cost of asthma treatment; HRQoL, health-related quality of life; ICS, inhaled corticosteroid SABA; short-acting beta agonist; GP, general practitioner.

B3.10 Subgroup analysis

Subgroup analysis was conducted to explore the effects when considering a lower starting cohort age to reflect the adolescent indication for the AR population.

As the P001 and TO-203-32 trials did not collect data on patients that could be used to inform rhinitis severity, such as the ARIA HRQoL items collected in the MT-06 trial, there are no adolescent specific subgroup data that can be used to populate the AR model. As highlighted in Section B.2.7, the adolescent and adult subgroup analyses in the P001 trial and the TO-203-32 trial saw a similar reduction in the average daily TCRS with 12 SQ-HDM treatment compared to placebo. Similarly, no major differences were found in the incidence of AEs between subjects aged 12 to 18 years and those aged at least 18 years. As such, it was assumed that efficacy estimates from the MT-06 trial informing patient transitions in the AR model would remain the same for adolescents and adults.

In this subgroup analysis, the mean age of the starting cohort in the AR model is set to 12 years to reflect an adolescent model starting cohort. The cost-effectiveness results are presented in Table 106. In the adolescent subgroup, 12 SQ-HDM results in a dominant ICER, and as such, is cost-effective at a WTP threshold of £20,000/QALY. The NMB at a WTP of £20,000/QALY is £7,469.

Table 106: AR - adolescent subgroup analysis results

AR	12 SQ-HDM	SOC AA+AR	Incremental	ICER
Total costs (£)	£8,292	£10,584	-£2,291	12 SQ-HDM dominant
Total LY	16.83	16.83	0.00	
Total QALYs	15.64	15.38	0.26	

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AR	12 SQ-HDM	SOC AA+AR	Incremental	ICER
Abbreviations: SOC, standard of care; LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; HDM, house dust mite; AA, allergic asthma; AR, allergic rhinitis				

B3.11 Benefits not captured in the QALY calculation

As reported previously, ARD can have a material impact on patients productivity at work, with productivity reduced by an average of 21% for ARD patients compared to the general population [19]. This reduced performance also extends to adolescents, increasing their likelihood to perform poorly in exams by 1.1-1.8 times when compared to the general population [20, 21]. This wider societal impact of ARD may result in additional reductions in health-related outcomes that are unlikely to be directly included in the QALY calculation.

B3.12 Validation

Internal quality assurance measures were undertaken throughout the model development. The model was validated through the use of extreme values and formula auditing to ensure the consistency of model estimates. Where appropriate, any errors were amended. Overall, the validation identified no issues with the structural or computational accuracy of the model.

Clinical inputs and assumptions were validated through an advisory board conducted in September 2023. The report containing anonymised and consolidated feedback is provided in Appendix M2.

B3.13 Interpretation and conclusions of economic evidence

The cost-effectiveness of 12 SQ-HDM compared with established clinical management for treating HDM-induced AA and/or AR has been evaluated in line with the NICE final scope.

The treatment effect of 12 SQ-HDM in the AA+AR population was derived from the results of the MT-04 trial, in which significantly greater proportions of patients in the 12 SQ-HDM treatment group achieved clinically meaningful reductions in the risk of

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moderate or severe asthma exacerbations (HR: 0.66 [95% CI, 0.47-0.93], p=0.02). The results of a meta-analysis, combining estimated treatment effects from the MT-04 and TO-203-31 (SABA subgroup) supported a statistically significant difference in time to first asthma exacerbation for 12 SQ-HDM versus placebo, with a pooled treatment effect of HR: 0.68 (95% CI 0.53,0.88; p=0.0027). To assess the cost-effectiveness analysis for the AA+AR population, the model structure was designed to reflect asthma control as defined in the GINA guidelines, and data collected during the MT-04 trial on asthma control were used to inform improvements in asthma control associated with 12 SQ-HDM. Data on asthma control collected from three non-interventional observational studies assessing the impact of 12 SQ-HDM were also considered in this appraisal.

The treatment effect of 12 SQ-HDM in the AR population was derived from the results of the MT-06 trial, in which significantly greater proportions of patients in the 12 SQ-HDM treatment are achieved a reduction in AR medication use and symptoms, as demonstrated by a significant reduction in the TCRS compared with placebo (RR: 18.2%, absolute difference: 1.22 [95% CI, 0.49-1.96], p=0.001). The results of a meta-analysis supported this improvement, with the pooled estimate from the MT-06, P001, and TO-203-32 trials demonstrating a statistically significant improvement in TCRS score in patients treated with 12 SQ-HDM versus placebo (relative difference: -0.91 (95% CI -1.21, -0.61)), with minimal statistical heterogeneity between studies (I^2 = 0%). To assess the cost-effectiveness analysis for the AR population, a model structure using the ARIA classification was designed to reflect rhinitis disease severity. To estimate treatment-specific transition probabilities to match the ARIA classifications, data on the presence or absence of impairment in the four HRQoL items – sleep, daily activities/sport, work/school, and troublesome symptoms were used.

Treatment-specific utilities captured during the MT-04 and MT-06 trial are used to inform the QALY gain in the AA+AR and AR populations, respectively. Utilities were applied in a multiplicative manner to appropriately adjust for the natural decline in QoL associated with age.

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Established clinical management costs for the AR population were estimated based on data collected on medication use throughout the MT-06 trial. Established clinical management costs for the AA+AR population were based on a microcosting approach, which calculated a weighted cost based on bundled treatment costs using treatment guidelines reflecting five levels of treatment steps with an estimated proportion of patients at each treatment step. All unit costs were identified from UK sources, including NHS reference costs, the British National Formulary (BNF), and EMIT drug costs databases.

Extensive scenario analyses demonstrate the base case cost-effectiveness results to be robust to variation in model inputs and assumptions, with none of the 29 scenarios resulting in an ICER that exceeded a WTP threshold of £20,000/QALY. Deterministic sensitivity analysis demonstrates the results to be sensitive to change in the treatment-specific utility scores.

In summary, the results of this analysis demonstrate that 12 SQ-HDM represents a cost-effective use of NHS resources for treating HDM-induced AA and/or AR, with a dominant ICER in both populations.

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B.4 References

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B.5 Appendices

Appendix C: Summary of product characteristics or information for use, UK public assessment report, scientific discussion or drafts

Please see relevant document in Appendices folder.

Appendix D: Identification, selection and synthesis of clinical evidence

Please see relevant document in Appendices folder.

Appendix E: Subgroup analysis

Not applicable.

Appendix F: Adverse reactions

Not applicable.

Appendix G: Published cost-effectiveness studies

Please see relevant document in Appendices folder.

Appendix H: Health-related quality of life studies

Please see relevant document in Appendices folder.

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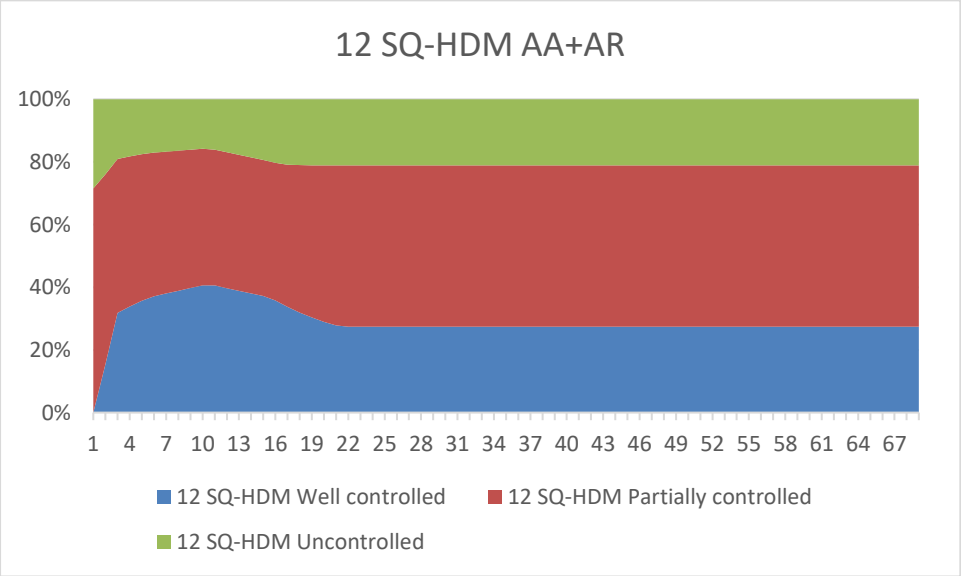
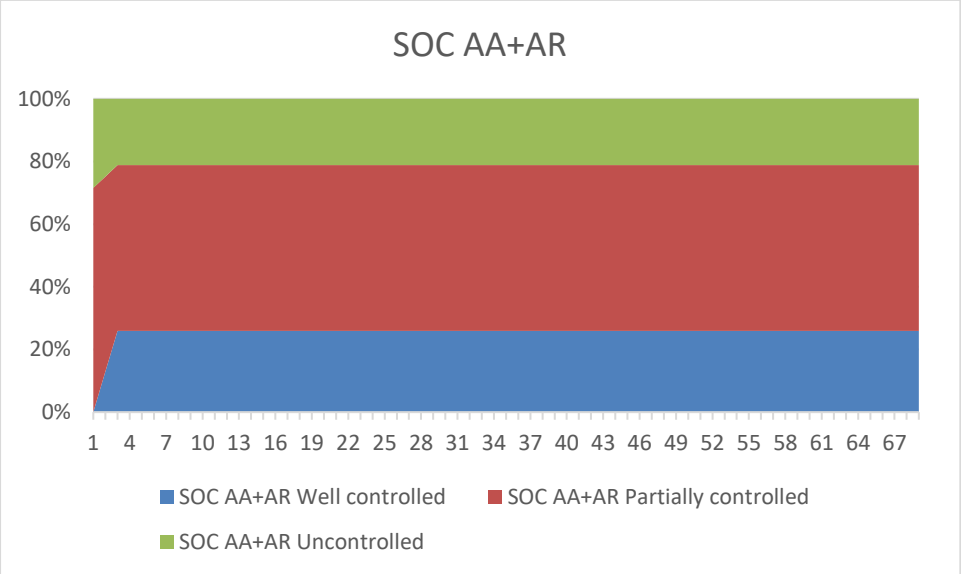
Appendix I: Cost and healthcare resource identification, measurement and valuation

Please see relevant document in Appendices folder.

Appendix J: Clinical outcomes and disaggregated results from the model

Please see below Markov traces for the AA+AR and AR model populations.





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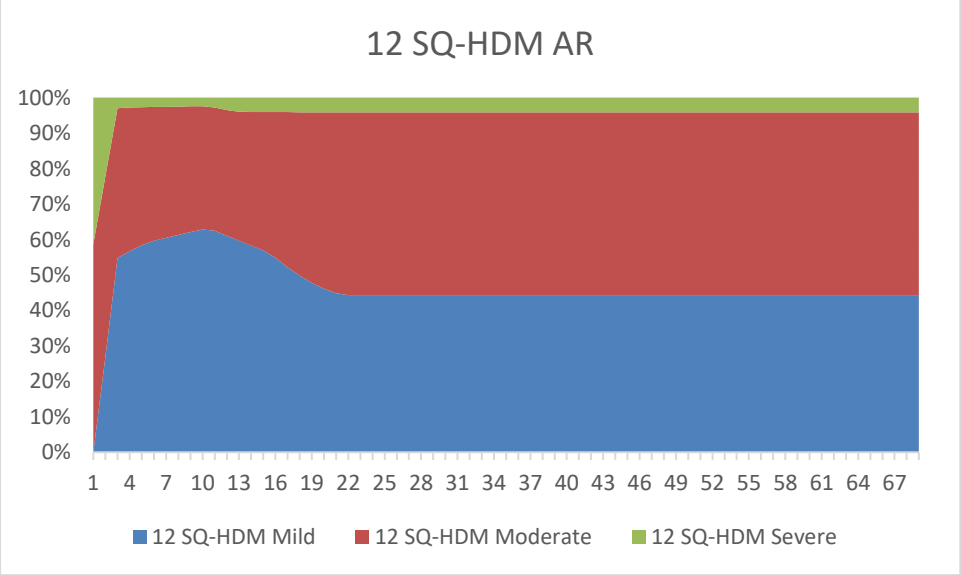

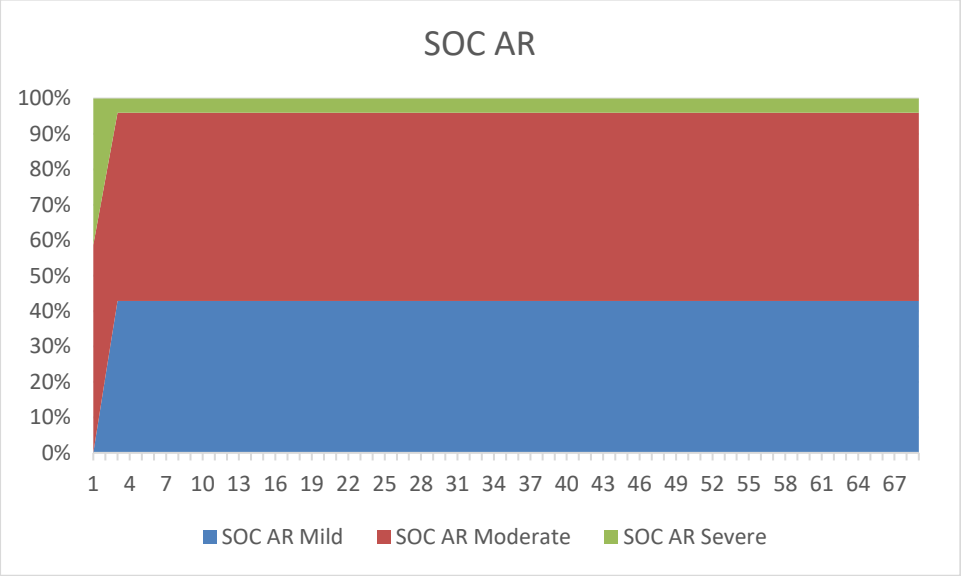

Appendix K: Price details of treatments included in the submission

Please see relevant document in Appendices folder.

Appendix L: Checklist of confidential information

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Appendix M1: Delphi panel summary report

Please see relevant document in Appendices folder.

Appendix M2: Advisory board summary report

Please see relevant document in Appendices folder.

Appendix N: Concomitant and prohibited medications of pivotal trials

Please see relevant document in Appendices folder.

Appendix O: Full detail, inclusion and exclusion criteria of clinical studies

Please see relevant document in Appendices folder.

Appendix P: Full detail, quality assessment of clinical studies

Please see relevant document in Appendices folder.

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Appendix Q: Table of pharmacotherapy costs

Please see table below.

SABA reliever	Weighting	Dose (per day)	Cost per pack	Unit per pack	Strength	Annual cost
Salbutamol	100%	400	£1.32	200	100	£9.64
EMIT price, Salbutamol 100micrograms/dose inhaler CFC Free 200 dose / Packsize 1; BNF dose, 100–200 micrograms up to 4 times a day for persistent symptoms.						

	ICS	Weighting	Dose (per day)	Cost per pack	Unit per pack	Strength	Annual cost
Low dose	Budesonide	25%	400	£8.86	200	100	£64.72
	BNF, Easyhaler Budesonide 100micrograms/dose dry powder inhaler, Orion Pharma (UK) Ltd.						
	Beclometasone dipropionate	25%	400	£14.93	200	200	£54.53
	BNF Eashyaler Beclometasone 200micrograms/dose dry powder inhaler, Orion Pharma (UK) Ltd.						
	Ciclesonide	25%	160	£30.17	120	80	£183.69
	EMIT price, Ciclesonide 80micrograms/dose inhaler CFC free 120 dose / Packsize 1.						
	Fluticasone propionate	25%	200	£4.02	60	100	£48.94
	BNF Flixotide 100micrograms/dose Accuhaler, GSK UK Ltd.						
						Weighted cost	**£87.97**

Medium dose	Budesonide	25%	800	£17.71	200	200	£129.37
	BNF, Easyhaler Budesonide 200micrograms/dose dry powder inhaler, Orion Pharma (UK) Ltd.						
	Beclometasone dipropionate	25%	800	£14.93	200	200	£109.06
	BNF Eashyaler Beclometasone 200micrograms/dose dry powder inhaler, Orion Pharma (UK) Ltd.						
	Ciclesonide	25%	320	£35.85	120	160	£218.24

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	EMIT price, Ciclesonide 160micrograms/dose inhaler CFC free 120 dose / Packsize 1.						
	Fluticasone propionate	25%	500	£4.23	60	250	£51.50
	BNF Flixotide 250micrograms/dose Accuhaler, GSK UK Ltd.						
						Weighted cost	**£127.04**

High dose	Budesonide	25%	1,600	£17.71	100	400	£258.74
	BNF, Easyhaler Budesonide 400micrograms/dose dry powder inhaler, Orion Pharma (UK) Ltd.						
	Beclometasone dipropionate	25%	1,600	£11.31	200	200	£165.24
	BNF, Beclu 200micrograms/dose inhaler (pressurised inhalation), Lupin Healthcare (UK) Ltd.						
	Ciclesonide	25%	640	£35.85	120	160	£436.47
	EMIT price, Ciclesonide 160micrograms/dose inhaler CFC free 120 dose / Packsize 1.						
	Fluticasone propionate	25%	1,000	£4.73	60	500	£57.59
	BNF Flixotide 500micrograms/dose Accuhaler, GSK UK Ltd.						
						Weighted cost	**£229.51**

	ICS/LABA	**Weighting**	**Dose (per day)**	**Cost per pack**	**Unit per pack**	**Strength**	**Annual cost**
Low dose	Beclometasone with formoterol	25%	2	£29.32	120	1	£178.49
	BNF, Beclometasone with formoterol inhalation powder, Fostair NEXThaler 100micrograms/dose / 6micrograms/dose dry powder inhaler Chiesi Ltd;.						
	Budesonide with formoterol	25%	2	£27.97	120	1	£170.27
	BNF, Budesonide with formoterol, DuoResp Spiromax 160micrograms/dose / 4.5micrograms/dose dry powder inhaler Teva UK Ltd.						
	Fluticasone with formoterol	25%	4	£14.40	120	1	£175.32
	BNF Flutiform 50micrograms/dose / 5micrograms/dose inhaler, Napp Pharmaceuticals Ltd.						
	Fluticasone with salmeterol	25%	4	£17.46	120	1	£212.58

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	BNF Seretide 50 Evohaler, GSK UK Ltd.						
						Weighted cost	**£184.16**

Medium dose	Beclometasone with formoterol	25%	4	£29.32	120	1	£356.97
	BNF, Beclometasone with formoterol inhalation powder, Fostair NEXThaler 100micrograms/dose / 6micrograms/dose dry powder inhaler Chiesi Ltd;.						
	Budesonide with formoterol	25%	4	£27.97	120	1	£340.53
	BNF, Budesonide with formoterol, DuoResp Spiromax 160micrograms/dose / 4.5micrograms/dose dry powder inhaler Teva UK Ltd.						
	Fluticasone with formoterol	25%	4	£28.00	120	1	£340.90
	BNF Flutiform 125micrograms/dose / 5micrograms/dose inhaler, Napp Pharmaceuticals Ltd.						
	Fluticasone with salmeterol	25%	4	£23.45	120	1	£285.50
	BNF Seretide 125 Evohaler, GSK UK Ltd.						
						Weighted cost	**£330.98**

High dose	Beclometasone with formoterol	25%	4	£29.32	120	1	£356.97
	BNF, Beclometasone with formoterol inhalation powder, Fostair NEXThaler 200micrograms/dose / 6micrograms/dose dry powder inhaler Chiesi Ltd;.						
	Budesonide with formoterol	25%	4	£27.97	60	1	£681.07
	BNF, Budesonide with formoterol, DuoResp Spiromax 320micrograms/dose / 9micrograms/dose dry powder inhaler Teva UK Ltd.						
	Fluticasone with formoterol	25%	4	£45.56	120	1	£554.69
	BNF Flutiform 250micrograms/dose / 10micrograms/dose inhaler, Napp Pharmaceuticals Ltd.						
	Fluticasone with salmeterol	25%	4	£29.32	120	1	£356.97
	BNF Seretide 250 Evohaler, GSK UK Ltd.						
						Weighted cost	**£487.43**

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LTRA	Weighting	Dose (per day)	Cost per pack	Unit per pack	Strength	Annual cost
Montelukast	100%	10	£0.68	28	10	£8.87
EMIT price, Montelukast 10mg tablets / Packsize 28; BNF dose, 10mg once daily.						

Theophylline	Weighting	Dose (per day)	Cost per pack	Unit per pack	Strength	Annual cost
Uniphyllin Continus	25%	400	£3.29	56	200	£10.73
BNF, Uniphyllin Continus 200mg tablets, Napp Pharmaceuticals Ltd; BNF dose, 200-400mg every 12 hours. *Advisory board indicated that the use of theophylinne in the UK is low and continues to decrease. An assumed weighting of 25% was used to reflect this.*						

Biologics	Weighting	Dose (per day)	Cost per pack	Unit per pack	Strength	Annual cost
Omalizumab	17%	12	£128.07	1	75	£7,517.82
BNF, Xolair 75mg/0.5ml solution for injection pre-filled syringes, Novartis Pharmaceuticals UK Ltd; SmPC dose based on weight and baseline [IgE] (75-600mg every 4 weeks, estimated dose per day 337.5/28)						
Mepolizumab	17%	4	£840.00	1	100	£10,957.50
BNF Nucala 100mg powder for solution for injection vials, GSK UK Ltd; BNF dose, 100mg every 4 weeks (estimated dose per day 100/28).						
Dupilumab	17%	21	£1,264.89	2	300	£16,500.04
BNF Dupixent 300mgl/2ml solution for injection pre-filled syringes, Sanofi; BNF dose, 300mg every 2 weeks (estimated dose per day 300/14).						
Tezepelumab	17%	8	£1,265.00	1	210	£16,501.47
BNF Tezspire 210mg/1.91ml solution for injection pre-filled syringes, Astrazeneca UK Ltd; BNF dose, 210mg every 4 weeks (esimated dose per day 210/28).						
Advisory board indicated that the only 2/3 patients will respond to biologic treatment.					Weighted cost	**£8,579.47**

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Other	Weighting	Dose (per day)	Cost per pack	Unit per pack	Strength	Annual cost
Prednisolone	n/a	40	£0.30	28	5	£31.31
EMIT price, Prednisolone 5mg tablets / Packsize 28; BNF dose, 40-50mg daily.						
Ipratropium bromide	n/a	5	£3.63	20	1	£331.46
BNF, Ipratropium bromide 500micrograms/2ml nebuliser liquid unit dose vials, Alliance Healthcare (Distribution) Ltd; BNF dose, 500micrograms every 4-6 hours as required (equivalent to 4-6 puffs per day).						

Rhinitis medication	**Weighting**	**Dose (per day)**	**Cost per pack**	**Unit per pack**	**Strength**	**Annual cost**
Tablets						
Desloratadine	n/a	5	£0.94	90	5	£3.81
EMIT price, Desloratadine 5mg tablets / Packsize 90; BNF dose, 5mg once daily.						
Cetirizine	n/a	10	£0.23	30	10	£2.80
EMIT price, Cetirizine 10mg tablets / Packsize 30; BNF dose, 10mg once daily.						
Loratadine	n/a	10	£0.32	30	10	£3.90
EMIT price, Loratadine 10mg tablets / Packsize 30; BNF dose, 10mg once daily.						
Nasal spray						
Xylometazoline hydrochloride	n/a	2	£3.42	107	1	£23.32
BNF, Sudafed Blocked Nose 0.1% spray, McNeil Products Ltd; BNF dose, 1 spray 1-3 times a day into each nostril (2-6 total per day). 15ml per pack, 0.14ml per spray (SmPC)						
Budesonide	n/a	4	£5.91	120	1	£71.95
BNF Budesonide 64micrograms/dose nasal spray, Sandoz Ltd; BNF dose, 2 sprays into each nostril per day (4 total per day).						
Ipratropium bromide	n/a	8	£6.54	180	1	£106.17
BNF, Rinaspray 21micrograms/dose nasal spray, Sanofi Consumer Healthcare; BNF dose, 2 sprays per nostril 2-3 times a day (8-12 total per day).						
Eye drops						
Azelastine	n/a	4	£5.99	267	1	£32.82

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BNF, Azelastine 0.05% eye drops, Brown & Burk UK Ltd; BNF dose, apply 2-4 times a day (4-8 total per day). 8ml of 0.5mg/ml solution per pack (4mg total), 0.015mg/drop (SmPC)						
Sodium cromoglicate	n/a	8	£6.51	300	1	£63.41
EMIT price, Sodum cromoglicate 2% eye drops 13.5ml / Packsize 1; BNF dose, apply 4 times a day (8 total per day). 13.5ml per pack, 0.045ml per drop (SmPC) -> 13.5/0.045 drops per pack.						

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Appendix R1: IQVIA HES data analysis briefing deck

Please see relevant document in Appendices folder.

Appendix R2: IQVIA HES data analysis excel file

Please see relevant document in Appendices folder.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Summary of Information for Patients (SIP)

October 2023

File name	Version	Contains confidential information	Date
ALK. Summary of Information for Patients. 12 SQ HDM.	Final	No	October 2023

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Executive summary: In only a few sentences please provide a top-level summary to describe the medicine. Please outline the main patient population it is proposed to treat:

Description of medicine:

Allergic respiratory disease (ARD), encompassing allergic rhinitis (AR) and allergic asthma (AA), is a prevalent condition affecting millions of individuals. ARD manifests in a range of symptoms, such as nasal congestion, runny nose, coughing, wheezing, and eye redness. The severity of ARD can vary, classified as mild, moderate, or severe.

People with moderate to severe ARD may experience a number of problems, including:

- Troublesome symptoms, such as sinusitis, conjunctivitis, oral allergy syndrome, and repeat respiratory infections.
- Sleep disturbance, such as difficulty falling asleep and frequent nocturnal awakenings.
- Impairment of school or work, such as reduced productivity and increased absences.
- Impairment of daily activities, leisure, and/or sport.
- Reduced quality of life and mental health concerns, such as anxiety and depression.

12 SQ-HDM contains an allergen extract from house dust mites. It comes in a form known as oral lyophilisates, which are like tablets but much softer and absorbed into the body by putting them under the tongue. 12 SQ-HDM works by increasing the immunological tolerance (your body's ability to cope) to house dust mites. The treatment may need to be taken for 8 to 14 weeks before any improvements are noticed.

Who it proposes to treat:

Adult patients (18-65 years) or adolescents (12-17) diagnosed by clinical history and positive test of house dust mite sensitisation with persistent allergic rhinitis despite use of current treatments.

Adult patients (18-65) diagnosed by clinical history and positive test of house dust mite sensitisation with allergic rhinitis and allergic asthma that is uncontrolled with current treatments.

1b) Name of the medicine (generic and brand name):

Generic name: 12 SQ-HDM oral lyophilisate

Brand name: ACARIZAX®

1c) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adult patients (18-65 years) diagnosed by clinical history and positive test of house dust mite sensitisation (skin prick test and/or specific IgE) with at least one of the following conditions:

- Persistent moderate to severe house dust mite allergic rhinitis despite use of symptom relieving medication.
- House dust mite allergic asthma not well controlled by inhaled corticosteroids and associated with mild to severe house dust mite allergic rhinitis. Patient asthma status should be carefully evaluated before initiation of treatment.

Adolescents (12-17 years) diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test and/or specific IgE) with persistent moderate to severe house dust mite allergic rhinitis despite use of symptom relieving medication.

1d) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

On 17th May 2021, 12 SQ-HDM oral lyophilisate was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of allergic rhinitis in adults and adolescents (12-65 years of age) and related allergic asthma, caused by house dust mites in adults (18-65 years of age) {A/S, 2021 #52}).

1e) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Allergy Research Ltd (ARL) - a subsidiary of the charity British Allergy Foundation £72,502
Support to aid further research into the development of treatments for patients with asthma

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Main conditions that the medicine plans to treat: ARD is a common and burdensome condition, estimated to affect 19.5 million people within the UK, with approximately 3.8 million of these being sensitised to HDM (1).

Of the UK ARD population, approximately 67% (11.3 million) are estimated to have allergic rhinitis (AR). Rhinitis and asthma are closely related, as over 80% of asthmatics have concomitant rhinitis (a disease which can occur alongside asthma), and poor control of rhinitis is a strong risk factor for asthma exacerbations (2, 3). Approximately 33% (5.6 million) of the UK ARD population have both allergic rhinitis and allergic asthma (AA), of which UK allergy specialists estimated that around 54% have a mild diagnosis, 34% have a moderate diagnosis, and 12% have a severe diagnosis (1).

Main symptoms of the disease: People with ARD can experience a wide range of symptoms, which vary from person to person due to things like what allergens you're exposed to, how sensitive your body is to them, and where in your airways the problems happen (4-6).

ARD patients present with a heterogenous set of symptoms including nasal (congestion, itchy and/or runny nose), respiratory (coughing, shortness of breath, chest tightness, and wheezing), and ocular symptoms (eye redness, itchy and/or watery eyes) (4-7). Approximately two out of three ARD patients present with AR symptoms only, with one out of three presenting with symptoms of both AR and AA (1).

ARD can be classified as mild or moderate to severe depending on the severity of symptoms and their impact on the patient's daily life. UK allergy specialists estimated around 64% have a mild diagnosis, 26% have a moderate diagnosis, and 9% have a severe diagnosis (1).

ARD patients can experience sinusitis (67-82% of ARD patients), conjunctivitis (75.6% of allergic rhinitis patients) which can result in visual impairment, oral allergy syndrome (22% of allergic rhinitis patients) which can lead to reactions to eating certain foods, such as fruits, vegetables, and nuts, as well as repeat respiratory infections (11.6% of AA patients). ARD patients even have a higher risk of dying due to their disease, with ~1,541 patients dying of acute respiratory failure each year (8-12).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

The ARD treatment pathway in the UK initially consists of self-care or pharmacy treatments, followed by patients visiting primary care services.

Patients are mostly diagnosed with ARD in primary care using a patients' clinical history, with 50% of AR and 79% of AR and AA patient diagnoses are made in primary care. If clinical history is unclear, further testing may be carried out. This most commonly takes the form of skin prick

testing, although some centres offer tests for the amount of specific IgE antibodies in the blood or a FeNO test which is a breath test that can detect inflamed airways. Diagnostic guidelines are rarely used by experienced GPs, although NICE and local guidelines are the most relevant for these patients.

Currently, a more advanced ARD diagnosis, including the specific allergen sensitisation and type of asthma/rhinitis, is made in secondary care, using clinical history, FeNO testing, skin prick tests, and/or blood test (IgE). Guidelines are rarely used directly in the specialist setting, but in practice clinicians follow the British Society for Allergy and Clinical Immunology (BSACI) guidelines.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The NICE Clinical Knowledge Summary on AR incorporates recommendations from the BSACI and the ARIA international guidelines (2016 revision) for the diagnosis and management of patients with AR. For patients with mild-to-moderate intermittent or mild persistent symptoms, oral or intranasal antihistamines are the first line of therapy. For patients with moderate-to-severe persistent symptoms, or those for whom initial treatment is ineffective, intranasal corticosteroids are recommended. If symptoms continue to persist despite these treatments, combination therapies can be explored, including combinations of oral antihistamines and intranasal corticosteroids, or combined preparations of intranasal corticosteroids and intranasal antihistamines.

The GINA guidelines are used for the diagnosis and management of AA and are based on the concept of control-based management. The NICE guideline (NG80) recommends a similar stepwise approach for treatment and management of asthma. The BTS and Scottish Intercollegiate Guidelines Network (SIGN) guideline provides recommendations based on current evidence for best practice management of asthma. A joint NICE/BTS/SIGN guideline for the diagnosis, monitoring, and management of chronic asthma is due to be released in July 2024. Pharmacotherapies for asthma are typically classified as controller medication for control of symptoms, reliever/rescue medication for short-term symptom relief, and add-on therapies for difficult-to-treat asthma. Controller and add-on therapies can include long-acting beta-2 agonist (LABA), ICSs, and leukotriene antagonists. For severe asthma, biologics may be considered, but this 12 SQ-HDM would not be used and is not suitable for patients with severe asthma.

Treatment with 12 SQ-HDM is recommended in steps 2, 3, and 4 of the GINA guidelines as an add-on therapy.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Despite appropriate administration of existing treatments, a subset of moderate-to-severe ARD patients have uncontrolled disease (36% moderate and 45% severe AR; 24% moderate and 44% AR+AA), and as such their treatment satisfaction is low (1). There is a clear unmet need for a better treatment option for these patients. Some patients' disease may be poorly controlled despite compliant use of existing treatment, and as such their treatment satisfaction may also be low: 59-66% of ARD patients are unsatisfied with their symptom control despite maximum use of pharmacotherapy.

57% of allergic rhinitis patients have trouble falling asleep which is disruptive to their everyday lives and 44.9% of AA patients tend to experience frequent nightly awakenings which impacts the quality of their sleep (13, 14).

Productivity at work is reduced on average by 21% for ARD patients vs. the general population (15). This reduced performance extends to adolescents, increasing their likelihood to perform poorly in exams by 1.1-1.8 times when compared to the general population (16, 17). Patients with ARD also have an increased number of absences from work due to their condition with on average 4.1 days absent per AR patient per year, equating to approximately £6 billion in lost revenue across the UK economy each year (1, 18, 19).

32.8% of AR patients report that their condition impacts their ability to take part in outdoor activities (20).

Consequently, ARD patients with persistent moderate to severe disease have reduced QoL and often have mental health concerns (13, 20-22). In patients with ARD, 39-47% experience anxiety/depression with asthma control for these patients being worse than for those without anxiety or depression (21, 22).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

12 SQ-HDM is an allergy immunotherapy that takes the form of a tablet that dissolves under your tongue, containing a highly standardised allergen extract from house dust mites.

Unlike current treatments, 12 SQ-HDM is an aetiological treatment (finding the root cause of a problem and treating it, not just relieving the symptoms) that aims to modify a patient's immune response to HDM allergens. This effect has been demonstrated through 12 SQ-HDM's induced increase in IgG4 antibodies (antibodies specific house dust mite allergens), which in turn block IgE antibodies (antibodies that would otherwise result in an unwanted allergic response from the patient's immune system) from binding to house dust mite allergens; however, the complete and exact mechanisms by which 12 SQ-HDM works regarding the clinical effect is not fully understood.

12 SQ-HDM works by addressing the cause of house dust mite respiratory allergic disease, and clinical effect during treatment has been demonstrated for both upper and lower airways. The underlying protection provided by 12 SQ-HDM leads to improvement in disease control and improved quality of life demonstrated through symptom relief, reduced need for other medications, and a reduced risk for flare-up. The treatment may need to be taken for 8 to 14 weeks before any improvement is noticed.

International treatment guidelines and consensus statements refer to a treatment period of 3 years for AIT to achieve disease modification after its cessation. If no improvement is observed during the first year of treatment with 12 SQ-HDM, there is no indication for continuing treatment.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

12 SQ-HDM is to be used as an add-on to current treatments.

12 SQ-HDM is an aetiological treatment (finding the root cause of a problem and treating it, not just relieving the symptoms) that aims to modify a patient's immune response to HDM allergens, as opposed to current treatments which aim to treat only symptoms of the disease.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

12 SQ-HDM should only be started by a doctor who has experience in treating allergic diseases.

The first dose should be taken under the supervision of a doctor, who will monitor the patient for at least 30 minutes to monitor for any immediate side effects. 12 SQ-HDM is a tablet that dissolves under your tongue.

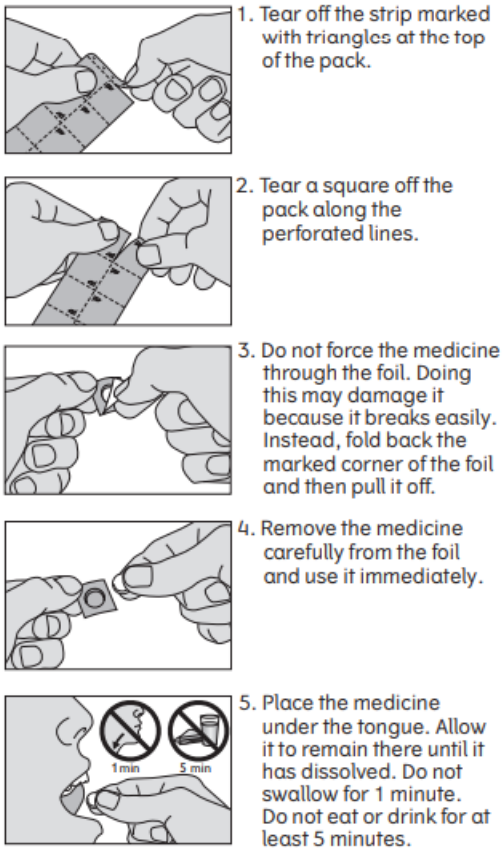

Figure 1: Administration of 12 SQ HDM

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Several clinical trials have been performed for 12 SQ-HDM, and are listed here:

Clinical Trial	Setting and location	Number of participants	Trial design	Duration of study
MT-04	109 sites across 13 European countries	834	Phase III, randomised, parallel-group, double-blind, placebo-controlled, multicentre trial	13-18 months

MT-06	100 trial sites across 12 European countries	992	Phase III, randomised, parallel-group, double-blind, placebo-controlled, multicentre trial	12 months
P001	182 trial sites across the US and Canada	1482	Phase III, randomised, parallel-group, double-blind, placebo-controlled, multicentre trial	12 months
TO-203-31	124 trial sites across Japan	824	Phase II/III, placebo-controlled, randomised, double-blind, multicentre, parallel intergroup comparison trial	19 months
TO-203-32	90 trial sites across Japan	861	Phase II/III, placebo-controlled, randomised, double-blind, multicentre, parallel intergroup comparison trial	12 months

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

For asthma patients:

- 12 SQ-HDM significantly reduced the risk of moderate to severe asthma exacerbations compared to placebo. In a meta-analysis, which combines the results of multiple studies, the combined treatment effect of 12 SQ-HDM in both the MT-04 and a subgroup of the TO-203-31 study supported a significant reduction in the risk of an exacerbation of 32%.
- Results from the MT-04 study also showed improved various asthma-related outcomes, including a decrease in asthma symptoms, reduced use of rescue inhalers, and better lung function.

For AR patients:

- 12 SQ-HDM significantly reduced the use of allergy medications and improved allergy symptoms. In a meta-analysis, which combines the results of multiple studies, the combined treatment effect of 12 SQ-HDM across the MT-06, P001, and TO-203-32 studies supported a significant reduction in the total combined rhinitis score, which measures rhinitis symptoms and medication use.
- In the MT-06 study, patients experienced better quality of life, including less nasal and non-nose/eye symptoms, practical problems, and sleep disturbances.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used

does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

For description of terms, please refer to the glossary.

Treatment with 12 SQ-HDM, can significantly improve the quality of life of people with AR and/or AA. This improvement has been shown in studies MT-06 and P001, as measured by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and Visual Analog Scale (VAS) scores (measurement tool used to assess the intensity or magnitude of a subjective experience or symptom, such as pain, anxiety, or other sensations. It consists of a straight line with endpoints representing extreme levels of the experience (e.g., no pain to worst pain imaginable). Patients are asked to mark on the line where their experience falls).

In study MT-06, people with AR who received 12 SQ-HDM had a significant improvement in their overall RQLQ score compared to those who received a placebo. This improvement was seen after 24 weeks of treatment and onwards. The improvement in RQLQ score was also seen for several specific domains, including nasal symptoms, non-nose/eye symptoms, practical problems, and sleep impairment.

In study P001, people with AR and/or AA who received 12 SQ-HDM reported less symptoms on the VAS compared to those who received a placebo. This result corresponds with the reduction in the Daily Symptom Score (DSS) (score ranges from 0 to 12 points and reflects 4 symptoms (cough, wheeze, shortness of breath, or chest tightness), each of which were measured from 0 (no symptoms) to 3 (severe symptoms)) also seen in the 12 SQ-HDM-treated subjects.

The results of study MT-04 suggest that 12 SQ-HDM may also improve the quality of life of people with asthma. More people in the active groups (6 SQ-HDM and 12 SQ-HDM) had a clinically relevant improvement in their Asthma Quality of Life Questionnaire (AQLQ) score than in the placebo group at 12 weeks of treatment. However, there were no statistically significant differences between the groups in the proportion of subjects with improvement when the analysis was controlled for change from baseline in inhaled corticosteroids (ICS).

Overall, the evidence suggests that 12 SQ-HDM can improve the quality of life of people with AR and/or AA.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

12 SQ-HDM has been found to be safe and well-tolerated in five important clinical studies. Most of the adverse events (unintended reactions to the treatment) reported by patients were mild and temporary. These adverse events were usually related to how the treatment was given. The most common adverse events included itching in the mouth, swelling in the mouth, irritation in the throat, and itching in the ears.

In the key asthma study (MT-04), less than half of the people who received 12 SQ-HDM experienced adverse events (46%), while even fewer had serious adverse events. The most common events had a median onset time on 1 or 2 days after start of treatment and a median resolution time of 4.5 days, 7 days, and 23 days for the 3 most common reactions.

In the key rhinitis study (MT-06), the majority of adverse events were reported as mild (72%) or moderate (24%), and 98% of subjects experiencing an adverse event had recovered by the end of the trial. The majority of the most frequent TEAEs had a median onset within 1 to 15 minutes, with very few new AEs starting at a later timepoint.

A similar safety profile was reported in the 3 additional studies conducted in North America and Japan.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Allergy Symptom Relief: 12 SQ-HDM offers relief from allergy symptoms, helping alleviate discomfort.

Long-Lasting Effect: 12 SQ-HDM's effects may persist even after completing the treatment, providing enduring relief.

Reduced Need for Other Medications: Effective treatment with 12 SQ-HDM may result in decreased reliance on other allergy medications, such as antihistamines or nasal corticosteroids. This can be especially valuable as those medications may have long-term side effects.

Potential Decrease in Severe Asthma Development: 12 SQ-HDM may potentially lower the risk of developing severe asthma, offering an additional benefit for those with allergies.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

It is proposed the 12 SQ-HDM be used alongside current symptomatic treatments offered on the NHS. Data from the key trials supports the idea that patients with moderate to severe allergic rhinitis, or not well controlled allergic asthma with allergic rhinitis have a greater response to treatment (i.e. reduced symptoms) that patients on placebo over a year. Evidence from real-world studies also suggest that this effect can persist up to 9 years post-treatment, with a potential to reduce the use of symptomatic treatments.

A model was constructed to calculate lifetime costs and benefits for treatment with 12 SQ-HDM compared with using current treatments alone. The model uses definitions of asthma control and rhinitis severity to model improvements in patients' health linked with the results of the key clinical trials.

Data collected during the clinical trials, and results from separate studies and published literature have shown that people with uncontrolled asthma or more severe rhinitis are more likely to visit primary care and secondary care services. As 12 SQ-HDM improves disease control and reduces symptoms, a reduced number of primary care visits and hospitalisations result in cost savings. Furthermore, patients' quality of life is improved as 12 SQ-HDM delays disease progression and reduces symptoms compared to current treatments alone.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

12 SQ-HDM is an aero-allergy immunotherapy, which aims to change patients' immune system response to allergens. There are currently no aero-allergy immunotherapies recommended by NICE.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

There are no known equality issues relating to the use of 12 SQ-HDM for treatment of HDM-induced AR in patients 12-65 years of age and HDM-induced AA in patients aged 18-65 years of age.

Despite the large burden of ARD for both patients and the NHS, there is a lack of accessible and well-resourced specialist services for ARD patients. Treatment is currently dependent on the patient's postcode, and the local secondary care service's capacity in terms of workforce and availability of SLIT treatment in the service, which fluctuates regionally (1). Results from a HES data analysis found that, across England, only 14% of patients referred to secondary care with an aero-allergen diagnosis, were seen at an allergy specialist centre(23). As the first dose of 12 SQ-HDM is administered in secondary care, this may be considered to represent a barrier to some patients for whom allergy services are less accessible.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

AE (Adverse Event): An adverse event is any unexpected and usually undesired medical occurrence in a patient or clinical trial participant who has received a medication or undergone a medical procedure. Adverse events can range from mild side effects, such as nausea or headache, to more serious or severe reactions.

AQLQ(S), or Asthma Quality of Life Questionnaire (Standardised): A tool used to assess the impact of asthma on a patient's quality of life, specifically focusing on aspects related to asthma symptoms, activity limitations, emotional function, and environmental stimuli.

ARD (Allergic Respiratory Disease): Allergic Respiratory Disease refers to medical conditions that affect the respiratory system and are triggered or exacerbated by allergies. This category includes conditions such as AR and AA, where respiratory symptoms are linked to allergen exposure.

Antihistamines: Medications that block the action of histamine, a natural substance produced by the body during allergic reactions. Histamine can cause symptoms like sneezing, itching, runny nose, and watery eyes. Antihistamines help relieve these allergy symptoms and are commonly used to manage AR (hay fever) and other allergic reactions.

Corticosteroids: Medications that reduce inflammation in the body. They work by suppressing the immune system's response to inflammation, helping to alleviate symptoms such as swelling, redness, and discomfort. Corticosteroids can be used to treat various conditions, including allergies, asthma, and skin conditions.

EQ-5D, or EuroQol-5D: A widely used generic health-related quality of life instrument. It evaluates a person's overall health by assessing five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D provides a comprehensive snapshot of an individual's health status and is often used for comparing the impact of different health conditions and treatments.

Quality of life: The overall enjoyment of life. Many clinical trials assess the effects of AR, AA, and their treatment on the quality of life. These studies measure aspects of an individual's sense of well-being and ability to carry out activities of daily living.

RQLQ, or Rhinoconjunctivitis Quality of Life Questionnaire: A tool commonly used to assess the impact of AR (hay fever) and related conditions on a person's quality of life. It measures various aspects such as nasal and eye symptoms, sleep disturbances, daily activities, and emotional well-being.

SAE (Serious Adverse Event): A serious adverse event is a specific type of adverse event that is typically more severe or harmful in nature. It may result in serious consequences, including hospitalisation, life-threatening situations, disability, or death. SAEs are closely monitored and reported during clinical trials and medical research.

SF-36, or Short Form-36 Health Survey: A widely used questionnaire that measures a person's overall health-related quality of life. It assesses various physical and mental health dimensions, providing insights into a person's well-being beyond specific medical conditions.

The Japanese AR Standard QoL Questionnaire (JRQLQ): A questionnaire comprising 24 questions rated on a 5-point scale (0-4) designed to measure the impact of AR on various aspects of a person's life, including physical well-being, daily activities, and emotional well-being.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Data on file. Modified Delphi advisory panel. 2023.
2. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008;63 Suppl 86:8-160.
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7. Valero A, Quirce S, Davila I, Delgado J, Dominguez-Ortega J. Allergic respiratory disease: Different allergens, different symptoms. Allergy. 2017;72(9):1306-16.
8. Bertelsen RJ, Carlsen KC, Carlsen KH. Rhinitis in children: co-morbidities and phenotypes. Pediatr Allergy Immunol. 2010;21(4 Pt 1):612-22.
9. Czarnecka-Operacz M, Jenerowicz D, Silny W. Oral allergy syndrome in patients with airborne pollen allergy treated with specific immunotherapy. Acta Dermatovenerol Croat. 2008;16(1):19-24.
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14. Diette GB, Markson L, Skinner EA, Nguyen TT, Algatt-Bergstrom P, Wu AW. Nocturnal asthma in children affects school attendance, school performance, and parents' work attendance. Arch Pediatr Adolesc Med. 2000;154(9):923-8.
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16. de la Hoz Caballer B, Rodrı´guez M, Fraj J, Cerecedo I, Antolin-Amerigo D, Colas C. Allergic rhinitis and its impact on work productivity in primary care practice and a comparison with other common diseases: The Cross-sectional study to evaluate work productivity in allergic rhinitis compared with other common diseases (CAPRI) study. American Journal of Rhinology & Allergy. 2012;26(5).
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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 [ID6280]

Clarification questions

November 2023

File name	Version	Contains confidential information	Date
ID6280 Clarification questions. ALK Responses. noACIC. 04.12.23	Final	No	04.12.23

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Background

The EAG has identified a number of fundamental issues with the company's submission that may severely limit its suitability to inform decision making. A summary of these fundamental issues are:

1. Use of the 'ICS reduction and efficacy assessment' phase of the MT-04 trial to inform treatment effectiveness (see questions A7, B9, and B15):

The MT-04 trial is the key source of evidence for the AA+AR population. In the asthma economic model (population AA+AR), the company has used phase 3 (ICS reduction/efficacy assessment phase) of the MT-04 to inform the short-term effectiveness in the model. The EAG is concerned that phase 3 may not be reflective of clinical practice as reduction of ICS would not be mandated; this has been confirmed by clinical advice. Previous economic analyses funded by the company have also recognised this issue and used phase 2 to inform treatment effectiveness.

2. Trial comparator arms (see questions A2, A6, and B15):

The comparator arm in MT-04 (population AA+AR) may not represent the standard of care / established clinical practice as the pharmacotherapy was constrained to budesonide 400-1200µg and SABA. In UK current clinical practice alternative therapies or add-ons could have been used e.g., higher dose SABA, LAMA, LTRA, depending on severity and symptoms. This issue may be less problematic if the company is formally requesting the appraisal of 12 SQ-HDM as a last line therapy. We have requested clarification from the company on this.

The EAG also notes that the company has not described any attempts to establish indirect comparisons between 12 SQ-HDM and other step-up strategies in the Company Submission (CS).

3. Model parameterisation (see questions B6, B7, B12, B17, B25 and B26):

In both AR and AA+AR models, parametrisation of effectiveness inputs is based on post-hoc definitions of mild/moderate/severe AR or well/partially/uncontrolled AA health states. Post-hoc fixed/deterministic patient proportions were estimated at start of trial and trial end to inform transitions between these health states. The EAG is

concerned with this post-hoc approach for several reasons, for instance: limited evidence is provided on how dropouts/censorship was dealt with, health state definition is subjective, the subsequent parameterisation is fully deterministic, and does not consider variability across time.

Furthermore, the EAG is concerned that the AR model does not reflect the full population for which 12 SQ-HDM is licensed in this indication, as it does not incorporate evidence for individuals aged 12-17 years old (available from P001 trial).

4. Alignment with existing cost-effectiveness evidence (see questions B2 and B9):

There are several previously published cost-effectiveness models assessing 12 SQ-HDM as an add-on therapy in AA and AA+AR funded by the company (Green et al 2017, Green et al 2019 and Hahn-Pedersen et al 2016 – see Table 64 of doc B of the CS). These models rely on simpler modelling approaches that do not require assumptions about health state occupancy, instead these consider difference in utilities and costs during 1 year and then extrapolate these to a 9-year time-horizon (with further assumptions about long-term effectiveness). In the case of AA+AR population, data from the phase 2 (treatment maintenance) of MT-04 is preferred to that of phase 3. The company does not justify why these model structures were not suitable to be adapted to the UK context. The EAG is concerned about the use of more complex model structures in the CS relying on post-hoc approaches when the evidence base informing previous models published by the company does not appear to have evolved.

Based on the current submission, the EAG considers that the submitted models do not confer any significant advantages compared to previous simpler analyses. Furthermore, the EAG is concerned by the post-hoc nature of these analyses, the lack of consistency between the clinical and cost-effectiveness sections, the limited description provided for many of these post-hoc analyses, utilisation of specific trial periods that are not representative of clinical practice (AA+AR population) and the reliance on deterministic analyses to inform state membership. Hence, the EAG is currently of the view that the preferred way forward would be to utilise simpler modelling approaches similar to those used in previous cost-effectiveness studies

published by the company. The EAGs clarification question provide an opportunity for the company to provide further justification and details to support the appropriateness of the current modelling approach and input parameterisation.

Section A: Clarification on effectiveness data

Decision problem

A1. For allergic rhinitis (AR), the NICE scope lists complications of allergic rhinitis (such as sinusitis or middle ear infections) as an outcome – please clarify whether these data were reported in the AR trials and (if so) where the results can be found.

Data on the most common (occurring in ≥2% of patients) treatment-related adverse events (TRAEs) were reported in Section B.2.10 of the company submission for the three key AR trials (MT-06, P001, and TO-203-32).

Neither sinusitis nor middle ear infections were identified as common TRAEs in the MT-06, P001, and TO-203-32 trials. In the MT-06 trial, sinusitis was reported as a treatment-emergent adverse event (TEAE) in 6 (2%) placebo patients, and 4 (1%) 12 SQ-HDM patients (Panel 10-4 of MT-06 ICTR). An adverse event was considered to be a TEAE if the AE start time was equal to or after the time of the first IMP intake. In the P001 trial, sinusitis was reported as a specific adverse event in 27 (3.7%) of placebo patients, and 30 (4%) of 12 SQ-HDM patients (Table 12-3 of P001 ICTR). For the TO-203-32 trial, acute sinusitis was reported as a common adverse event in 18 (5.6%) of placebo patients, and 15 (4.8%) of 12 SQ-HDM patients (Table 12.2-9 of TO-203-32 ICTR).

A2. Priority question: Positioning of intervention in current treatment pathway: The company state that "12 SQ-HDM is intended to be an addition to the formulary, rather than a replacement for an existing drug in the treatment pathway".

a) **For AR, Fig 2 (CS) suggests SQ HDM SLIT may be used as last line of therapy, when symptoms persist after all other relevant treatments have been tried. Please clarify that this is the positioning envisaged by the company for the AR population.**

Figure 2 in the company submission refers to the current British Society of Allergy and Clinical Immunology (BSACI) guidelines on AR. The BSACI guidance states that therapy using a stepwise pharmacotherapeutic approach should be undertaken. A

combination of treatments is often needed for more severe disease, and it is here that the option of immunotherapy should also be considered.

It is recommended that 12 SQ-HDM be added as an additional step in the management of allergic rhinitis. The company proposes that 12 SQ-HDM be positioned in line with the marketing authorisation which does not state that all other relevant treatments must have been exhausted, rather that patients have persistent moderate to severe HDM AR despite use of other symptom-relieving medications.

b) **For AA, Table 4 (CS) mentions add-on therapies such as biologics. However, Fig 3 (CS) notes that HDM SLIT could be used at steps 2 to 4 and does not mention biologics. Please clarify where the company expect this therapy to be given in NHS clinical practice, should it be recommended by NICE. Please comment on whether patients would be expected to still have symptoms after biologics have been tried before being eligible for SQ HDM SLIT, or whether SQ HDM SLIT is expected to be used to replace escalation to biologics.**

   Note that if the intervention is expected to be used instead of existing recommended therapies, these should be used as comparators in the clinical evidence (via indirect comparisons if required) and in the economic model.

Table 4 and Figure 3 of the company submission refer to the Global Initiative for Asthma (GINA) guidelines. In an advisory board conducted in September 2023 (Appendix M2 of CS) it was noted that the GINA and BTS/SIGN guidelines are the guidelines most commonly referenced by respiratory clinicians for managing allergic asthma patients. Table 67 (Section B.3.2.3) in the company submission provides a more comprehensive overview of the recommended treatment options/steps for adults and adolescents with asthma. With reference to Figure 3, the GINA guidelines recommend treatment with HDM SLIT (12 SQ-HDM) as an other controller option under treatment Steps 2, 3, and 4. Biologics are only recommended in Step 5 of the GINA guidelines. The GINA guidelines provide further definitions on asthma severity, with mild asthma currently defined as asthma that is well-controlled with as-needed ICS-formoterol, or with low dose ICS plus as-needed SABA. Moderate asthma is

defined as asthma that is well-controlled with Step 3 or Step 4 treatment (e.g. with low or medium dose ICS-LABA in either treatment track). Severe asthma is defined as asthma that remains uncontrolled despite optimised treatment with high dose ICS-LABA. Only a definition of severe asthma is provided in the BTS/SIGN 2019 guidelines, which states that severe asthma is defined as more than two asthma attacks a year or persistent symptoms with SABA use more than twice a week despite specialist-level therapy. Annex 3 notes PEF>33-50% of best or predicted.

As discussed in the Decision Problem meeting with NICE on 9th August 2023, the company highlighted that the inclusion of omalizumab (a biologic therapy) as a comparator is inappropriate as omalizumab is indicated for severe allergic asthma and requires patients with FEV1 <80% of predicted value, and patients must have multiple documented severe exacerbations despite high-dose ICS-LABA. This is conflicting with the marketing authorisation for ACARIZAX 12 SQ-HDM whereby patients cannot have a FEV1 <70% of predicted at initiation of treatment and cannot have experienced a severe asthma exacerbation within the 3 months prior to initiation of treatment. Additionally, the GINA 2022 treatment guideline recommends HDM SLIT as an option in treatment steps 2, 3 and 4. Under the same guidance, omalizumab (an anti-IgE) is only recommended in treatment step 5.

The NICE team agreed with this assessment of the inappropriate inclusion of omalizumab as a comparator product, which was subsequently removed from the NICE Final Scope PICO table. The company consider the exclusion of omalizumab to apply to all anti-IgE products recommended by NICE, as all are indicated for patients with severe asthma.

Regarding the positioning of 12 SQ-HDM, the company proposes that 12 SQ-HDM be positioned in line with the marketing authorisation which states that patients must have HDM AA not well controlled by inhaled corticosteroids (ICS) and associated with mild to severe HDM AR, and that patients' asthma status should be carefully evaluated before the initiation of treatment. The evaluation of asthma status specifies only that patients have a FEV1 ≥70% of predicted value and that patients cannot have experienced a severe asthma exacerbation within the 3 months prior to initiation of treatment.

This positioning does not specify any treatment dosage (i.e. low, medium, or high dose ICS), rather that patients' asthma is categorised as 'not well controlled' despite treatment with ICS. Hence, this positioning aligns with GINA guidance whereby 12 SQ-HDM may be used as an additional controller option for treatment Steps 2, 3, and 4.

Whilst it was noted as clinically plausible that SLIT therapy may result in a reduced likelihood of mild-to-moderate AA patients progressing to a state of severe asthma, 12 SQ-HDM is not an option for severe asthma as an alternative to biologics, as this would be beyond the marketing authorisation for 12 SQ-HDM.

Efficacy and effectiveness data

A3. The proportion of placebo group participants with mild allergic rhinitis (Table 68) or well-controlled asthma (Table 71) at the end of trials MT-06 and MT-04 illustrates the presence of large and durable non-specific (or placebo) effects. Please comment on the possible reasons for the size and duration of these effects.

In both the MT-04 (Table 71 reference) and MT-06 trials (Table 68 reference), the investigational medicinal products (IMP; either 12 SQ-HDM, 6 SQ-HDM, or placebo) were given to patients in addition to their existing symptomatic/controller medication. This is in line with the NICE decision problem, which specifies the intervention is SQ-HDM SLIT as an add-on to standard therapy.

As a result, it could be expected that disease severity or symptoms in patients receiving placebo may not worsen. The improvement in disease severity in the placebo arm may be attributable to participants' awareness of being part of the study (Hawthorne effect). Additionally, patients in MT-04 and MT-06 were re-trained on how to use symptomatic medications at touchpoints during period 2. This would likely improve adherence to and optimisation of symptomatic medications, which would not be realised in clinical practice. It is widely recognised that the most common cause of a lack of asthma control is due to poor inhaler technique. This not only adds to the barrier to use for asthmatic individuals but also acts as one of they key reasons as to poor inhaler compliance. Fundamentally, if the inhaler is not being used correctly, the appropriate drug deposition into the lung is not taking place and a reduced or lack of therapeutic benefit is observed.

The company also note that the results observed in the AA clinical trials are in line with other asthma trials, also showing substantial improvements in the placebo group. It is likely that the regular visits to a specialist with repeated instruction in the use of ICS and other symptomatic medications with a consequently better adherence, account for this.

The company would emphasize that improvements in disease severity attributable to the placebo effect and improved adherence to symptomatic medications would not be observed in the real-world in the absence of a clinical trial. As reported in Section B.3.3.1.1 of the CS, the patient-reported improvements from non-interventional studies at end of trial are larger, and likely to be more reflective of what patients will experience, when comparing the symptom-burden before and after treatment with 12 SQ-HDM.

A4. Please provide the protocol documents for trials MT-04, MT-06, P-001, P-003, TO-203-31 and TO-203-32.

The company have attached the additional documentation.

A5. Priority question: For each of the five pivotal trials please:

- **Provide full CSRs i.e. with functional links to all tables and figures. In particular, we need access to Table 2.9 and Listing 2.08 for MT-06 (and the equivalent tables for MT-04), Appendix I.6. and Listing 2.13 for trial MT-06, and Table 8.6.1, Table 8.6.2, Listing 2.14 and Listing 8.04 for trial MT-06.**

The company have attached the additional documentation.

For the MT-04 and MT-06 trial, additional post-hoc analyses were conducted on asthma control, and health resource use that have been included as separate documents.

- **State at which timepoints skin prick tests were performed prior to randomisation.**

MT-04: Visit 1: 5 to 7 weeks prior to randomisation.

MT-06: Visit 1: 15 days prior to randomisation.

P001: Visit 1: 7 days to 52 weeks prior to randomisation. Selected preapproved sites combined visit 1 and 2 procedures into one visit, occurring 5 days to 6 weeks prior to randomisation.

P003: Visit 1: 6 weeks prior to randomisation.

TO-203-31: Performed between the day of informed consent and the first day observation or within 1 year before the day of informed consent.

TO-203-32: SPT not used.

A6. Priority question: The lists of prohibited concomitant medications (Appendix N) are long for all trials. Please explain why so many treatments were prohibited, given that the submission states that: "*12 SQ-HDM is intended to be an addition to the formulary, rather than a replacement for an existing drug in the treatment pathway*." Please also discuss the impact this may have on the applicability of trial results to the NHS setting.

In the MT-04 and MT-06 trials, subjects were switched to comparable doses of ICS, including combination products, to reduce variability in the respective standard of care treatments among the trial population, which was conducted across Europe. The aim of this design was to improve the comparability of trial subjects across treatment groups. Furthermore, several medications were excluded due to possible interference with diagnostic testing, efficacy assessment, and in rare cases, effects of adrenaline in response to severe allergic reactions. See Panel 5-4 in the MT-04 ICTR, and Panel 5-3 in the MT-06 ICTR for detail.

In line with the company's response to question A2, the positioning of 12 SQ-HDM is in patients with persistent moderate to severe HDM AR despite use of other symptom-relieving medications, and HDM AA not well controlled by ICS and associated with mild to severe HDM AR.

Whilst 12 SQ-HDM is indeed intended to be an addition to the formulary, it is also to be in patients for whom current symptomatic treatment is insufficient.

Therefore, whilst patients in the clinical trials were switched from their regular controller/symptomatic medication to more limited permitted concomitant medication,

at screening, patients were required to be symptomatic despite their regular controller/symptomatic medication. Furthermore, as patients were removed from additional controller/symptomatic medications (such as LABA and LTRA), it could have been expected that patients in the placebo arm would have experienced worse symptoms and/or a decline in disease control. As noted in question A3, the opposite response was observed across all clinical trials. This may indicate:

1. The placebo response discussed in response to question A3 is likely largely attributable to the placebo effect and/or the re-optimisation of symptomatic therapies preceding regular interactions with trial investigators.

2. The additional controller/symptomatic therapies were insufficient in managing patients' disease and would likely offer no additional benefit if included in the trials.

In further support of point 2., the company note that LABA was only prohibited following randomisation in the MT-04 trial and from the first day of observation in the TO-203-32 study. It would therefore be expected that any worsening of symptoms associated with the removal of symptomatic medication providing a positive effect would have been observed during the trial. Furthermore, whilst LTRAs and oral or topical antihistamines were prohibited for the duration of the MT-06 trial, patients were allowed to restart these medications after the run-in criteria were met until Visit 9 in the P001 trial. As the results of the MT-06 trial and P001 trial were consistent, this further suggests that the prohibited concomitant therapies do not provide added benefit for the target patient population.

Whilst the clinical trials were more restrictive than clinical practice in regard to background symptomatic therapies, the company believe that this does not limit the generalisability of the trial results in the licensed indication; AA and AR patients for whom current treatment is insufficient.

A7. Priority question: For trial MT-04, please:

- **Provide asthma exacerbation data as well as other relevant outcomes (e.g., asthma symptoms, asthma control, SF-36) for period 2, if available**

The purpose of MT-04 was to evaluate the efficacy of the HDM tablet compared to placebo in subjects with HDM induced asthma, as measured by reducing the risk for an asthma exacerbation.

During period 1 (screening period) eligible subjects were switched from their regular asthma controller medication (including combination products) to equivalent doses of ICS (budesonide) and short-acting β2-agonist (SABA) as needed.

At randomisation and throughout period 2 (treatment maintenance period), subjects received investigational medicinal product (IMP) in addition to ICS and SABA. During the last approximately 4 weeks of period 2 (designated period 2B), the subject started filling in the electronic dairy and recorded asthma symptoms, medication use and lung function twice daily.

Period 3 (ICS reduction/withdrawal period) began in October 2012. During the first half of this period (period 3A), the subjects had their daily ICS dose reduced by 50% and for the second half (period 3B) ICS was completely withdrawn. Subjects continued treatment with IMP for the entire period and additionally had SABA provided for use as needed. If subjects experienced an asthma exacerbation during period 3A (ICS reduction period), the dose of ICS could be adjusted at the discretion of the investigator and the subject be offered to continue in the trial at the adjusted ICS dose level for the rest of the trial (e.g. the subject should not have the ICS completely withdrawn at a later time point). If subjects experienced an asthma exacerbation during period 3B (ICS withdrawal period), when they did not use any ICS, the subjects should be discontinued from the trial.

The primary endpoint, time to first moderate or severe asthma exacerbation, was measured from start of period 3 (ICS reduction/withdrawal) until the time of first asthma exacerbation or discontinuation of trial (after which the subject would be censored from the primary analysis).

The evaluation of efficacy in the context of a stepwise reduction of controller medication was in accordance with EMA’s guidelines and the stepwise ICS reduction/withdrawal period reduced the ethical and safety concerns associated with an immediate cessation of ICS in subjects with persistent asthma. Due to the design of the study, asthma exacerbations were only collected in period 3.

The following tables of asthma symptoms and asthma control are available in the MT-04 CSR:

- Table 3.32 Average asthma daytime symptom score over period 2B (FAS)
- Table 3.33 Average asthma nocturnal symptom score over period 2B (FAS)
- Table 3.34 Average number of nocturnal awakenings during period 2B (FAS)
- Table 3.34 Average SABA intake during period 2B (FAS)
- Table 3.36 Prescribed total daily dose of ICS (mcg) by visit (FAS)

Although the MT-04 trial was designed and powered as an ICS reduction/withdrawal trial with the primary aim of investigating asthma exacerbations, active treatment also had effects on asthma endpoints prior to the ICS reduction period (assessed during period 2B). Thus, all secondary asthma symptom and medication endpoints were numerically improved in the actively treated subjects compared to placebo treated subjects during period 2B (the last 4 weeks of the treatment maintenance period). The difference between 12 SQ-HDM and placebo in the daily asthma symptom score was statistically significant (post hoc analysis). Likewise, the difference between the 12 SQ-HDM and placebo group in the proportion of subjects with no nocturnal awakenings was statistically significant (post hoc analysis).

SF-36 was in period 2 only collected at visit 6. A summary of SF-36 health domain scales (0-100) by visit is shown in Table 3.20 in the End-of-Text in the MT-04 CSR.

Regarding additional data that may be supportive of asthma exacerbations in Period 2, the following new outputs have been generated based on collection of adverse events in the safety data, see Appendix A.:

- MT-04 – Selected asthma preferred terms by System Organ Class in period 2B (safety set)
- MT-04 – Selected asthma preferred terms by System Organ Class in period 2 (safety set)

For Period 2 and 2b, patients in the 12 SQ-HDM treatment arm have fewer adverse events that may be correlated with asthma exacerbations compared with patients in

the placebo arm. However, limited inference can be made across groups, as the number of events and patients experiencing events is low and appears to be equally distributed for both treatment groups.

- **Comment on the applicability of the trial's results to the NHS setting (and the marketing authorisation), given the practice of protocol mandated ICS reduction and withdrawal in both trial arms.**

The current BTS/SIGN 2019 asthma management guidelines state (Section 7.6):

"*Patients should be maintained at the lowest possible dose of inhaled corticosteroid. Reduction in inhaled corticosteroid dose should be slow as patients deteriorate at different rates. Reductions should be considered every three months, decreasing the dose by approximately 25–50% each time.*"

As such, in relation to current clinical guidelines, the mandated ICS reduction during Period 3a can be considered reflective of current clinical practice.

Furthermore, it is widely recognised that participation in a clinical trial improves asthma control, including in patients receiving placebo, and surveys of asthma patients in real-life settings indicate that the incidence of exacerbations is much higher than seen in patients recruited for clinical trials (MT-04 ICTR). As stated previously in response to question A3, patients in MT-04 and MT-06 were re-trained on how to use symptomatic medications at touchpoints during Period 2. This would likely improve adherence to and optimisation of symptomatic medications, which would not be realised in clinical practice and likely explains the substantial improvements in the placebo group. Therefore, the mandated ICS reduction may be a better reflection of the level of symptom management observed in clinical practice, in which, on average patients experience worse asthma control and are more susceptible to asthma exacerbations.

The company would further note that, as detailed in Section B.3.3.1 of the company submission, three non-interventional studies were considered relevant to this submission and provide data on asthma control. All three studies showed a benefit in the levels of asthma control achieved following treatment 12 SQ-HDM consistent with the results of MT-04.

- **Comment on the relevance of the comparator arm which was restricted to budesonide 400-1200µg and SABA, when clinical advice to the EAG suggests other therapies could have been used (e.g., LAMA, higher SABA dose).**

With regards to the ICS dosage, budesonide 400-1200µg reflects a standard dose range across NICE, BTS/SIGN, and GINA guidance for low to high dose ICS. Across all guidance, ICS and SABA are the primary treatment options for asthma.

Please see response to A6 with regards to the exclusion of additional symptomatic therapies.

- **Comment on the upper age restriction in the marketing authorisation and the possible impact on results since the trial included over 65s. Please provide results with over 65's data removed.**

There was no upper age limit in the inclusion criteria for MT-04. During the Decentralised Procedure, DE/H/1947/001/DC, a Concerned Member State pointed to the fact that a low number of people >65 years (n=2 in 12 DU, n=6 in placebo) were enrolled in the study. As such, it was agreed to introduce an upper age restriction in the Marketing Authorisation (indication). The UK SmPC mirrors the EU SmPC.

It is not expected that removal of participants over 65 years of age will impact the results as only 8 subjects were over 65 years (6 in the placebo group and 2 in the 12 SQ-HDM group).

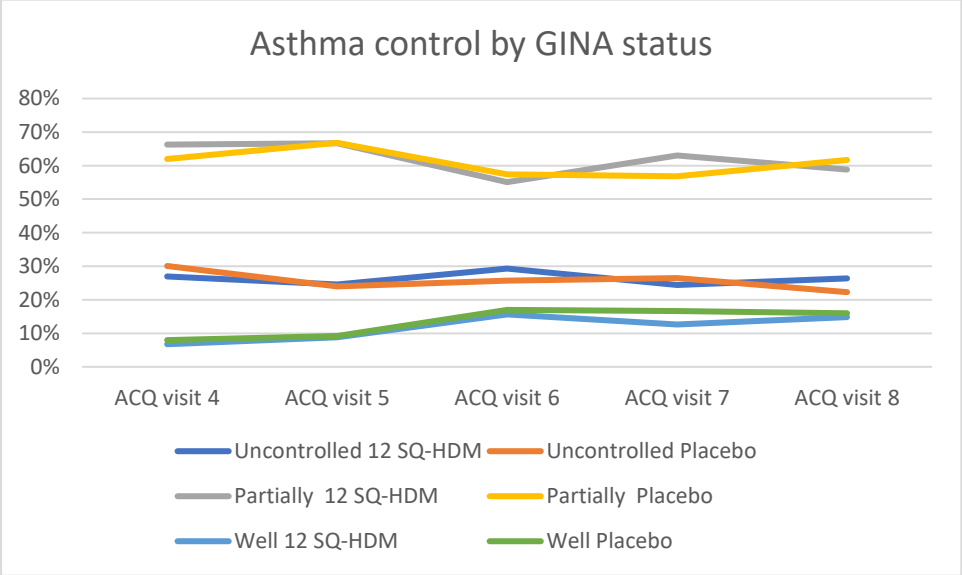
- **Explain why, during Period 1, eligible patients were switched from their regular asthma controller medication to equivalent doses of ICS (budesonide) and SABA as needed, and comment on how these changes may have affected the stability of asthma control.**

Subjects were switched to comparable doses of ICS, including combination products, to reduce variability in the respective standard of care treatments among the trial population, which was conducted across Europe (MT-04). The

aim of this design was to improve the comparability of trial subjects across treatment groups.

In the AA trials, participants were required to have not well controlled HDM AA at inclusion. The treatment maintenance period was conducted for 7-12 months prior to the efficacy assessment period, and concomitant medications were allowed to be prescribed at the discretion of the investigator according to the local standard of care if considered necessary for the subject's well-being. As such, it is expected that asthma control would have stabilised during this period and prior to the efficacy assessment period. The level of asthma control by GINA classification as mapped from ACQ scores (Section B.3.3.1 of CS) for the treatment maintenance period of the MT-04 trial is presented in Figure 1. As can be seen, asthma control remains relatively stable for both treatment groups. This is further confirmed by the pre-specified analysis of ACQ score up until Visit 9, which did not reveal any statistically significant difference between treatment groups (page 130 of MT-04 ICTR).

Figure 1: Asthma control by GINA status; treatment maintenance MT-04



- **Explain how the number of participants who attended an end-of-trial visit or had an asthma exacerbation fulfilling the primary endpoint was calculated in Figure 10 (p 93; total n=693), whether it included some who**

discontinued, and why this differed from the number who completed the trial in Table 39 (p 92; total n=617).

As shown in Figure 10 of the company submission, the participants discontinuing the trial following an exacerbation were included as participants who attended and end-of-trial visit or had an asthma exacerbation fulfilling the primary endpoint. This was clarified in the following footnote in the corresponding table in the first reference to the table (Virchow et. al, 2016): "The protocol defined that, following an asthma exacerbation, participants were offered to continue in the trial at an adjusted ICS dose and provide data to secondary end points. The participants discontinuing the trial following an exacerbation were considered to have completed the trial (26 participants in the 6 SQ-HDM group, 22 in the 12 SQ-HDM group, and 28 in the placebo group)."

In Table 39 of the company submission, the participants discontinuing the trial following an exacerbation were not included in the "Completed trial" line in the table.

A8. For trial MT-06, please:

- Clarify the meaning, in Table 37, of "It was considered reasonable to adjust the reported symptom score to account for the symptomatic medications used, in order to get a more accurate representation of symptomatology" – what adjustments were made? Please provide unadjusted results.

The primary endpoint is TCRS, the total combined rhinitis score, which is the sum of the symptom score and the medication score. In other words, TCRS is the reported symptom score adjusted to account for the symptomatic medication used. The unadjusted symptom score is just the rhinitis DSS, which is the first key secondary endpoint. The analysis results for rhinitis DSS are provided in the CSR.

- The European Academy of Allergy and Clinical Immunology suggested a more standardised model to score daily medication use. Is it possible to provide adjusted results using this standardisation?

Please see attached analysis in Appendix A.

- Clarify antihistamine use – in Table 37 they appear to be both permitted and prohibited.

In Table 37 of the company submission, the following is stated:

- Permitted concomitant medication: Subjects were provided with nasal steroid, oral antihistamine, and antihistamine eye drops to be used as needed.
- Disallowed concomitant medication: Antihistamines

Whilst, this may strictly be defined as a contradiction, the study was designed so as to not allow the use of antihistamines as regular prophylactic concomitant medication as rhinitis medication score was considered a key endpoint, yet antihistamines could be prescribed to treat symptoms at the discrepancy of the investigator.

- Provide patterns of missingness in patient characteristics for those who continued versus discontinued treatment and clarify whether a missing at random assumption was applied to the FAS-MI population.

See Appendix A for data on the patient demographic and baseline characteristics for subjects who completed and discontinued the MT-06 study.

The analysis for the FAS-MI population used multiple imputation with all missing values imputed from the placebo group. This is the most conservative approach leading to the smallest treatment effect. The assumption here is that subjects with missing values would have had an effect similar to the effect in the placebo group. As values for the active group were imputed from the placebo group, there is no direct assumption about MAR in the active group. It could be argued that there is an assumption about MAR in the placebo group. However, this may be considered conservative, as there is no reason to believe that subjects on placebo who discontinue would perform better than patients who remain within the study.

- For FAS-MI, an assumption of no treatment effect was made. Please clarify what are the implications of this assumption? Please provide information on why other assumptions were not also tested (e.g., negative treatment effect)?

In Table 44 of the company submission, it is stated that "The primary analysis set was the FAS with multiple imputations for missing data (FAS-MI), which conservatively treated all patients with missing data as having no treatment effect." As stated, the assumption of no treatment effect is a very conservative assumption, as subjects who discontinued prior to the efficacy assessment period may have been treated with 12 SQ-HDM for up to 12 months. As evidenced in the P003 trial, whereby statistically significant improvements in efficacy could be observed as early as 8 weeks following initiation of 12 SQ-HDM, it is likely that some patients who discontinued during period 2 and received 12 SQ-HDM will have had an improvement in their disease. However, to be conservative, it was assumed that the treatment has had no effect, and therefore multiple imputation of the missing data using data from the placebo group was used.

Please note that "no treatment effect" is a (conservative) assumption and not something that can be tested. Generally, assumptions for multiple imputation are not testable. Instead, usually a series of sensitivity analyses are performed. However, no additional sensitivity analyses were conducted by the company.

A9. Priority question: For both MT-04 and MT-06 please comment on the applicability of the trial results to the NHS setting, given the restriction on the timing of the primary endpoint assessment to between October and March. Does this restriction suggest that efficacy only applies at this time of year, with no or little effect expected between April and September?

Appendix B presents the results of a post-hoc analysis of HDM-sensitised subjects with and without grass and/or tree sensitisation throughout the year (including pollen season) for the MT-06 primary efficacy endpoint (TCRS). Slide 1 shows a clear and consistent separation between active and placebo treatment groups during the entire study period (March to January). As can be seen in slide 2, there is no difference in the trend of TCRS score between patients with and without an additional seasonal allergy sensitisation. Regardless of the pollen season, patients treated with both 12 SQ-HDM and placebo show a reduction in the average TCRS score.

For the MT-04 trial, whilst the primary efficacy endpoint was not assessed outside the efficacy period, patients' asthma control remained relatively stable for both treatment groups throughout the treatment maintenance period (see Figure 1), and

there was no difference in efficacy in mono- versus poly-sensitised patients in subgroup analysis (See Section B.2.7.1 of CS).

A10. Please provide a summary table of results for study P003 for all outcomes relevant to this appraisal's scope.

*References: **P003 CSR and Nolte et al., 2015**. Ref 42 from the company's submission.*

The P003 trial is a randomised, double-blind, placebo-controlled Phase 2 trial that was conducted in an allergen exposure chamber with the objective to determine the dose-related efficacy and onset of action of the HDM sublingual immunotherapy.124 adults with HDM AR with or without HDM AA/ARC were randomised and received at least 1 dose of the study drugs: 12 SQ-HDM, 6 SQ-HDM, or placebo daily for 24 weeks. Participants underwent 6-hour exposure challenges at screening and Weeks 8, 16, and 24, preceded by a washout of all allergy pharmacotherapy [42].

The primary endpoint was the total nasal symptom score during chamber challenges at Week 24. 12 SQ-HDM had a significant improvement of 49% (95% CI [35%,60%], p<0.001) in TNSSs at week 24 relative to placebo, with the placebo group having a TNSS of 7.45 [95% CI: 6.57,8.33], while the 12 SQ-HDM group scored 3.83 [95% CI: 2.94,4.72], corresponding to a 3.62 absolute difference. The 12 SQ-HDM group also showed a statistically significant difference compared to placebo at Week 16, with mean scores of 4.82 and 6.90 respectively, reflecting a 2.08 (30%) difference (95% CI [17%-42%], p<0.001). Additionally, at 8 weeks, the mean scores were 5.34 and 6.71 for 12 SQ-HDM and placebo, respectively, resulting in a 1.37 (20%) difference (95% CI [7%;33%], p=0.007).

12 SQ-HDM had a significant improvement in the total ocular symptom score (TOSS) at weeks 8 and 24 relative to placebo, with the greatest difference observed at week 24 with a relative difference of 67.9%.

12 SQ-HDM had a significant improvement of 52% (95% CI [37%,65%], p<0.001) in total symptom score (TSS) at week 24 relative to placebo, with the placebo group having a TSS of 9.27 [95% CI: 7.98,10.57], while the 12 SQ-HDM group scored 4.43 [95% CI: 3.20,5.66], corresponding to a 4.84 absolute difference. A significant difference between 12 SQ-HDM and placebo was also observed at weeks 8 and 16 with a relative difference of 23% (95% CI NC, p=0.004) and 31% (95% CI NC,

p<0.001) respectively. The trial's findings demonstrated that 12 SQ-HDM in a controlled setting reduced nasal and ocular symptoms and exceeded the World Allergy Organization's established clinical efficacy criteria (>20% improvement vs placebo). The onset of action for 12 SQ-HDM of MK-8237 was at Week 8.

The asthma symptom score was an exploratory endpoint of the P003 trial. For the total study population, 12 SQ-HDM-treated patient's asthma symptom scores were numerically lower at weeks 8,16 and 24 in comparison to those receiving placebo, see Figure 2. The difference between the 12 SQ-HDM and placebo treatment groups was greatest at week 16 with an absolute difference of 0.80. No statistical analyses were conducted for asthma symptoms.

Figure 2: P003, asthma symptom score

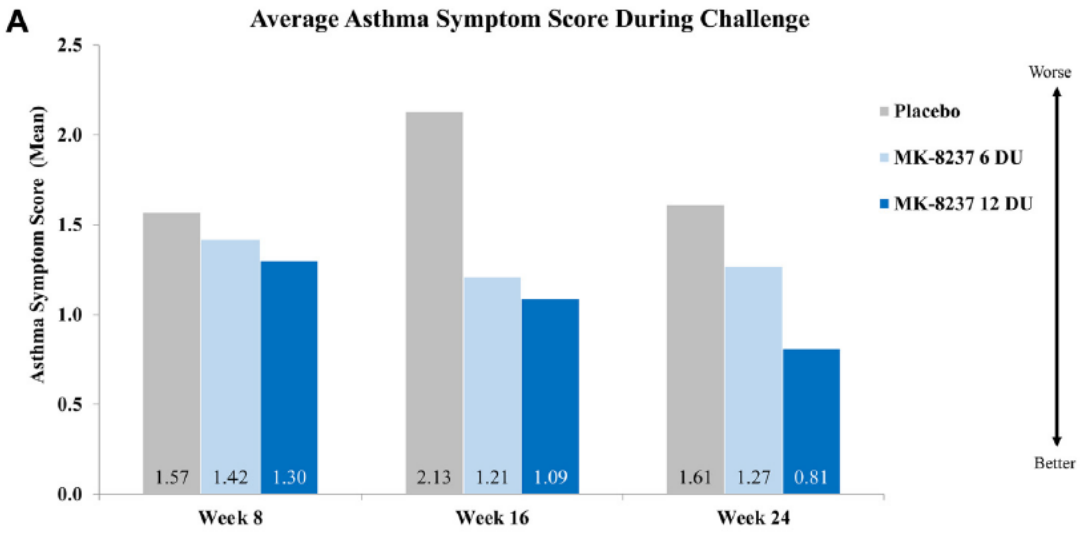


Table 1: Summary results of P003 study

P003 results	12 SQ-HDM		Placebo		Treatment effect		p-value
	n	Score	n	Score	Absolute difference (95%CL)[b]	Relative difference[c]	
Average Total Nasal Symptom Score (TNSS), FAS[a] (LS mean)							
Week 24	36	3.83	34	7.45	3.62 [2.39, 4.85]	49%	<0.001
Week 16	36	4.82	34	6.90	2.08 [1.03,3.14]	30%	<0.001
Week 8	40	5.34	39	6.71	1.37 [0.39,2.34]	20%	0.007
Total Ocular Symptom Score (TOSS), FAS[a] (LS mean)							
Week 24	36	0.61	34	1.87	1.27 [0.62,1.92]	67.9%	<0.001
Week 16	39	1.14	38	1.67	0.53 [0.07,1.13]	31.7%	0.082
Week 8	40	1.18	39	1.79	0.61 [0.09,1.14]	34.1%	0.023
Average Total Symptom Score (TSS), FAS[a] (LS mean) [sum of TNSS and TOSS]							
Week 24	36	4.43	34	9.27	4.84 [3.09,6.59]	52%	<0.001
Week 16	39	5.95	38	8.58	2.62 [1.13,4.12]	31%	<0.001
Week 8	40	6.51	39	8.48	1.97 [3.30,0.64]	23%	0.004

n: number of subjects in treatment group with data available for the analysis. CL: confidence limits. TNSS, Total Nasal Symptom Score. Endpoint score range: 0 - 12. The endpoint was calculated based on diary entries over the last 4 hours of the chamber session. Baseline endpoint value was calculated based on the Screening Challenge. TOSS = Total Ocular Symptom Score. Endpoint score range: 0 - 6. The endpoint was calculated based on diary entries over the last 4 hours of the chamber session. Baseline endpoint value was calculated based on the Screening Challenge. TSS = Total Symptom Score. Endpoint score range: 0 - 18. The endpoint was calculated based on diary entries over the last 4 hours of the chamber session. Baseline endpoint value was calculated based on the Screening Challenge.LS, Least square.

[a] FAS: full analysis set. All randomized subjects who receive at least one dose of study treatment and have at least one post-randomization observation.

[b] Absolute difference placebo minus 12 SQ-HDM, 95% confidence limits.

[c] Relative difference to placebo: placebo minus 12 SQ-HDM divided by placebo*100%.

A11. Please provide a breakdown of the reasons why 3015 patients were not randomised in study P001.

Reasons for subjects not randomised are given in the CSR in Table 10-1. Reasons for not meeting inclusion and/or exclusion criteria are given in the end-of-text table 14.1.1.2: Study entry criteria not met by non-randomised subjects.

In summary, 93.2% of patients that were not randomised were classified as screen failure. 40.1% and 23.2% of patients failed to meet the inclusion criteria IN04 (IgE test) and IN03 (skin prick test) which specify the inclusion of an allergy to house dust mite.

A12. Please present a risk of bias appraisal for the REACT (real-world) study using an appropriate tool (e.g. ROBINS-I).

Although the REACT study was downgraded in one domain due to the possibility of attrition bias being introduced in the loss of subjects of which no good matches were found (Pre-existing asthma cohort: 4,635; No asthma cohort: 3,911), the study has been judged to generally be of a low risk of bias and is therefore relevant to the submission.

Study name	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	**Overall bias**
REACT	+	+	+	+	?	+	+	+

Cochrane ROBINS-1 tool, risk of bias grading:
+ Low risk of bias. ? Moderate risk of bias. X Serious risk of bias. ! Critical risk of bias.

Critical risk of bias.

A13. Please explain why patients who discontinued treatment but were still willing to be followed up, were not evaluated for outcomes at timepoints after discontinuation but instead had their data imputed (based on placebo group data).

The final protocol for MT-06 is from 2011. This is many years before the ICH E9 R1 addendum about estimands. At that time there was no focus on keeping subjects in a trial although they discontinued treatment. Therefore, allowing subjects to discontinue treatment but stay in the trial was not part of the design of MT-06. Please note however, that the treatment effect from the primary analysis where all missing data are imputed from placebo is a conservative approach, generally resulting in a lower treatment effect than if subjects who discontinued treatment had been evaluated for efficacy.

A14. Please provide meta-analyses of quality of life outcomes (for both indications) and severity of rhinitis symptoms (e.g. DSS) for the latest timepoints of trial period 2 (visit 8 for MT-04 and visit 6 for MT-06), where the trial methods, populations and outcomes are similar enough to allow this.

For the AA trials:

- The MT-04 study assessed quality of life using the AQLQ.
- The TO-203-31 study assessed quality of life using the AHQ-JAPAN questionnaire. Additionally, this was only assessed at the first day of study treatment prior to the efficacy assessment period.

No additional meta-analyses can be conducted for the AA trials.

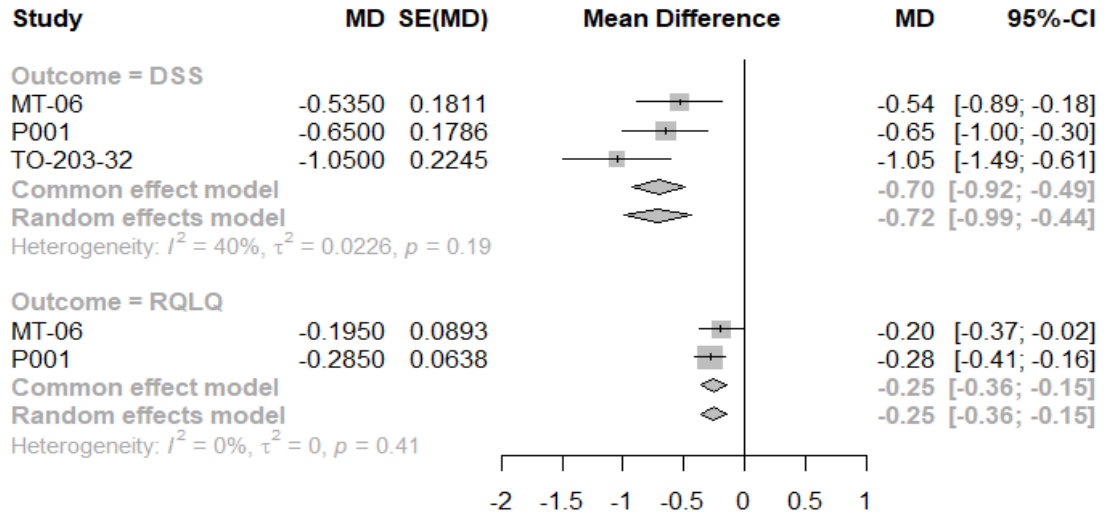
For the AR trials:

- In MT-06 study RQLQ and DSS scores are available at visit 6 and the efficacy assessment period.
- In P001, DSS was recorded at Visit 9 prior to the efficacy assessment period and at Visit 10/11 in the efficacy assessment period. RQLQ was only collected at Visit 6, which was only 4 weeks into the treatment phase.

- In TO-203-32, DSS was recorded at Visit 9 at the final visit prior to efficacy evaluation period. Only the Japanese RQLQ was collected and therefore cannot be included in the meta-analysis.

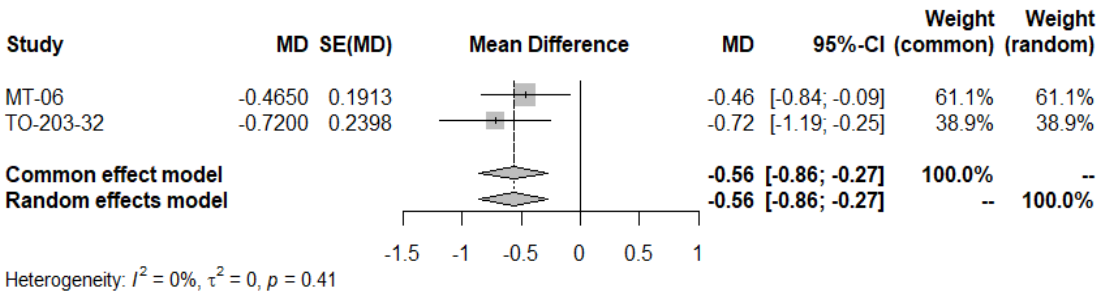
During the efficacy assessment period, based on the pooling of results from MT-06, P001, and TO-203-32 there was evidence to support a statistically significant difference in DSS score among patients treated with 12 SQ-HDM versus those receiving placebo. The pooled effect estimate from the fixed effect model was -0.70 (95% -0.92, -0.490.88) and -0.72 (95% -0.99,-0.44) from the random effects model. Between study variability was low (I2 statistic = 40%). Regarding change from baseline in total RQLQ, pooling estimates from MT-06, P001 resulted in a mean treatment difference of -0.25 (95% -0.36, -0.15), indicating superiority of 12 SQ-HDM versus placebo.

Figure 3: Meta-analysis showing Mean difference (MD) in DSS score and total RQLQ for AR patients treated with 12 SQ-HDM versus placebo – during efficacy evaluation period



When assessing change from baseline in DSS score prior to the efficacy evaluation period, pooled estimates from MT-06 and TO-203-32 also demonstrated a statistically significant improvement for patients treated with 12 SQ-HDM versus placebo (-0.56 (95% -0.86, -0.27)). The I^2 statistic returned a value of 0%, indicating minimal between study heterogeneity.

Figure 4: Meta-analysis showing Mean difference (MD) in DSS score for AR patients treated with 12 SQ-HDM versus placebo – prior to efficacy evaluation period



A15. Priority question: Trial RoB assessments (Appendix P):

- **The MT-06 trial has an imbalance in the numbers randomised (318 for 12 SQ-HDM vs 338 for placebo). Please comment on how this happened, given that block randomisation was used.**

The MT-06 trial protocol states that, “Approximately 900 subjects with HDM allergic rhinitis will be randomised in the trial. The target is that 600 subjects will receive active treatment (ALK HDM AIT 6DU or 12DU) and 300 subjects will receive placebo. More than 80 sites in 12 European countries will be involved.”

Randomisation is stratified by trial site, which in practice can be thought of as each site receiving their own randomisation list. With more than 80 sites an imbalance like this can occur even with block randomisation, as there will be some uncompleted blocks.

- **For all trials except TO-203-32 the details on allocation concealment in Appendix P relate more to methods to minimise unblinding during the trial, rather than to avoid selection bias at randomisation. Please describe if/how upcoming treatment allocations in the randomisation sequence were concealed from study staff.**

All trials had a double-blind design, and the concealment of treatment allocation was ensured by using industry standard methodology by either sequentially numbered packages or use of an interactive voice response system/interactive web response system (IVRS/IWRS). Within each trial, all investigational medicinal product (IMP) packages had the same visual appearance, irrespective of treatment or dose.

Table 2: Details on trial allocation concealment

Trial ID	Details on allocation concealment
MT-04	A randomisation list was prepared by a trial-independent statistician according to a sponsor-generated allocation schedule. Block randomisation for trial sites ensured that participants were stratified by sites. Trial staff were instructed to always pick the IMP package with the lowest available randomisation number on stock at time of randomisation of each participant. Compliance with this allocation scheme was verified during the trial.
MT-06	A randomisation list was prepared by a trial-independent statistician according to a sponsor-generated allocation schedule. Block randomisation for trial sites ensured that participants were stratified by sites. Trial staff were instructed to always pick the IMP package with the lowest available randomisation number on stock at time of randomisation of each participant. Compliance with this allocation scheme was verified during the trial.
P001	The IVRS/IWRS with central randomisation and treatment allocation, ensured that trial staff had no impact on allocation of treatment for any of the participants. The specific drug number to dispense to each participant was assigned by the IVRS/IWRS.
P003	The sponsor (Biostatistics and Research Decision Sciences department) generated the randomised allocation schedule for study treatment assignment. All participants were randomised according to this computer-generated randomisation schedule. Randomisation numbers were assigned to subjects by providing the next available number and kit (ordered sequentially).
TO-203-31	The IWRS with central randomisation and treatment allocation, ensured that trial staff had no impact on allocation of treatment for any of the participants. The specific drug number to dispense to each participant was assigned by the IWRS.
TO-203-32	The IWRS with central randomisation and treatment allocation, ensured that trial staff had no impact on allocation of treatment for any of the participants. The specific drug number to dispense to each participant was assigned by the IWRS.

Systematic literature review

A16. Please provide the following missing information from the original 2015 search strategies presented in Appendix A (p.66) of the ALK Clinical Review document:

- Search strategies for Embase and The Cochrane Library.

The PubMed/ MEDLINE search strategy was translated and adapted (syntax altered in line with database/ interface) for Embase and the Cochrane Library databases prior to being run. They however retained the same key structure in identifying the population, allergen of interest, and type of therapy (immunotherapy) being investigated, as demonstrated in the table below. Regrettably, the full search strategies and number of hits recorded for each search string in Embase and the Cochrane Library, are not available to be shared with the EAG.

#	Search string
1	exp rhinitis/ or exp asthma/
2	(asthma* or allerg* or hayfever or hay fever or rhinitis).ti,ab.
3	1 or 2
4	exp "antigens, dermatophagoides"/ or exp pyroglyphidae/ or dust mite*.ti,ab. or hdm.ti,ab.
5	3 and 4
6	exp immunotherapy/ or immunologic*.ti,ab. or immunotherap*.ti,ab.
7	5 and 6
8	limit 7 to clinical trial all

- The interface that was used to search MEDLINE, Embase and The Cochrane Library

MEDLINE/ PubMed: NCBI NLM NIH interface (http://www.ncbi.nlm.nih.gov/pubmed)

Embase: Elsevier Science interface

Cochrane Library: Cochrane Library / Wiley Interscience interface

- Further details on the search filter used to limit retrieval to clinical trials in MEDLINE (lines 8 and 9), in particular if search lines 8 and 9 represent a validated RCT search filter.

#	Search string	Rationale
8	Search #7 Filters: Clinical Trial	The use of a PudMed/MEDLINE indexing term as a search filter to limit all search results (search string 7) to clinical trials. This string was picked up in search string 12

9	Search trial[Title/Abstract] OR study[Title/Abstract] OR enrolled[Title/Abstract] OR efficac*[Title/Abstract].	A further step to retrieve all articles that report on keywords related to clinical trials such as: trial, study, enrolled, and efficacy, in their title or abstract
10	Search #7 AND #9	Although the indexing term 'filter: Clinical Trial' was applied in string 8, it is not always instantly applied to recently added records on PubMed/MEDLINE, thus additional steps- strings 9, was introduced to ensure that the search retrieved all relevant articles that reported on a clinical trial, or used keywords associated with clinical trials (trial, study, enrolled and efficacy) in their titles and/or abstracts.

In addition to the index term filter for clinical trials (search string 8), string 9 ensured that the search was restricted to all relevant articles that reported on a clinical trial, as such articles would have used keywords associated with clinical trials (trial, study, enrolled and efficacy) in their titles and/or abstracts.

- The date that the searches were carried out for each database and resource listed.

The database searches in MEDLINE/ PubMed, Embase and the Cochrane Library were conducted on January 20, 2015.

A17. Please provide further details on the search filters that were used to limit retrieval to clinical trials in the 2023 update search strategies for MEDLINE and Embase (p.68-70) presented in Appendix B of the ALK Clinical Review document.

The searches ran for the 2023 Clinical SLR update used the following clinical trial filters:

- MEDLINE (replica of the 2015 SLR search strategy, with a date limit)

#	Search string	Rationale
8	Limit 7 to clinical trial all	In line with the 2015 Clinical SLR, the search term 'clinical trial' was used to limit all search results (search string 7) to clinical trials. This string was picked up in search string 12
9	(trial or study or enrolled or efficac*).ti,ab.	To retrieve all articles that report on keywords related to clinical trials such as: trial, study, enrolled, and efficacy, in their title or abstract

10	7 and 9	To ensure the limit on all search results (search string 7) to articles that report on keywords associated with clinical trials (search string 9), is as broad as possible

Search string 8 ensured that the search limited results to being clinical trials only, and search string 9 was used an additional filter to confirm that the search was restricted to all relevant articles that reported on a clinical trial, as such articles would have used keywords associated with clinical trials (trial, study, enrolled and efficacy) in their titles and/or abstracts. In addition, during the screening process, all non-clinical trials (if any) would have been further excluded following independent title & abstract and full text screening by two reviewers.

- Embase

#	Search string	Rationale
23	(random* or factorial* or placebo* or assign* or allocat* or crossover*).tw.	These validated search filters (https://www.nice.org.uk/guidance/ng50/documents/search-strategies) were applied with the intention to limit all retrieved studies to clinical trials (see string 44). However, a typo has been identified in line 45 which should have read '22 and 44' and filtered all searches for clinical trials. However, this does not impact the results of the SLR as during the screening process, all clinical trials were included following independent title & abstract and full text screening by two reviewers.
24	(cross adj over*).tw.	
25	(trial* and (control* or comparative)).tw.	
26	((blind* or mask*) and (single or double or triple or treble)).tw.	
27	(treatment adj arm*).tw.	
28	(control* adj group*).tw.	
29	(phase adj (iii or three)).tw.	
30	(versus or vs).tw.	
31	rct.tw.	
32	crossover procedure/	
33	double blind procedure/	
34	single blind procedure/	
35	randomization/	
36	placebo/	
37	exp clinical trial/	
38	parallel design/	
39	latin square design/	
40	or/23-39	

A18. Please provide details (including sources and search strategies) to show how relevant previous health technology assessments and systematic reviews were identified for both the original 2015 review and the 2023 review.

The eligibility criteria for the Economic SLR (there was no original/ update, solely a 2023 SLR with no date limit) detailed that systematic reviews retrieved from database searches would only be used as sources of reference for additional studies which may have been missed during the search. As such, no search strings were written with the intent to retrieve systematic reviews for the SLR. The eligibility detailed the following study designs as being of interest to the review: budget impact analysis, cost minimisation analysis, cost effectiveness analysis, cost benefit analysis, and cost utility analysis.

Database sources utilised to retrieve these relevant articles include: MEDLINE, Embase, Cochrane Library (Cochrane Database of Systematic Reviews <2005 to March 02, 2023>, EBM Reviews - ACP Journal Club <1991 to February 2023>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Cochrane Clinical Answers <February 2023>, EBM Reviews - Cochrane Central Register of Controlled Trials <February 2023>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>)

In addition, EconLit, the CEA registry and the NICE website were searched to retrieve all relevant economic evaluations.

Ovid MEDLINE(R) ALL <1946 to March 02, 2023>

Search date: 3rd March 2023

#	Search terms	Hits
1	exp Asthma/	140854
2	asthma$.ti,ab,kf.	179015
3	exp Rhinitis/	38091
4	rhiniti$.ti,ab,kf.	31740
5	or/1-4	231047
6	mites/	12038

7	exp Pyroglyphidae/	3644
8	Antigens, Dermatophagoides/	3485
9	Dust/	24593
10	(dust or dusts or mite or mites).ti,ab,kf.	61441
11	(HDM or HDMs).ti,ab,kf.	3224
12	pyroglyphid$.ti,ab,kf.	271
13	(dermatophagoid$ or d farinae or d pteronyss$).ti,ab,kf.	4850
14	(euroglyphus$ or e maynei).ti,ab,kf.	127
15	(blomia or b tropicalis).ti,ab,kf.	427
16	(perennial$ or nonseasonal$ or non-seasonal$).ti,ab,kf.	15970
17	indoor allergen$1.ti,ab,kf.	799
18	or/6-17	87364
19	rhinitis, allergic, perennial/	7616
20	(5 and 18) or 19	19735
21	exp cost effectiveness analysis/ or exp cost utility analysis/ or exp economic evaluation/ or exp cost-effectiveness model/	91873
22	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or unit$ or estimat$ or variable$)).ab.	200747
23	21 or 22	243902
24	20 and 23	141

Embase <1974 to 2023 March 02>

Interface: OvidSP®

Search date: 3rd March 2023

#	Search terms	Hits
1	exp asthma/	298280
2	asthma$.ti,ab,kw.	264107
3	exp rhinitis/	107098
4	rhiniti$.ti,ab,kw.	46794
5	or/1-4	408856
6	mite/	11776
7	exp pyroglyphidae/	13743
8	house dust allergen/	6143
9	house dust allergy/	2925
10	dust/ or house dust/ or dust exposure/	29895
11	(dust or dusts or mite or mites).ti,ab,kw.	77407
12	(HDM or HDMs).ti,ab,kw.	6309

13	pyroglyphid$.ti,ab,kw.	301
14	(dermatophagoid$ or d farinae or d pteronyss$).ti,ab,kw.	7299
15	(euroglyphus$ or e maynei).ti,ab,kw.	178
16	blomia tropicalis/	686
17	(blomia or b tropicalis).ti,ab,kw.	815
18	(perennial$ or nonseasonal$ or non-seasonal$).ti,ab,kw.	17164
19	indoor allergen$.ti,ab,kw.	1278
20	or/6-19	108157
21	perennial rhinitis/	4093
22	5 and 20	25536
23	21 or 22	27653
24	exp cost effectiveness analysis/ or exp cost utility analysis/ or exp economic evaluation/ or exp cost-effectiveness model/	349710
25	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or unit$ or estimat$ or variable$)).ab.	281524
26	24 or 25	494007
27	23 and 26	328

Cochrane Library; ALL EBM Reviews

Interface: OvidSP®

Search date: 3rd March 2023

#	Search terms	Hits
1	Asthma.mp.	36441
2	asthma*.ti,ab.	35723
3	allerg*.ti,ab.	28438
4	1 or 2 or 3	59813
5	Rhinitis.mp.	11278
6	hayfever*.ti,ab.	89
7	hay fever*.ti,ab.	512
8	rhinitis*.ti,ab.	8470
9	5 or 6 or 7 or 8	11489
10	4 and 9	8989
11	Pyroglyphidae.mp.	228
12	Antigens, Dermatophagoides.mp.	330
13	dust mite*.ti,ab.	1552
14	HDM.ti,ab.	708
15	11 or 12 or 13 or 14	1872

16	10 and 15	790
17	Immunotherapy.mp.	12691
18	immunologic*.ti,ab.	10271
19	immunotherap*.ti,ab.	10718
20	17 or 18 or 19	22166
21	16 and 20	500
22	exp cost effectiveness analysis/ or exp cost utility analysis/ or exp economic evaluation/ or exp cost-effectiveness model/	9728
23	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	32725
24	22 or 23	34930
25	21 and 24	9

EconLit

Interface: OvidSP®

Search date: 3rd March 2023

#	Search terms	Hits
1	asthma$.af.	289
2	rhiniti$.af.	11
3	1 or 2	299
4	(dust or dusts or mite or mites).af.	225
5	(HDM or HDMs).af.	9
6	pyroglyphid$.af.	0
7	(dermatophagoid$ or d farinae or d pteronyss$).af.	0
8	(euroglyphus$ or e maynei).af.	0
9	(blomia or b tropicalis).af.	0
10	(perennial$ or nonseasonal$ or non-seasonal$).af.	701
11	indoor allergen$1.af.	0
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	935
13	3 and 12	6

CEA Registry

Interface / URL: https://cevr.tuftsmedicalcenter.org/databases/cea-registry

Search date: 12th April 2023

#	Search terms	Hits
1	house dust	3

2	dust mite	3
3	dust mites	0
4	hdm	3
5	hdms	0
6	pyroglyphid	0
7	pyroglyphids	0
8	pyroglyphidae	0
9	pyroglyphidaes	0
10	dermatophagoid	0
11	dermatophagoids	0
12	dermatophagoide	0
15	dermatophagoides	0
16	d farinae	0
17	d pteronyssinus	0
18	euroglyphus	0
19	e maynei	0
20	blomia	0
21	b tropicalis	0
22	perennial	1
23	nonseasonal	0
24	non-seasonal	0
25	non seasonal	10
24	indoor allergen	0
25	indoor allergens	1

National Institute for Health and Care Excellence (NICE)

Interface / URL: https://www.nice.org.uk/

Search date: 15th February 2023

#	Search terms	Hits
1	dust OR dusts OR mite OR mites OR HDM or HDMs OR pyroglyphid OR pyroglyphids	2 (21 results returned, 2 selected)
2	pyroglyphidae OR pyroglyphidaes OR dermatophagoid OR dermatophagoids	0
3	dermatophagoide OR dermatophagoides OR "d farinae" OR "d pteronyssinus"	0
4	euroglyphus OR "e maynei" OR blomia OR "b tropicalis"	0 (8 results, 0 selected)

5	perennial OR nonseasonal OR "non-seasonal" OR "non seasonal"	0 (3 results, 0 selected)
6	"indoor allergen" OR "indoor allergens"	0

A19. Please provide further details on how evidence was identified and selected for the non-systematic review of real-world evidence (referred to on page 34).

As part of ongoing work for an internal review paper focused on the efficacy and safety of SLIT-tablets (not limited to HDM), a literature review (including the non-systematic review of real-world evidence) was carried out. An internal information specialist drew up the search strategies and performed the searches in PubMed, ClinicalTrials.gov, and EU Clinical Trials Register on 1st July 2023.

A supplementary manual search of records against the internal clinical database, was also performed. Non-English language, Phase I-III trials, and publications published prior to 2006 (prior to the first marketing authorization for SQ SLIT-tablet), were excluded. Likewise, studies assessing cost-effectiveness, or published in other disease areas or medicinal products, were excluded during the screening process. Title and abstract, full publication screening, and data extraction were performed by one reviewer. Studies relevant to the decision problem were identified from this review and included in the submission (page 34 of Document B).

PubMed/ MEDLINE search strategy employed:

("Product Surveillance, Postmarketing"[MH] OR "post-marketing" OR "post-authorization" OR "cohort" or "case-control" OR "observational" OR "non-interventional" OR prospective OR "real-world" OR retrospective OR "drug utilization" OR longitudinal) AND (grazax OR itulazax OR ragwizax OR acarizax OR grastek OR itulatek OR ragwitek OR miticure OR odactra OR ALK[AD] OR ALK-abello[AD]) AND ("2006/01/01" [PDAT] : "2023/07/15"[PDAT])

A20. Section 2.3.3 of the clinical SLR document states that the risk of bias (RoB) 2 tool was used. Results are only provided for the older (2011) version of the tool –

please clarify if RoB version 2 assessments are available and, if so, please provide them.

In line with the 2015 Clinical SLR, the methodology of all studies synthesised in the submitted Clinical SLR document were appraised using the Cochrane RoB tool and further re-appraised using the more recent Cochrane RoB 2 tool (results are provided below).

In general, most studies were judged to be of unclear risk of bias due to lack of adequate reporting on the allocation sequence (how patient allocation to treatment arm was made random), lack of reporting on assignment and adherence to intervention, and selective non-reporting (result figures with no data tables, and little means of properly interpreting results). It is worth noting that most of the studies which were judged to be of a high risk of bias were published prior to 2006 (prior to the first marketing authorization for SQ SLIT-tablet), also at a time when reporting standards for published studies/ trials were not rigorous. None of the studies which reported on the clinical efficacy of 12 SQ-HDM sublingual tablets were judged to be of a high risk of bias.

Quality assessment of studies included in Clinical SLR using the Cochrane RoB 2 tool

Study	Random sequence generation	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
AL1402ac	Unclear	Low	Low	Low	Low	**Unclear**
Aydrogan et al., 2013	Low	Low	Low	Low	Low	**Low**
Baba et al., 2021	Unclear	Low	Low	Low	Low	**Unclear**
Bahçeciler et al., 2001	Unclear	Low	Unclear	Low	Low	**High**

Study	Random sequence generation	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Basomba et al., 2002	Unclear	Unclear	Low	Low	Low	**High**
Bergmann et al., 2014	Low	Unclear	Low	Low	Low	**Unclear**
Bozek et al., 2017	Low	Low	Low	Low	Low	**Low**
Bozek, Starczewska-Dymek, and Jarzab 2017	Low	Low	Low	Low	Low	**Low**
Bozek et al., 2021	Unclear	Low	Low	Low	Low	**Unclear**
Bousquet et al., 1999	Unclear	Low	Unclear	Low	Low	**Low**
Chen et al., 2020	Low	Unclear	Low	Low	Low	**Unclear**
de Bot et al., 2012	Unclear	Low	Low	Low	Low	**Unclear**
Demoly et al., 2015	Low	Low	Low	Low	Low	**Low**
Demoly et al., 2020	Low	Unclear	Low	Low	Low	**Unclear**
Devillier, Fadel, and de Beaumont, 2016	Unclear	Low	Low	Low	Low	**Unclear**
Garcia-Robaina et al., 2006	Unclear	Low	Low	Low	Low	**Unclear**
Guez et al., 2000	Unclear	Low	Low	Low	Low	**Unclear**
Gunawardana et al., 2017	Low	Low	Unclear	Low	Low	**Unclear**
Guo et al., 2017	Low	Low	Low	Low	Unclear	**Unclear**
Hirsch et al., 1997	Unclear	Low	Unclear	Low	Low	**High**
Hoshino et al., 2020	Low	Low	Unclear	Low	Low	**Unclear**

Study	Random sequence generation	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Hui et al., 2014	Unclear	Low	Low	Low	Low	**Unclear**
Kim et al., 2018	Low	Low	Low	Low	Low	**Low**
Ippoliti et al., 2003	Unclear	Low	Unclear	Low	Low	**High**
Lin et al., 2015	Unclear	Low	Low	Low	Low	**Unclear**
Liu et al., 2021	Low	Low	Low	Low	Low	**Low**
Lue et al., 2006	Unclear	Low	Low	Low	Low	**Unclear**
Masuyama et al., 2018	Low	Low	Low	Low	Low	**Low**
McHugh et al., 1990	Unclear	Low	Unclear	Low	Low	**High**
Mosbech et al., 2015	Low	Unclear	Low	Low	Low	**Unclear**
MT-11 Trial	Unclear	Low	Low	Low	Low	**Unclear**
Nieto et al., 2022	Low	Low	Low	Low	Low	**Low**
Niu et al., 2006	Unclear	Unclear	Low	Low	Low	**High**
Nolte et al., 2015	Low	Low	Low	Low	Unclear	**Unclear**
Nolte et al., 2016	Low	Low	Low	Low	Unclear	**Unclear**
Okamoto et al., 2017	Unclear	Low	Low	Low	Unclear	**High**
Okamoto et al., 2019	Low	Low	Low	Low	Low	**Low**
Okubo et al., 2016	Unclear	Low	Low	Low	Low	**Unclear**
Pfaar et al., 2016	Low	Low	Low	Low	Low	**Low**
Pham-Thi et al., 2007	Unclear	Low	Unclear	Low	Low	**High**
Potter et al., 2015	Unclear	Low	Low	Low	Low	**Unclear**

Study	Random sequence generation	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Riechelmann et al., 2010	Unclear	Low	Low	Low	Low	**Unclear**
Rondon et al., 2016	Unclear	Low	Low	Low	Unclear	**High**
Roux et al., 2016	Low	Low	Low	Low	Unclear	**Low**
SLITOne	Unclear	Low	Low	Low	Low	**Unclear**
Soyyigit et al., 2016	Unclear	Unclear	Low	Unclear	Low	**High**
Tahamiler et al., 2007	Unclear	Low	Low	Low	Unclear	**High**
Tanaka et al., 2020	Low	Low	Low	Low	Low	**Low**
Tonnel et al., 2004	Unclear	Low	Low	Low	Low	**Unclear**
Tseng et al., 2008	Unclear	Low	Unclear	Low	Low	**High**
Unal 2020	Unclear	Low	Low	Low	Low	**Unclear**
Valero et al., 2022	Unclear	Low	Low	Low	Low	**Unclear**
Varney et al., 2003	Low	Low	Low	Low	Low	**Low**
Virchow et al., 2016	Low	Low	Low	Low	Low	**Low**
Wang et al., 2006	Unclear	Low	Unclear	Low	Low	**High**
Xu et al., 2016	Unclear	Low	Low	Low	Unclear	**High**
Yu et al., 2021	Unclear	Low	Low	Unclear	Low	**High**
Zieglmayer et al., 2016	Unclear	Low	Unclear	Low	Unclear	**High**

Section B: Clarification on cost-effectiveness data

B1. The economic model for allergic rhinitis (AR) is structured by considering 3 health states of the AR pathway representing mild, moderate and severe AR. The EAG considers that the structural approach taken by the company is insufficiently justified, in light of existing cost-effectiveness models funded by the company (see question B2). Furthermore, parameterising the structure selected by the company imposes a reliance on post-hoc definitions of mild/moderate/severe AR (see question B7). Please justify the use of this model structure.

Hahn-Pedersen et al., (2016) and Green et al., (2019) present cost-effectiveness analyses in the AA+AR population, using data from the MT-04 trial. Green et al., (2017) present a cost-effectiveness analysis in the AR population, using data from the MT-06 trial. All three analyses use identical modelling approaches, whereby a decision tree approach is adopted, with patients treated with either 12 SQ-HDM or pharmacotherapy. As all three analyses adopt the same model, and since the AR and AA company models adopt a three-state Markov model approach, **the company considers the response to this question applicable to the response for question B8.**

The model structure adopted in the analyses of Hahn-Pedersen et al., (2016), Green et al., (2017), and Green et al., (2019) does not directly consider any of the clinical data quantifying the burden of AA or AR from the MT-04 and MT-06 trials, rather uses only quality of life data collected to quantify the magnitude of the benefits of treatment with either 12 SQ-HDM or pharmacotherapy. Furthermore, treatment costs and health resource use are fixed across treatment groups and applied equally across all years in the model.

Philips et al., (2004)[1] provide a checklist for the critical appraisal of decision-analytic models developed for health technology assessment. For attributes of good practice regarding model structures, under the rational for model structure and disease states/pathways (dimension S3 and S8), the authors note that the treatment pathways (disease states or branches) should be chosen to reflect the underlying

[1] Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;8(36)

biological process of the disease in question. To this standard, the current submission models define health states using well-recognised definitions of rhinitis severity and asthma control that form part of the marketing authorization of 12 SQ-HDM, and which are used commonly in current clinical practice.

For the AR model, the definitions of AR severity are used throughout clinical guidelines on AR including the NICE Clinical Knowledge Summary on AR. This guidance makes clear recommendation on the management of AR in line with definitions of disease severity. For patients with mild-to-moderate, intermittent, or mild persistent symptoms, oral or intranasal antihistamines are the first line of therapy. For patients with moderate-to-severe persistent symptoms, or those for whom initial treatment is ineffective, intranasal corticosteroids are recommended. If symptoms continue to persist despite these treatments, combination therapies can be explored, including combinations of oral antihistamines and intranasal corticosteroids, or combined preparations of intranasal corticosteroids and intranasal antihistamines. In order to accurately depict the treatment needs and utilization of healthcare resources for individuals with AR, the company deems it essential to model health states linked to the severity of AR. Using definitions of AR severity aligned with verbal rating scales used in clinical practice facilitates the incorporation of evidence elicited from clinical opinion in the form of Delphi panels and advisory boards.

For the AA model, according to both the GINA and BTS/SIGN guidance, the primary function of pharmacological management in AA is to achieve long-term asthma disease control. The model defines health states using well-recognised definitions of asthma control that form part of the marketing authorization of 12 SQ-HDM, and which are used commonly in current clinical practice and throughout clinical guidelines on asthma including the GINA, NICE, and BTS/SIGN. The GINA guidelines define asthma control as well-controlled, partly controlled, or uncontrolled on the basis of answers to 4 questions relating to the presence of daytime asthma symptoms more than twice per week, night waking due to asthma, need for reliever/rescue treatment, and activity limitation due to asthma. The GINA guideline further references the asthma control questionnaire (ACQ) and asthma control test (ACT) as examples of numerical asthma control tools for assessing symptom control.

Both the ACQ and ACT are recommended in NICE's quality standard on asthma (QS25). ACT scores are done in practice as part of QOF in primary care in which the scores are used to assess asthma status and the potential need to step up or down on asthma treatments. In MT-04 trial, the level of asthma control was classified in GINA levels of control by transforming results from the ACQ, with data provided across 11 trial visits. In order to accurately depict the treatment needs and utilization of healthcare resources for individuals with AA, the company deems it essential to model health states linked to the asthma control.

Economic model structure – AR population

B2. Priority question: A cost-effectiveness analysis of SQ-HDM SLIT in a German setting and using data from the MT-06 trial has been published by Green et al (CE&OR, 2017 – reference 64 of the CS). Using regression approaches, the authors' analysis considers differences in change from baseline utility values between SQ-HDM and placebo arms of the MT-06 trial at 1 year, also making assumptions on the long-term impact of each treatment option over the remaining time (time horizon of 9 years). A similar approach was undertaken for health care resource consumption. Please justify why a structural approach to economic modelling around severity levels is advantageous compared with the simpler modelling approach proposed by Green et al (2017).

The economic analysis by Green et al., (2017) adopts a simplified decision tree analysis to model the AR population, whereby patients receive either 12 SQ-HDM or pharmacotherapy (equivalent to established clinical management in this submission). The model does not consider any of the clinical data quantifying the burden of AR from the MT-06 trial, rather uses only quality of life data collected in the trial to quantify the magnitude of the benefits of treatment with either 12 SQ-HDM or pharmacotherapy.

Green et al., (2017) include the same estimates of utility as used in the company's basecase submission, however, model the long-term benefit of 12 SQ-HDM by assuming a 5% increase in utility during each year of treatment, followed by a 10% decrease in utility during the years 6 to 9. As the analysis by Green et al., (2017) adopted the perspective of the German market, detail of the unit costs applied in the

model are not considered further. However, the analysis applied the treatment-specific resource use data collected in the MT-06 trial equally across all years in the model.

Please see response to question B3 for a detailed critique of Green et al., (2017) with additional comparison to the differences resulting from the simplified model approach. In summary, exploring uncertainty in the long-term benefit of 12 SQ-HDM using only changes in treatment-specific utility scores collected in the trials results in unrealistic estimates of HRQoL. Furthermore, the simplified approach fails to accurately reflect the health resource use and treatment requirements of individuals with AR in real-world clinical practice.

B3. Priority question: It is the EAG's view that the company's model and the model published by Green et al (2017) are in essence informed by the same effectiveness and HRQoL evidence source, i.e., the MT-06 trial. Other than differences in jurisdictions and time horizon, please comment on the differences in cost-effectiveness results between the two analyses given these use the same main source of data.

The model by Green et al., (2017) adopts a simplified approach in modelling the benefit associated with 12 SQ-HDM.

Incremental QALYs:

Green et al., (2017) include the same estimates of utility as used in the company's basecase submission, however, model the long-term benefit of 12 SQ-HDM by assuming a 5% increase in utility during each year of treatment, followed by a 10% decrease in utility during the years 6 to 9. Green et al., (2017) report that SQ HDM SLIT tablet patients generated 6.96 QALYs compared with 6.65 for pharmacotherapy patients. The resulting incremental QALY gain was 0.31 over a 9-year time horizon. Although not reported in Green et al., (2017) these results are replicated below.

When not accounting for the 5% improvement and 10% decrease in utility, the results of Green et al., (2017) would show the following results (Table 3):

Table 3: Green et al., (2017) replication without utility gain or reduction

	12 SQ-HDM			Pharmacotherapy		
	Utility score	**Discounted utility**	**Cumulative disc. Utility**	**Utility score**	**Discounted utility**	**Cumulative disc. Utility**
Year 1	0.919	0.892	0.892	0.898	0.872	0.872
Year 2	0.919	0.866	1.759	0.898	0.846	1.718
Year 3	0.919	0.841	2.600	0.898	0.822	2.540
Year 4	0.919	0.817	3.417	0.898	0.798	3.338
Year 5	0.919	0.793	4.210	0.898	0.775	4.112
Year 6	0.919	0.770	4.979	0.898	0.752	4.864
Year 7	0.919	0.747	5.727	0.898	0.730	5.594
Year 8	0.919	0.726	6.453	0.898	0.709	6.303
Year 9	0.919	0.704	7.157	0.898	0.688	6.991
Discontinuation rate set to 3%						

The results shown in Table 3 can be replicated in the company's submission model by:

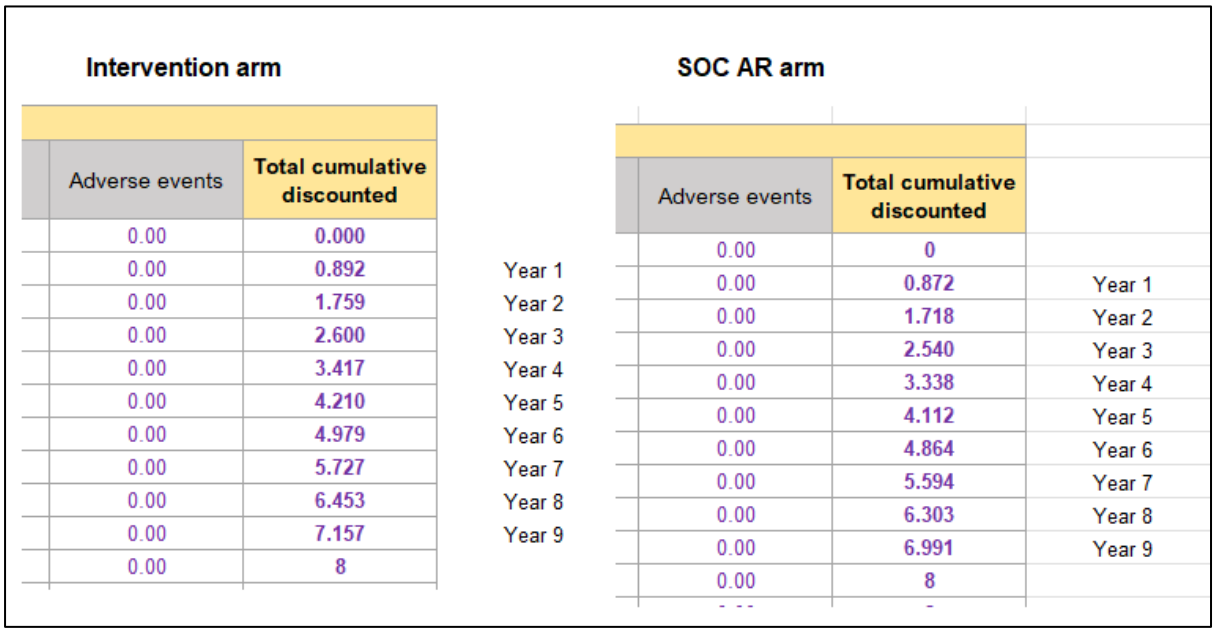
- Setting discontinuation of treatment to zero, including AE discontinuation
- Removing general mortality from the model (included functionality)
- Removing age-adjusted utilities from the model
    - Changing cell L12 in both the Intervention AR and Comparator AR sheets to fix value H12 removes this functionality.

      Original =IFERROR(VLOOKUP(H12,HRQoL!$E$73:$F$175,2,FALSE),0)

      New= IFERROR(VLOOKUP($H$12,HRQoL!$E$73:$F$175,2,FALSE),0)
- Setting discount rate to 3% to match the German perspective

Figure 5 presents a snapshot of the company's model engine showing replicated results to those of Green et al., (2017) without the percentage improvements and reductions in utility. These percentage increase could be manually added to the model engine, but the company do not feel this additional change is necessary to answer the EAGs question.

Figure 5: Snapshot CS model replication of Green et al., (2017)



Intervention arm

Adverse events	Total cumulative discounted	
0.00	0.000	Year 1
0.00	0.892	Year 2
0.00	1.759	Year 3
0.00	2.600	Year 4
0.00	3.417	Year 5
0.00	4.210	Year 6
0.00	4.979	Year 7
0.00	5.727	Year 8
0.00	6.453	Year 9
0.00	7.157	
0.00	8	

SOC AR arm

Adverse events	Total cumulative discounted	
0.00	0	
0.00	0.872	Year 1
0.00	1.718	Year 2
0.00	2.540	Year 3
0.00	3.338	Year 4
0.00	4.112	Year 5
0.00	4.864	Year 6
0.00	5.594	Year 7
0.00	6.303	Year 8
0.00	6.991	Year 9
0.00	8	

The company would further add to the response of this question by replicating the exact method used in Green et al., (2017). Table 4 presents the utility results when including the percentage increase and decrease described in the publication.

As can be seen, given the overly simplified approach by Green et al., (2019), the model produces utility estimates that which imply that patients are at perfect health for Years 3 to 5. Furthermore, in keeping with NICE's preference to appropriate age-adjust utilities, the Green et al., (2017) model provides estimates of utility that are greater than matched general population utility up to Year 5, then decline below matched general population utility to Year 9. Compared with the company's current submission which assumes that the utility decrement associated with AR captured in the MT-06 trial remains the same regardless of age, the relevant utility in the SOC/pharmacotherapy arm would be 0.874 compared with a general population utility of 0.895 at Year 9. The results of Green et al., (2017) imply that a person with AR receiving 12 SQ-HDM at Year 9 would have a utility of 0.656, a disutility relative to general population of 0.239, which is more than 10 times higher than the disutility observed in the MT-06 trial. Furthermore, this analysis also implies that patients receiving 12 SQ-HDM in addition to pharmacotherapy would have a materially worse HRQoL compared to those who receive pharmacotherapy alone. There is no clinical rationale to suggest that beyond any short-term AE associated disutility, patients receiving 12 SQ-HDM in addition to pharmacotherapy would experience worse

HRQoL compared to patients who receive pharmacotherapy alone. Even if patients do not experience any clinical benefit of 12 SQ-HDM, their HRQoL would be determined by the level of disease severity under the effects of adjunct pharmacotherapies.

Table 4: Green et al., (2017) utilities score replicated

	12 SQ-HDM			Pharmacotherapy		
	Utility score	**Discounted utility**	**Cumulative disc. Utility**	**Utility score**	**Discounted utility**	**Cumulative disc. Utility**
Year 1	0.919	0.892	0.892	0.898	0.872	0.872
Year 2	0.965	0.910	1.802	0.898	0.846	1.718
Year 3	1.000	0.915	2.717	0.898	0.822	2.540
Year 4	1.000	0.888	3.606	0.898	0.798	3.338
Year 5	1.000	0.863	4.468	0.898	0.775	4.112
Year 6	0.900	0.754	5.222	0.853	0.714	4.826
Year 7	0.810	0.659	5.881	0.810	0.659	5.485
Year 8	0.729	0.575	6.456	0.770	0.608	6.093
Year 9	0.656	0.503	6.959	0.731	0.561	6.654
Discontinuation rate set to 3% 12 SQ-HDM; 5% improvement years 1-3, 0% change years 4-5, 10% reduction years 6-9 Pharmacotherapy; 0% change years 1-5, 5% reduction years 6-9						

Incremental Costs:

Similar to the approach adopted for the application of utilities, Green et al., (2017) applied the treatment-specific resource use data collected in the MT-06 trial equally across all years in the model.

Adopting the decision tree approach does not allow for the appropriate estimation of health resource use incurred by people with AR. As highlighted in Green et al., (2017), as resource use within the trial was protocol-driven, using data solely from the MT-06 does not accurately reflect real-life practice. In particular, patients received more overall supervision and better education than patients in an everyday clinical setting, which reduced the number of additional healthcare visits. Furthermore, specialist visits were not separated from general practice visits during the data collection for the MT-06 trial (see answer B21 for more detail). Given the large cost difference between health care visits in primary and secondary care

settings, the results of Green et al., (2017) likely underestimate the true cost of AR to the health care system.

As the unit costs reported in Green et al., (2017) reflect the German payer perspective, no replication has been attempted in the company submission model.

B4. Priority question: Please consider providing an alternative and simplified economic model for AR, using a similar modelling approach to that of Green et al (2017) updated to align with the NICE reference case and including evidence from trial P001 (see question B6 for further details on the relevance of this trial to the decision problem).

The company consider this inappropriate given the rationale and clarification provided as to the current model developed for this submission. The company have also provided a detailed examination of the Green et al., (2017) analysis in response to question B3, which outlines the considerable limitations of adopted analytical approach. Furthermore, Green et al., (2017) directly state that AR is a progressive condition with patients experience regular changes in their overall health, adding that these variations would be better captured using a more complex modelling approach, such as a Markov model, which facilitates the use of health states to predict changes in patient outcomes.

With regards to the inclusion of data from the P001 trial, as stated in the company submission, no data were collected in the P001 trial that would allow for the population of health states that align to definitions of disease severity used in current clinical practice in England. The company have provided a meta-analysis that corroborates the consistency of the primary efficacy endpoint for all 3 AR phase 3 trials and demonstrates a statistically significant improvement in TCRS score in patients treated with 12 SQ-HDM versus placebo (see Section B.2.8.3 of CS). Additionally, the company have conducted further analysis of the EQ-5D data collected in the P001 trial that has been added to the company model. Utility results from the P001 align with those collected in the MT-06 study with a utility gain associated treatment with 12 SQ-HDM versus placebo.

B5. Priority question: A cycle length of 1 year is considered in the company's AR model. The company claims that a shorter cycle length was considered but

not implemented given the uncertainty in long-term effectiveness. The EAG agrees with the company that the 1-year cycle length does not capture the fluctuations in rhinitis severity.

- **Please provide a comprehensive justification on why a shorter cycle length would "lead to unreliable estimates of disease control and severity in the long run" (quoted from doc B, p178).**

Whilst patients may fluctuate in disease severity over the period of year, these changes may be subtle, and the duration of these variations may not be considerable. As a result, not all fluctuations will result in meaningful differences in HRQoL or health resource use. Therefore, if data were available to model changes in patients' disease severity over a shorter time period, these data would need to accurately capture the duration of these changes and assess the relative HRQoL and resource use data usage.

Whilst a key consideration in judging the appropriate model cycle length is to limit the probability that a given patient could experience more than one event each period of the cycle, this is conditional on the consideration that each model state has a discrete set of costs and QALYs. Therefore, if, in the real-world, fluctuations in AR severity are short, and would not result meaningful differences in HRQoL or health resource use, then to model these changes result in inappropriate accrual of costs and QALYs.

Therefore, as stated in the company submission, to reduce the impact of the short-term fluctuations in disease severity with no meaningful differences in HRQoL or health resource use, a one-year cycle length is used, which assumes that an average cohort of AR patients will be distributed across levels of disease severity over a year. This approach is believed to more appropriately reflect the total time spent in each health state by the cohort of patients. The company would also highlight that a half-cycle correction is applied in each cycle to account for the fact that events and transitions can occur at any point during the cycle.

- **Please provide a revised version of the AR economic model reflecting a shorter cycle length (e.g. 3 months), which considers the possible fluctuations in rhinitis severity (and disease control) over time more**

appropriately and/or that mimics the data collection timepoints across both the treatment maintenance and efficacy evaluation periods of the MT-06 trial.

As stated in the company submission, in the MT-06 trial, subjects were asked about the presence of impairment of 3 ARIA HRQoL items (sleep disturbance, impairment of daily activities/sport, and impairment of work or school) at baseline and during the last 2 weeks of the efficacy assessment period; approximately 12 months apart.

Therefore, the cycle length used in the company AR model currently mimics the data collection timepoints of the MT-06 trial. Additionally, there are no data available that can inform patients' movement between disease severity states for time periods shorter than this, as such, reducing model cycle length would reveal no additional granularity in health outcomes or resource use.

B6. Priority question: The population of interest for AR includes people aged 12 to 17 years of age in addition to adults (18-65 years). The phase 3 trial P001 (Nolte et al 2016) is presented to support evidence on the clinical-effectiveness of SQ-HDM for this age range. Nevertheless, the company considered that the outcomes from this study are not transferable to the cost-effectiveness model (Table 5, p28 of the CS). The AR economic model relies solely on the MT-06 trial, which had a more restricted population in terms of age (18-65 years old) than the one defined by the current license for 12 SQ-HDM.

- **Please provide a thorough justification for not using evidence from P001 to inform the AR economic model.**

Please see response to question B5.

- **Please justify the use of evidence from an adult AR population (as per MT-06 trial) to inform the full AR population in the model, i.e. the clinical validity of generalising evidence from an adult population into an adolescent population (as the model implicitly assumes that there are no differences between the two subpopulations).**

As highlighted in response to question B5, the AR model was developed to be generalisable to the UK clinical practice, reflecting the AR treatment pathway whilst

incorporating data from the key phase 3 trials. The MT-06 trial was the only trial to collect data that could be transferable to the well-established definitions of disease heath states. In line with NICE guidance on evidence synthesis (Section 3.4 of the NICE HTA manual), the company have considered all relevant studies in the assessment of clinical effectiveness and have provided a meta-analysis on the primary endpoints (and additionally secondary endpoints; question A14) of the key 3 AR trials evidencing the clinical effectiveness of 12 SQ-HDM.

As detailed in Section B.2.8.4 of the CS, the comparative assessment of MT-06, P001, and TO-203-32 highlighted some areas of heterogeneity regarding study population and study design of each trial, namely the inclusion of adolescents in the TO-203-32 and P001 trials, the presence of AA at baseline, and duration of rhinitis. However, there was good alignment between the reported outcomes of the trials (I2 = 0%). The meta-analysis for average TCRS demonstrated a statistically significant treatment effect versus placebo when pooling the results of the 3 trials.

In the P001 and TO-203-32 trials, adults and adolescents both demonstrated a significant improvement in TCRS compared with placebo, regardless of age group, suggesting similar efficacy across the two groups. In P001, for adults, a 19.2% reduction in TCRS was shown for 12 SQ-HDM compared with placebo (Hodges-Lehmann estimate of shift: -0.9 [95% CI -1.30, -0.40]). For adolescents, a 22.4% reduction in TCRS was shown for 12 SQ-HDM compared with placebo (Hodges-Lehmann estimate of shift: -1.0 [95% CI -2.00,-0.10]). The TO-203-32 study reports that a relative difference of 17% (adjusted MD: -0.88), 16% (adjusted MD: -0.77), and 22% (adjusted MD: -1.11) for 12 SQ-HDM compared to placebo can be observed in the 12-18, 18-30, and 30-40 age subgroups, respectively.

Given the alignment of the 3 AR studies demonstrated in the meta-analysis of the primary and secondary endpoints, the company consider the subgroup analysis of adults and adolescents demonstrated independently in the P001 and TO-203-32 trials showing similarity of efficacy to be an appropriate validation of the assumption that that there are no differences between the two subpopulations in the CE model.

- **The CS (p9) suggests that the company is not seeking for 12 SQ-HDM to be appraised in an adult population only for the AR indication. Please confirm if the EAG interpretation is correct.**

The EAG is correct. The company is seeking a joint appraisal of adults and adolescents in the AR indication.

- **If the company is seeking for 12 SQ-HDM to be appraised in the full licensed population in AR (12 years +), then the EAG considers that the AR model should try to incorporate evidence from the P001 trial and requests that for the model parameters currently informed by the MT-06 and where corresponding data was collected in the P001 trial:**
    - **If feasible, please provide estimates (both point estimates and measures of uncertainty [e.g., S.E.s]) using pooled evidence from the MT-06 and P001 trials and present cost-effectiveness results for a scenario using these data.**
    - **Please provide estimates sourced (both point estimates and measures of uncertainty [e.g., S.E.s]) from the P001 trial for the i) overall population, ii) adults only subpopulation, and iii) adolescents only subpopulation (12 to 17 years old). Present cost-effectiveness analyses for these three (sub)populations.**

As detailed in previous questions, it is not possible to incorporate any point estimates from the P001 trial in the cost-effectiveness model for AR.

The AR efficacy is driven by changes in patients AR severity. The ARIA classification has been used to model changes in patients' AR severity over the duration of the MT-06 trial. At baseline and during the last 2 weeks of the efficacy assessment period in the MT-06 trial, subjects were asked about the presence of 3 ARIA QoL items (sleep disturbance, impairment of daily activities/sport, and impairment of work or school). To complete the 4th item of the ARIA classification (troublesome symptoms), the DSS was used, as recorded in the MT-06 trial. This analysis was conducted using a subset of patient level data from the MT-06 trial.

The summary point estimates of patients average DSS (sub-component of TCRS) are insufficient for estimating the 'troublesome symptoms' item of the ARIA component at an individual patient level, which is required in order to estimate an overall ARIA severity classification for each patient. Therefore, neither the P001 point estimates, or the meta-analysis point estimates can be used to update efficacy used in the CE model.

Economic model natural history and short-term treatment effectiveness parameterisation - AR population.

B7. Priority question: To populate the different AR severity levels as portrayed by the economic model structure, a distribution of patients at MT-06 baseline and trial end was estimated post-hoc using a modified version of the "Allergic Rhinitis and its impact on Asthma" (ARIA) classification. The post-hoc patient-level data analysis of the MT-06 trial was conducted using data on patients' rhinitis DSS, and 3 ARIA HRQoL components.

- **Please justify the use of a post-hoc analysis to inform the distribution of patients at MT-06 baseline and trial end, i.e., the effectiveness parameterisation in year 1 of the model.**

As stated in the company submission, the AR model structure was designed to be generalisable to UK clinical practice. The model defines health states using well-recognised definitions of AR severity that form part of the marketing authorization of 12 SQ-HDM, and which are used commonly in current clinical practice and throughout clinical guidelines on AR including the NICE Clinical Knowledge Summary on AR.

The primary endpoint of the MT-06 trial was the average TCRS during the primary efficacy evaluation period (Period 3, between Visit 7 and Visit 8). The TCRS is calculated as the sum of rhinitis symptom (DSS) and medication scores (DMS), which were assessed independently as secondary endpoints. Whilst the TCRS appropriately measures the impact of treatment on disease symptoms and use of medication to manage symptoms, the TCRS score does not correspond to any recognised categories of AR severity. So, whilst a higher score indicates a greater disease burden, the relative impact of a one-point increase in TCRS on health

outcomes or health resource use (beyond medication use) are unknown. This is problematic for cost-effectiveness modelling.

The ARIA classification provides a method for assessing AR severity (mild, moderate, and severe) on the basis of the presence or absence of impairment in any of four HRQoL items. As the company is not aware of any existing cut-offs based on AR severity categories for the TCRS score, a post-hoc analysis using data on patients' rhinitis DSS, and 3 ARIA HRQoL components was necessary to inform the distribution of patients at baseline and Year 1 in the AR model.

- **Please clarify how patients that dropout and/or are censored within the MT-06 baseline and trial end period are dealt with, justifying assumptions of the approach taken to consider these patients and their impact on cost-effectiveness results.**

No methods were used by the company to address missing observations. As detailed in Section B3.3.1.1 of the CS, of the 992 patients included in the full data set, only 914 had 3 valid ARIA assessment values indicated with either a 'Yes' or 'No' response for presence of the HRQoL item. Of those, 871 patients had a reported rhinitis DSS. Of the 871, 576 patients were treated with either placebo (n=296) or 12 SQ-HDM (n=280), with the remaining 296 patients having received 6 SQ-HDM.

- **Please provide justifications on the clinical validity of the use of 3 HRQoL items relating to sleep disturbance, impairment of daily activities/sport and impairment of work/school to inform ARIA severity levels.**

The validation of the original ARIA classification in which the 4 HRQoL items were defined is provided in Bousquet et al., (2008). The validation of the modified ARIA classification and use of HRQoL items is provided in Valero et al., (2007). Both sources have been provided in the company submission.

- **Please provide justification on the clinical validity of the use of 4 items of the rhinitis's daily symptom score (DSS) to inform ARIA severity**

levels, and more specifically, to inform the break down between moderate and severe levels.

The company believe that this may be a misunderstanding.

The ARIA classification is based on the presence or absence of impairment in any of the four HRQoL items: sleep, daily activities/sport, work/school, and troublesome symptoms. The modified ARIA classification from Valero et al., (2007) was used to inform AR disease severity using the MT-06 data. Of the 4 HRQoL items, patients with mild AR have no affected items, patients with moderate AR have 1 to 3 affected items, and patients with severe AR have all 4 affected items.

Justification of the clinical validity of the ARIA classification items is provided in response to the previous bullet question.

The MT-06 trial only collected three out the of the four items, with troublesome symptoms being excluded. To complete the fourth item of the ARIA classification (troublesome symptoms), the rhinitis DSS was used, as recorded in the MT-06 trial. The rhinitis DSS was the total of 4 rhinitis symptom scores (runny nose, blocked nose, sneezing, and itchy nose), which were measured on a 4-point scale from 0 (no symptoms) to 3 (severe symptoms) and ranged from 0-12.

- **Please justify the DSS score cut-offs to define the presence of 'troublesome symptoms' for the base case and scenario analyses.**

Two approaches were considered in estimating the cut-off for the presence of 'troublesome symptoms' item.

In the model base case, whether or not the cut-off for the 'troublesome symptoms' item was impaired was determined by whether patients had an average rhinitis DSS score of 4. This means that if a subject scored at least 1 on all 4 rhinitis symptoms or had a severe symptom (score of 3) and a mild symptom (score of 1), it was determined that the 'troublesome symptom' item was affected.

As a model scenario, a rhinitis DSS score of at least 6 or a score of at least 5 with one symptom being severe was used. To reach a rhinitis score of 6, subjects had to score at least 2 symptoms as being moderate (i.e. definite awareness of symptom

that is bothersome but tolerable). A score of at least 5 with one symptom being severe means that the subject had at least 1 symptom that was hard to tolerate (i.e. causes interference with activities of daily living and/or sleeping). This definition was used as the criteria for trial inclusion, whereby only subjects who had experienced an appropriate minimum level of rhinitis symptoms despite treatment with symptomatic medications could be enrolled in the MT-06 trial. This was done to ensure that the trial population represented subjects with a medical need for alternative treatment.

- **Please justify the use of fixed rules and assumptions around using the 4-item rhinitis DSS instead of the 6 items (including eye-related symptoms), and 3 ARIA HRQoL components to classify patients in the different severity levels e.g., clinical validity of all 4 HRQoL items affected to classify patients as being severe.**

The additional conjunctivitis symptom scores were not included to classify patients under different severity levels of allergic rhinitis. Whilst allergic conjunctivitis can be a common comorbidity, this is not the same as allergic rhinitis. In keeping with the licensed indication for 12 SQ-HDM, conjunctivitis symptoms were not included in the modelling of rhinitis severity.

The validity of the four ARIA HRQoL components has been discussed previously.

- **Given that the short-term effectiveness is a key effectiveness parameter, please explain how the approach taken by the company (i.e., of using rhinitis DSS, and 3 ARIA HRQoL components) captures uncertainty on this set of parameters informing the health states definition.**

The company have provided two options for modelling short-term effectiveness which takes into account uncertainty in the cut-off for the HRQoL item, 'troublesome symptoms' as this had to be imputed using the rhinitis DSS score.

The company consider that both scenarios appropriately reflect uncertainty in the DSS score cut-offs to define the presence of 'troublesome symptoms'. The base case scenario reflects the presence of mild rhinitis symptoms, whilst the scenario analysis reflects the presence of moderate symptoms in two of four rhinitis symptom components. As the ARIA classification requires a binary response to the presence

or absence of impairment in any of the four HRQoL items: sleep, daily activities/sport, work/school, and troublesome symptoms. The company considers the current model analyses sufficient in reflecting the uncertainty associated with the estimation of short-term effectiveness.

- **Please provide comprehensive scenario analysis on the assumptions around the ARIA HRQoL components and DSS score cut-offs for troublesome symptoms (e.g., consider presence of sleep disturbance as severe AR) to define model health states, providing different alternative distributions of patients at MT-06 baseline and trial end, and their consequences in terms of cost-effectiveness. Please report alternative patient distributions for the alternative health state definitions (as seen in Table 68 of the CS) and cost-effectiveness results (as seen in Table 100 of the CS) for each implemented scenario analysis.**

As the modified ARIA classification has been validated (see Valero et al., 2007), the company do not consider that changes in disease severity definitions appropriate.

The company would highlight that, under the company basecase, using treatment-specific utilities, with treatment-specific reductions in health care use, changes in the short-term effectiveness has a non-material impact on the ICER.

Economic model structure – AA+AR population

B8. The economic model for the AA+AR population is structured by considering 3 health states of the AA+AR pathway representing well-controlled, partially controlled, and uncontrolled AA. The EAG considers that the structural approach taken by the company is insufficiently justified, particularly in light of existing cost-effectiveness models funded by the company (see question B9). Furthermore, parameterising the structure selected by the company imposes a reliance on post-hoc definitions of well/partially/uncontrolled AA health states.

- Please justify the use of this model structure.

Please see response to question B1.

- Parra-Padilla et al (2020) proposed a Markov model considering GINA step 2, GINA step 3 and Asthma in remission state, with a decision tree relating to asthma exacerbations embedded in GINA step 3 and GINA step 2 states. Please compare and contrast Parra-Padilla et al model structure with your structure and justify differences.

The CEM presented by Parra-Padilla et al., (2020) provides no detail as to the validation and rationale for the chosen model structure, and limited information as to the sources of clinical data informing transition probabilities between health states.

The model proposed by Parra-Padilla et al., (2020) attempts to directly model changes in patients AA treatment, using the defined treatment steps in the GINA guidance. Whilst it may be appropriate to model changes in patients' AA treatment, as patients can be on multiple combinations of symptomatic therapies, estimates of efficacy informing patient transitions between treatment subgroups would be limited. Furthermore, as the 12 SQ-HDM randomised trials had limitations on the use of symptomatic treatments to minimize the interference with the efficacy assessment, patients in the trial could not be grouped by GINA treatment step.

B9. Priority question: Four previous cost-effectiveness analyses of SQ-HDM SLIT in four jurisdictions other than the UK and using data from the MT-04 trial[2] have been published by Green et al (EAACI, 2019 – ref 65, company's doc B of the CS) and Hahn-Pedersen et al (CTA, 2016 - ref 66, company's doc B of the CS).

- **Please justify the use of a structural approach to economic modelling around asthma control levels (as per the CS) instead of the simpler modelling approach proposed by Hahn-Pedersen et al (2016) and also used by Green et al (2019).**

As noted in response to question B.1, according to both the GINA and BTS/SIGN guidance, the primary function of pharmacological management in AA is to achieve

[2] The EAG notes that while these 4 studies and the CS all use evidence from MT-04 to inform their cost-effectiveness analyses, the previous studies used evidence from the treatment maintenance period (phase 2) of the MT-04 trial as this period was considered by the authors to be more reflective of clinical practice/real world setting than the ICS reduction/efficacy assessment period (phase 3) used to inform the CS model.

long-term asthma disease control. The model defines health states using well-recognised definitions of asthma control that form part of the marketing authorization of 12 SQ-HDM, and which are used commonly in current clinical practice and throughout clinical guidelines on asthma including the GINA, NICE, and BTS/SIGN. The GINA guidelines define asthma control as well-controlled, partly controlled, or uncontrolled on the basis of answers to 4 questions relating to the presence of daytime asthma symptoms more than twice per week, night waking due to asthma, need for reliever/rescue treatment, and activity limitation due to asthma. The GINA guideline further references the asthma control questionnaire (ACQ) and asthma control test (ACT) as examples of numerical asthma control tools for assessing symptom control. Both the ACQ and ACT are recommended in NICE's quality standard on asthma (QS25). ACT scores are done in practice as part of QOF in primary care in which the scores are used to assess asthma status and the potential need to step up or down on asthma treatments. In MT-04 trial, the level of asthma control was classified in GINA levels of control by transforming results from the ACQ, with data provided across 11 trial visits. In order to accurately depict the treatment needs and utilization of healthcare resources for individuals with AA, the company deems it essential to model health states linked to the asthma control.

Hahn-Pedersen et al., (2016), Green et al., (2017), and Green et al., (2019) use identical modelling approaches, whereby a decision tree approach is adopted, with patients treated with either 12 SQ-HDM or pharmacotherapy. As all three analyses adopt the same model, the company's critique of Green et al., (2017) in response to question B.3 is directly applicable to the analyses of Hahn-Pedersen et al., (2016) and Green et al., (2019).

- **Please consider providing the EAG with an alternative and simplified economic analysis for AA+AR, using a similar modelling approach to that of Green et al (2019) and Hahn-Pedersen et al (2016) updated to align with the NICE reference case. Similar to these previous cost-effectiveness analyses, please use evidence collected in the treatment maintenance phase (phase 2) of MT-04, instead of the ICS reduction/efficacy assessment phase (phase 3).**

As stated in response to question B.4, The company consider this inappropriate given the rationale and clarification provided as to the current model developed for this submission. The company have also provided a detailed examination of the Green et al., (2017) analysis in response to question B3, which outlines the considerable limitations of adopted analytical approach, which is directly applicable to the analyses of Hahn-Pedersen et al., (2016) and Green et al., (2019).

As noted in response to question A7, no data on exacerbation were collected prior to Period 3 of the MT-04 trial. Data on asthma control during Period 2 has been added to the model in cells E226:Q234 on the 'Effectiveness' sheet.

B10. Priority question: A cycle length of 1 year is considered in the company's AA+AR model. Please provide a revised version of the AA+AR economic model considering a shorter cycle length (e.g., a 3-month cycle length as seen in Parra Padilla et al (2020)), which reflects fluctuations in asthma control levels over time more appropriately and aligns better with the data collection timepoints across the MT-04 trial).

As presented in the answer to question A7, asthma control for the MT-04 cohort remained relatively stable over the duration of the treatment maintenance period, which was conducted for 7-12 months, with nominal improvements observed in the 12 SQ-HDM treatment arm by the end of trial.

Please also see the company's response for question B5, as not all fluctuations in asthma control will result in meaningful differences in HRQoL or health resource use.

Economic model natural history and short-term treatment effectiveness parameterisation – AA+AR population

B11. The GINA guidelines were used to populate the different AA+AR asthma control levels, as portrayed by the economic model structure. Please justify the use of GINA guidelines as opposed to the use of the BTS/SIGN 2019 and NICE 2017 guidelines, which are also commonly used in clinical practice for asthma control level classification.

In clinical practice, the definitions of asthma control are likely to be very similar, with the GINA guidance referencing the asthma control questionnaire (ACQ) and asthma

control test (ACT) as examples of numerical asthma control tools for assessing symptom control. Both the ACQ and ACT are recommended in NICE's quality standard on asthma (QS25). ACT scores are done in practice as part of QOF in primary care in which the scores are used to assess asthma status and the potential need to step up or down on asthma treatments.

As shown in Table 67 of the CS, the recommended treatment options and steps for adults and adolescents are very similar between the GINA, BTS/SIGN, and NICE guidelines. The company would highlight that treatment options are similar across all asthma guidance, and as symptomatic treatments are low cost, they have a very limited impact on cost-effectiveness.

B12. Priority question: The distribution of patients at MT-04 baseline and trial end was estimated post-hoc covering both period 2 (treatment maintenance) and 3 (ICS reduction/efficacy assessment). The level of asthma control was classified in GINA levels of control by transforming results from the ACQ.

- **Please justify the use of a post-hoc analysis to inform the distribution of patients at MT-04 baseline and trial end, i.e., the effectiveness parameterisation in year 1 of the model.**

As stated in the company submission, the AA model structure was designed to be generalisable to UK clinical practice. The primary function of pharmacological management is to achieve long-term asthma disease control. The model defines health states using well-recognised definitions of asthma control that form part of the marketing authorization of 12 SQ-HDM, and which are used commonly in current clinical practice and throughout clinical guidelines on asthma including the GINA, NICE, and BTS/SIGN.

In order to align with the primary aim of asthma management, the company conducted a post-hoc analysis of the MT-04 trial to determine patients' asthma control at baseline and Year 1 in the AA model.

- **Please clarify how patients that dropout and/or are censored within the MT-04 baseline and trial end period are dealt with, justifying assumptions of the approach taken to consider these patients.**

Data on patients ACQ score is presented on page 130 of the MT-04 ICTR. A LME model was used for the analysis of the overall ACQ as well as change from baseline in overall ACQ at/to each visit (4, 5, 6, 7, 8 and 9) up to visit 9 (end of treatment maintenance) with ACQ at visit 3 as baseline value. Last observation carried forward (LOCF) was used to manage missing data. No other imputation of data was used to manage missing data, but all available data was used.

- **Using the GINA guidance, please provide the distribution of patients at MT-04 baseline and end of period 2 (maintenance phase).**

Data on asthma control during Period 2 has been added to the model in cells E226:Q234 on the 'Effectiveness' sheet.

Table 5: ACQ score MT-04 trial

	12 SQ-HDM			Placebo		
	Well controlled	**Partially controlled**	**Uncontrolled**	**Well controlled**	**Partially controlled**	**Uncontrolled**
ACQ visit 3	0.00%	70.92%	29.08%	0.00%	72.20%	27.80%
ACQ visit 4	6.74%	66.29%	26.97%	7.97%	61.96%	30.07%
ACQ visit 5	8.81%	66.67%	24.52%	9.23%	66.79%	23.99%
ACQ visit 6	15.63%	55.08%	29.30%	16.98%	57.36%	25.66%
ACQ visit 7	12.60%	62.99%	24.41%	16.67%	56.82%	26.52%
ACQ visit 8	14.80%	58.80%	26.40%	16.02%	61.72%	22.27%
ACQ visit 9	16.60%	60.32%	23.08%	15.18%	59.14%	25.68%
ACQ visit 10	21.25%	55.83%	22.92%	16.87%	54.22%	28.92%
ACQ visit 11	23.50%	52.99%	23.50%	20.68%	54.43%	24.89%
ACQ visit 12	23.96%	57.14%	18.89%	24.77%	55.05%	20.18%
ACQ visit 13	31.53%	49.26%	19.21%	25.96%	52.88%	21.15%

- **Please provide an alternative scenario with the distribution of patients at MT-04 baseline and end of period 2 (maintenance phase) using the GINA guidelines. Please present the cost-effectiveness results of such scenario.**

Table 6: Scenario analysis: Asthma control at Visit 9 (end of treatment maintenance)

AA+AR	12 SQ-HDM	SOC AA+AR	Incremental	ICER
Total costs (£)	£24,268	£26,372	-£2,105	12 SQ-HDM dominant
Total life years (LY)	22.55	22.55	0.00	
Total QALYs	16.10	15.73	0.37	
Abbreviations: SOC, standard of care; LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; HDM, house dust mite; AA, allergic asthma; AR, allergic rhinitis				

- **Please provide alternative scenarios of the distribution of patients at MT-04 baseline and end of period 2 (maintenance phase) using the BTS/SIGN 2019 and NICE 2017 guidelines. Please provide the distributions obtained for each scenario, as in Table 71 of the CS, and their consequences in terms of cost-effectiveness.**

This is not feasible, as this mapping was done to match the GINA 2010 definitions of disease control. The BTS/SIGN or NICE guidelines do not have independent definitions of disease control.

Economic model medium and long-term effectiveness (beyond 1 year) – AR and AA+AR populations

B13. Priority question: Due to the lack of clinical trial data to support the possible transitions of patients across health states in both the AA+AR and AR models, the company assumed an annual rate of change across 4 time periods (2Y-5Y, 5Y-10Y, 10Y-20Y, >20Y). The company claims that no evidence exists that can inform transition probabilities post 2 years, and, thus, for both populations, assumes for the treatment arm improvements up to year 10, treatment waning between 10-20Y and stable state >20Y. For the established clinical management arm, it was assumed that patients would remain stable during all years following Year 1.

- **Please provide a justification for the 4 time periods used and their clinical validity.**

The four time periods were chosen to reflect a simplified time range over which treatment efficacy may vary.

- **Please justify the values of annual rates of change used for each treatment period, clarifying where those values were sourced from.**

As stated in the CS, in a modified Delphi advisory panel, conducted with eight secondary care allergy specialists across Ireland, it was agreed that after cessation of 12 SQ-HDM, treatment effectiveness is likely to have a sustained and clinically significant effect for at least 10 years with potential waning over the subsequent decade, with treatment effectiveness unlikely to completely disappear for HDM-sensitised AA patients. These results were presented in a second advisory board conducted with 12 clinical experts across the UK who similarly agreed that treatment effectiveness is likely to have a sustained and clinically significant effect for at least 10 years with potential waning over the subsequent decade.

As such, in the base case for both the AA+AR and AR models, for the 12 SQ-HDM treatment arm it was assumed that patients would improve by 5% each year from Year 2 to Year 5, reduced to a 2.5% improvement from Year 5 to Year 10, followed by a period of waning of 2.5% each year to Year 20. After Year 20, it is assumed that patients remain stable in their state. It is assumed that patients receiving established clinical management will remain stable during all years following Year 1.

- **The modified Delphi panel referenced by the company mentions that "treatment effectiveness is likely to have a sustained and clinically significant effect for at least 10 years with potential waning over the subsequent decade". Please justify why annual improvements in effect were modelled up to 10 years, when experts have stated the expectation of a sustained effect over the same period.**

An annual improvement for the first 10 years of the model was included to reflect the results of the REACT study (Fritzsching et al., 2021), which showed a continued reduction in the number of AR prescriptions, a greater likelihood of stepping down asthma treatment, and reduction in severe asthma exacerbations in comparison with the control group at Year 3, 5 and 9.

- **Please justify why, for the established clinical management arm, it was assumed that patients would remain stable during all years following Year 1 and comment on the clinically plausibility of this assumption. Note that Figure 1 of the Fritzsching et al (2021) study shows a sustained effect of both treatment and control over 9 years.**

Fritzsching et al., (2021) note that the control group also experienced reductions in AR prescriptions with a progressive trend mimicking the AIT group. However, the authors go on to note that this is likely explained by regressions towards to the mean. Whilst it cannot be denied that this effect may impact the AIT group, a larger sustained effect across all years for the majority of outcomes was found in the AIT. To avoid over complicating the extrapolation of asthma control, the established clinical management arm was assumed to remain stable, with improvements and waning modelled solely on the 12 SQ-HDM arm.

The company would highlight that modelling an improvement in the established clinical management arm whilst retaining the same relative effect size will have a non-material impact on the ICER.

B14. The REACT study, with 9 years of follow-up, is highlighted by the company as a potential source of evidence for the long-term effectiveness of AIT for the treatment of AR and AA in a real-world setting.

- Please justify why preference was given by the company to model long-term effectiveness up to 9 years based on assumptions rather than use existing empirical evidence from the REACT study.

Given the differences in study design between the REACT study and the MT-04 trial, it is not possible to robustly estimate the comparative effect sizes between the two studies.

Furthermore, whilst the Fritzsching et al., (2021) demonstrated sustained, long-term reductions in the number of severe asthma exacerbations (Year 9, 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, this data cannot be used to suitably estimate changes in asthma control.

- As highlighted by the company, evidence from REACT showed "sustained (…effect of AIT…) for 9 years" and "a treatment benefit with AIT, with no evidence of treatment waning over the 9 years of follow-up" (p187-188 of the CS). Given this evidence, please justify the assumption of annual improvements in effect up to 10 years and treatment effect waning post 10 years.

As noted in response to question B13, the results of Fritzsching et al., (2021) showed a continued reduction in the number of AR prescriptions, a greater likelihood of stepping down asthma treatment, and reduction in severe asthma exacerbations in comparison with the control group at Year 3, 5 and 9.

Regarding treatment waning, whilst this was not evidenced in Fritzsching et al., (2021), it was noted by clinical experts that treatment would likely wane over the subsequent decade (Year 10 onwards).

Exacerbations – AA+AR population

B15. Priority question: For the AA+AR population, the company's model considers the results on the number of patients experiencing an exacerbation in the MT-04 trial during the ICS reduction/efficacy assessment phase. The EAG is concerned that phase 3 may not be reflective of clinical practice as clinical advice to the EAG suggests that a reduction of ICS would not be considered for the comparator arm. If exacerbations data from period 2B of MT-04 trial or external evidence is available to estimate the number of patients experiencing an exacerbation, please update the model to include these data and provide cost-effectiveness results for corresponding analyses.

Asthma exacerbations were not collected in period 2B. Please see answer to question A7 for full details.

Discontinuation

B16. The company model assumes that 50% of those who discontinued SQ-HDM (i.e., due to lack of efficacy, loss to follow-up, withdrawal of consent, and other reasons) would continue receiving treatment benefit, irrespective of how long patients had been on-treatment before discontinuation (e.g., 50% of those who discontinued after ½ year would have similar treatment effects to those discontinued after 2.5 years). Please revise the economic model to consider scenarios where the proportion of patients receiving the treatment effect post-discontinuation is dependent on the treatment duration prior to discontinuation.

This functionality is already included in the model by changing the values in cells F22:H22 on the 'Effectiveness' sheet.

Health-related Quality of Life

B17. Priority question: EQ-5D-5L data was collected within P001 study (Table 37, p79-89 of the CS).

- **Please justify why EQ-5D data from study P001 was not used to inform HRQoL in the AR economic model, in particular EQ-5D data for the 12-17 age range.**

At the time of the company submission, the EQ-5D-5L data collected in the P001 study had not been transformed into utility scores, and as such could not be included in the modelling.

The company have now conducted this mapping and attached the results in Appendix C.

- **Please provide a revised version of the AR model that considers as an option the use of utility scores derived from the EQ-5D-5L data collected with study P001 sample overall and split by 12-17 and 18-65 age ranges.**

The model has been updated to include utility estimates for the AR model from the P001 trial. The following adjustments have been made to the HRQoL model sheet.

- Functionality has been added to the drop down selection in cell F47

- The P001 mean study age for all participants and split by adult and adolescent has been added to cells O268:273
- Utility summary scores have been added in cells I282:N285
- Utility breakdown scores have been added in cells E343:R358

Appendix C provides detail of the methodology. In summary, the average utility and SD values for Visits 3, 6, 10 and 11 have been estimated (see Table 7). As Visit 6 was conducted only 4 weeks after randomisation, data on Visit 6 has not been used in the economic model. The primary efficacy assessment period of the P001 trial was approximately the last 8 weeks of the treatment period between Visit 10 and Visit 11. The primary analysis assessed how HRQoL changed over the full duration of the trial (i.e. from Visit 3 to Visit 11).

For both, the difference from Visit 3 to 10 and Visit 3 to 11, the adolescent subgroup showed a greater improvement in HRQoL compared with the adult subgroup.

It is important to note that during the trial, the decision was made to limit the number of subjects answering the EQ-5D-5L questions at Visit 10 and Visit 11, reducing the number from approximately 800 in each arm to approximately 400 in each arm, as per a protocol amendment (page 68 of P001 protocol). Accordingly, the number of EQ-5D-5L observations at Visit 10 and 11 is roughly half of the number at Visit 3.

When looking to address missing observations, it was assumed that data were missing completely at random, and therefore the data sample is likely still representative of the population. Whilst this is a strong assumption, there was no information available in the trial protocol to suggest that patients were chosen systematically. As a result, no imputation was conducted. Whilst acknowledging that a LOCF approach could be used given that Visit 6 data was available (4 weeks post-randomization), however, the company do not believe that the results collected at the time point are reflective of HRQoL at the end of the trial. This is supported by the overall positive trend in the data as shown in Figure 6 and Figure 7.

Table 7: Average HRQoL utility values from P001 for Visits 3, 6, 10, and 11

Age group	Treatment	Analysis Visit	N	Mean	Std Dev
All	**12 SQ-HDM**	Visit 3 (Randomization)	388	0.889	0.135

		Visit 6 (Treatment Phase)	336	0.907	0.120
		Visit 10 (Efficacy Assessment)	285	0.925	0.091
		Visit 11 (Final/Discontinuation)	388	0.926	0.104
	Placebo	Visit 3 (Randomization)	375	0.903	0.121
		Visit 6 (Treatment Phase)	359	0.911	0.136
		Visit 10 (Efficacy Assessment)	308	0.919	0.128
		Visit 11 (Final/Discontinuation)	375	0.928	0.101
<18	**12 SQ-HDM**	Visit 3 (Randomization)	43	0.846	0.183
		Visit 6 (Treatment Phase)	37	0.878	0.190
		Visit 10 (Efficacy Assessment)	35	0.922	0.087
		Visit 11 (Final/Discontinuation)	43	0.941	0.100
	Placebo	Visit 3 (Randomization)	53	0.882	0.139
		Visit 6 (Treatment Phase)	51	0.878	0.179
		Visit 10 (Efficacy Assessment)	44	0.892	0.153
		Visit 11 (Final/Discontinuation)	53	0.925	0.102
>=18	**12 SQ-HDM**	Visit 3 (Randomization)	345	0.895	0.128
		Visit 6 (Treatment Phase)	299	0.911	0.108
		Visit 10 (Efficacy Assessment)	250	0.925	0.092
		Visit 11 (Final/Discontinuation)	345	0.925	0.104
	Placebo	Visit 3 (Randomization)	322	0.906	0.118
		Visit 6 (Treatment Phase)	308	0.916	0.127
		Visit 10 (Efficacy Assessment)	264	0.923	0.123
		Visit 11 (Final/Discontinuation)	322	0.928	0.101

Figure 6: Relative change in utility score; 12 SQ-HDM and PBO

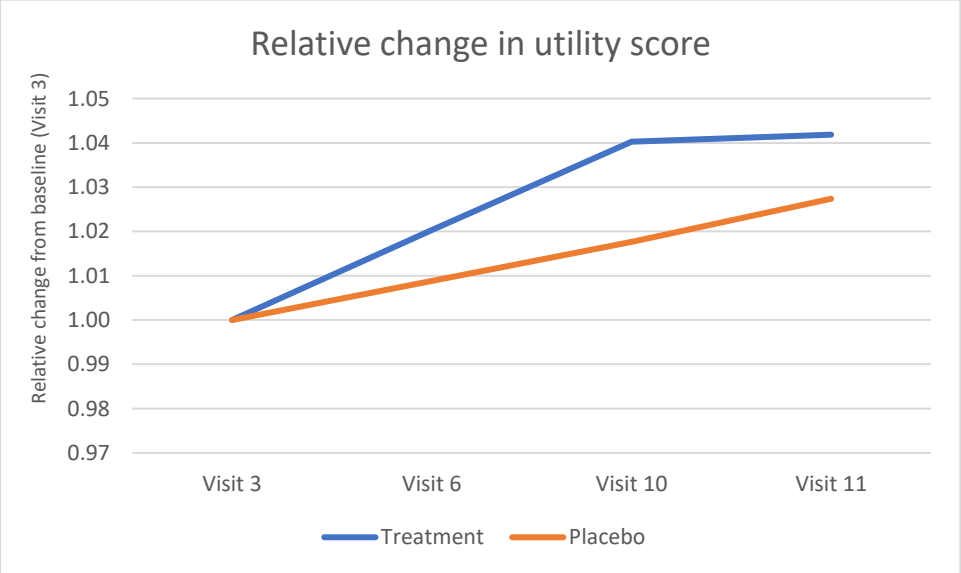
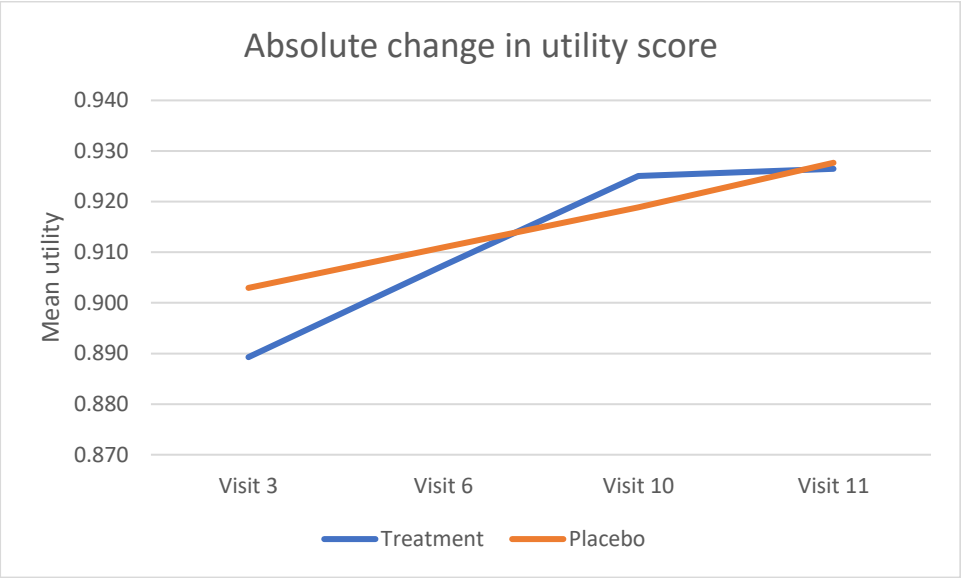


Figure 7: Absolute change in utility score; 12 SQ-HDM and PBO



B18. Priority question: For both AR and AA+AR populations, treatment-specific and health state specific utilities have been estimated and the economic model is enabled to use either approach.

- **Please provide a rationale for the two alternative approaches to estimate utilities, explicitly stating the assumptions these rely on.**

Treatment-specific and health state-specific utilities were included in the model as these were estimated from the MT-06 and MT-04 clinical trial data. For the AR model, health state-specific utilities were estimated using the post-hoc analysis of disease severity from the MT-06 trial. For the AA model, health state-specific utilities were informed by the mapping study conducted by Briggs et al., (2021), which used the same post-hoc analysis of disease severity as discussed in previous responses.

- **Please justify the use of treatment-specific utilities as the company's preferred approach.**

Treatment-specific utilities were chosen as the company's preferred approach as they were the most robust estimates reflecting the benefit associated with 12 SQ-HDM. Using the full trial data set versus a subgroup of data to estimate the utility benefit offers greater statistical power, with a larger sample size reducing the variability in the estimates.

B19. Priority question: The MT-04 trial collected data on HRQoL using AQLQ and the SF-36. The SF-6D preference-based algorithm was used to generate utility scores.

- **Please provide treatment-specific mean and SE utility scores estimates generated by the SF-6D preference-based algorithm for the treatment maintenance period of MT-04 study only, by AA+AR health state and treatment arm.**

Table 8: MT-04 treatment specific utilities

	Mean utility score from MT-04 (SD)	
	12 SQ-HDM N=172	Placebo N=172
Visit 3; baseline	0.7277 (0.0983)	0.7573 (0.1028)
Visit 9; end of trt. Maint	0.7592 (0.1157)	0.7632 (0.1096)
Visit 13; end of study	0.7768 (0.1121)	0.7743 (0.1154)

- **Please provide health state specific mean and SE utility scores estimates generated by mapping AQLQ to EQ-5D-3L (as per Briggs et al, 2021), rather than using SF-6D, for the treatment maintenance period of MT-04 study only, by AA+AR health state and treatment arm.**

Briggs et al., (2021) derived utilities for 5 health states by mapping AQLQ data using the definition of asthma exacerbations used in the trial and GINA asthma control status.

Data on AQLQ were collected at Visit 3 (randomisation), Visit 6 and 8 (treatment maintenance), and Visits 9 to 13 (efficacy assessment). As reported by Briggs et al., (2021), if patients had an exacerbation within a given number of days after a visit, the AQLQ data was categorized as a moderate or severe exacerbation at that visit. All remaining AQLQ data points were grouped according to the GINA asthma control status of the patient.

Utility data were reported for within 7 ,14, 21, and 28 days from a reported asthma exacerbation. Therefore, no data were reported that can be used to reflect only the treatment maintenance period.

B20. Priority question: The company imposed a restriction in the economic model which limited the sampling of utilities so that if treatment-specific utility values are used, treatment with 12 SQ-HDM could not result in a lower utility score compared with treatment established clinical management alone (p230 of the CS). Please provide a justification for this restriction. Please introduce a switch into the economic model so this restriction can be easily enabled/disabled.

There is no clinical rationale to suggest that beyond any short-term AE associated disutility, patients receiving 12 SQ-HDM in addition to pharmacotherapy would experience worse HRQoL compared to patients who receive pharmacotherapy alone. Even if patients do not experience any clinical benefit of 12 SQ-HDM, their HRQoL would be determined by the level of disease severity under the effects of adjunct pharmacotherapies.

The current functionality of the model would allow for treatment with 12 SQ-HDM to result in a lower utility compared with established clinical management alone. However, in the MT-04 trial, the majority of AEs were reported as mild (67%) or moderate (31%). Of the 7 TRAEs modelled, 6 had a median duration of under 11 days, with mouth oedema having a median duration of 23 days. In the MT-06 trial, the majority of AEs were reported as mild (72%) or moderate (24%). Of the 8 TRAEs modelled, 7 had a median duration of under 15 days, with mouth oedema having a median duration of 21 days. Therefore, given the reported severity and duration of the reported TRAEs, any AE-specific utility decrements would not have a material impact on the relative annual utility for patients receiving 12 SQ-HDM.

A switch has been added to cell J22 in the parameters sheet to control the sampling of utilities. When TRUE is selected, treatment with 12 SQ-HDM cannot result in a lower utility score compared with treatment established clinical management alone when treatment-specific utilities are selected.

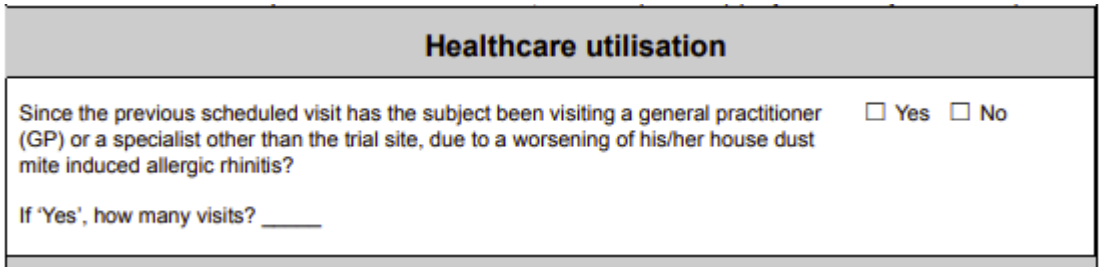
Health resource use and costs

B21. In the MT-06 Clinical Study Report, Wurt et al., 2015, section Patient satisfaction assessments, p56: “Visits to GP and specialists due to allergic rhinitis since the previous scheduled visit were recorded at visits 2, 3, 4, 5, 6, 7, and 8”.

- Please clarify whether in MT-06 trial data the number of GP visits include visits to specialists. If yes, please provide the number of GP visits separately from specialist visits. If not, please justify why the number of GP/specialist visits reported in the MT-06 trial are considered as GP visits (solely) in the submission.

As can be seen in the image below (screenshot of the MT-06 Appendix I.2: Sample case report form (CRF) for Visit 3 onwards), for all relevant visits, the number of GP visits and specialist visits cannot be distinguished, as patients were asked about visits to either a GP or specialist other than the trial site.

Figure 8: MT-06 CRF Visit 3 onwards



Healthcare utilisation

Since the previous scheduled visit has the subject been visiting a general practitioner (GP) or a specialist other than the trial site, due to a worsening of his/her house dust mite induced allergic rhinitis? ☐ Yes ☐ No

If ‘Yes’, how many visits? _____

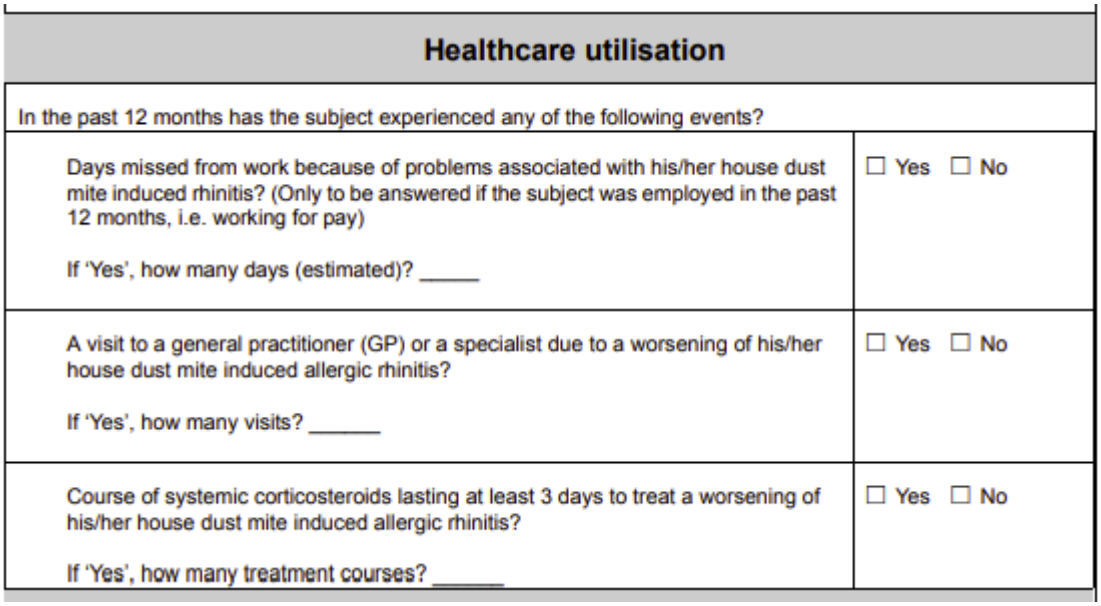
In the economic model and company submission, it was conservatively assumed that these visits would be costed as all GP appointments.

- The approach taken to estimate the relative reduction in annual GP visits associated with 12 SQ-HDM for the AR population excludes the number of GP/specialist visits at visit 2 of MT- 06 (see cells F225:G231, Management cost tab, electronic version of the model). Could you please clarify whether the figures in cells F225 and G225 refer to the period prior to randomisation (which would justify their exclusion) and if not comment on why these estimates were excluded from the calculation. Please also comment on any differences in the approach taken to estimate the relative reduction in annual

GP visits for the AA and AA+AR populations (e.g., did both exclude pre-randomisation GP visits).

As can be seen in the image below (screenshot of the MT-06 Appendix I.2: Sample case report form (CRF) for Visit 2), for Visit 2 at randomisation, patients were asked about their healthcare utilisation over the previous 12 months. Therefore, these values were appropriately excluded from the number of GP/specialist visits estimated in cells F225:G231, Management cost tab.

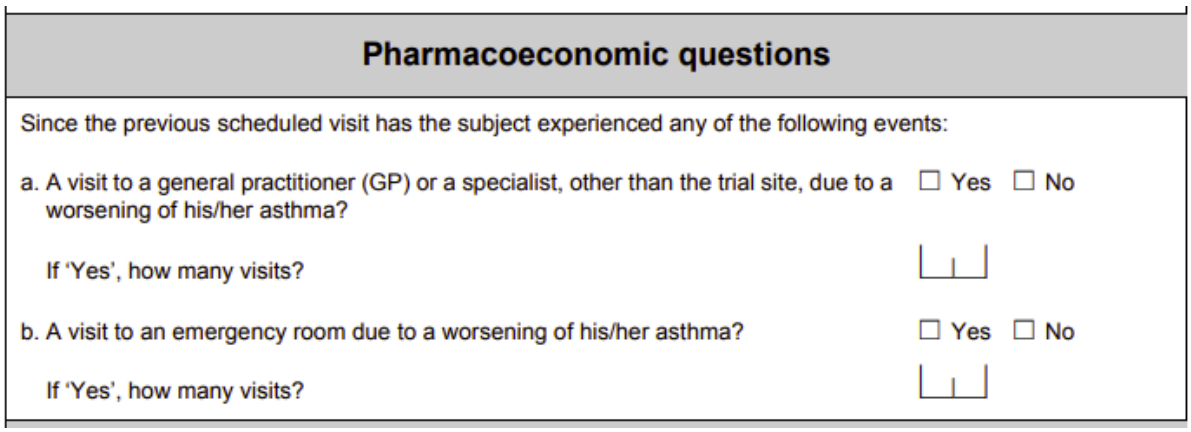
Figure 9: MT-06 CRF Visit 2



Healthcare utilisation	
In the past 12 months has the subject experienced any of the following events?	
Days missed from work because of problems associated with his/her house dust mite induced rhinitis? (Only to be answered if the subject was employed in the past 12 months, i.e. working for pay) If 'Yes', how many days (estimated)? _____	☐ Yes ☐ No
A visit to a general practitioner (GP) or a specialist due to a worsening of his/her house dust mite induced allergic rhinitis? If 'Yes', how many visits? _____	☐ Yes ☐ No
Course of systemic corticosteroids lasting at least 3 days to treat a worsening of his/her house dust mite induced allergic rhinitis? If 'Yes', how many treatment courses? _____	☐ Yes ☐ No

This approach was not consistent with the estimates for the MT-04 trial data. Upon inspection, data for Visit 3 in the MT-04 trial would include GP/specialist visits between Visit 2 and Visit 3 (prior to randomisation).

Figure 10: MT-04 CRF Visit 2 onwards



Pharmacoeconomic questions	
Since the previous scheduled visit has the subject experienced any of the following events:	
a. A visit to a general practitioner (GP) or a specialist, other than the trial site, due to a worsening of his/her asthma?	☐ Yes ☐ No
If 'Yes', how many visits?	⌊_⌋⌊_⌋
b. A visit to an emergency room due to a worsening of his/her asthma?	☐ Yes ☐ No
If 'Yes', how many visits?	⌊_⌋⌊_⌋

An additional calculation in Row 217 has been added to the economic model which includes an updated number of GP/specialist visits which excludes data from Visit 3.

This amendment can be seen to have a reduction in the number of both GP/specialist visits in the placebo and 12 SQ-HDM arms. From the original company basecase the relative reduction in GP/specialist visits associated with 12 SQ-HDM changes from 25.76% to 31.19%.

This has been updated in the new model basecase.

B22. Priority question: The company estimated, the average number of episodes per patient in hospital settings at national level (categorised by financial year for all types of allergies), using HES registry data. The proportion of patients diagnosed with asthma and rhinitis related allergies are available in the Appendix R1 – slide 13

- **For the AA+AR population, please clarify whether the HES data analysis included exacerbation-related outpatient visits. To avoid double counting, please provide an estimate from the HES data of the number of outpatient visits of patients without asthma exacerbations. If this information is not available, please comment on how the company's approach avoids double counting of asthma exacerbation related outpatient contacts for the AA+AR population in the treatment management costs by health care state.**

Appendix R1 was an analysis conducted that was not specific to the NICE submission. This deck provides insights into the patient pathway for allergy in the UK, and importantly provides detail on the diagnosis and procedure codes used to identify the relevant patient cohort. Appendix R2 provides the average number of episodes per patient for each hospital setting (elective day case, elective inpatient, emergency, outpatient) and by financial year with corresponding standard deviations, for the overall allergy patient cohort as defined in Appendix R1 at a national level. No additional analyses were conducted that report the cause of the hospital episodes.

Furthermore, as no data were available to inform the number of outpatient appointments by disease severity, in the model, outpatient visits were modelled as

treatment specific. This approach allowed data collected in the MT-04 and identified in literature to inform estimates of a relative reduction in outpatient visits associated with treatment with 12 SQ-HDM.

To avoid any potential double counting of asthma exacerbation related outpatient contacts, the company have provided a scenario in which asthma exacerbation costs are set to zero, see Table 9.

Table 9: Scenario analysis: AA exacerbation costs set to zero

AA+AR	12 SQ-HDM	SOC AA+AR	Incremental	ICER
Total costs (£)	£21,983	£23,654	-£1,672	12 SQ-HDM dominant
Total life years (LY)	22.55	22.55	0.00	
Total QALYs	16.10	15.73	0.37	
Abbreviations: SOC, standard of care; LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; HDM, house dust mite; AA, allergic asthma; AR, allergic rhinitis				

- **Please provide the average number of outpatient episodes per patients specific to rhinitis, and specific to asthma allergies, respectively.**

As can be seen in Appendix R2, data on the average number of outpatient episodes were not reported separately for rhinitis and asthma allergies.

B23. Priority question: The average number of annual GP and secondary care visits for the AA-AR population are available in MT-04 trial. The relative reduction in resource use between SQ-HDM and SOC during all visits of the trial is applied in the company's base case.

- **Please revise the economic model to consider the option of estimating the relative reduction associated with 12 SQ-HDM solely based on the treatment maintenance phase of the MT-04 trial (ensuring that parameter uncertainty is appropriately reflected when using this option).**

The following scenario is presented in Table 10, correlating to values in rows 213:217 of the Management Costs sheet.

- GP visits relative reduction from 25.76% to 18.73%

- Secondary care visits relative reduction from 54.58% to 60.32%

Table 10: Scenario analysis: Relative reduction from treatment maintenance phase AA:AR model

AA+AR	12 SQ-HDM	SOC AA+AR	Incremental	ICER
Total costs (£)	£23,826	£26,217	-£2,392	12 SQ-HDM dominant
Total life years (LY)	22.55	22.55	0.00	
Total QALYs	16.10	15.73	0.37	
Abbreviations: SOC, standard of care; LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; HDM, house dust mite; AA, allergic asthma; AR, allergic rhinitis				

- **Please clarify whether visits due to exacerbations were excluded in the GP reduction associated with AIT reported for MT-04 trial (Table 94 of the CS).**

As shown in Figure 10, patients were asked about the number of GP/specialist visits due to a worsening of his/her asthma. As such, it is not possible to examine if and how many visits were associated explicitly with exacerbations.

- **Please provide the number of GP visits, secondary care visits, exacerbation visits for UK sites only, within the ICS reduction/treatment maintenance phase (i.e., period 2) of MT-04 trial by treatment arm.**

The study only included 28 subjects in UK out of the total of 834 subjects in FAS. There were 8 UK subjects in the 12 SQ-HDM group, and 11 UK subjects in the placebo group. As a result of small patient numbers, no additional analyses have been performed.

B24. The EAG could not validate one of the alternative estimates for the number of GP visits per year in Table 94 (CS) from the reference Romano et al. (2023) study (ref.95 in the CS). This may be because reference 95 does not report results

separately for children aged 12-17 in UK population. Please clarify how these estimates were obtained.

The company have made a minor error in the reporting of the value from Romano et al., (2023). The value reported in the CS and model was 3.8 GP visits per year, which should be 3.9 GP visits per year as per Figure 4 in Romano et al., (2023).

The EAG is correct that this source reflects the child and adolescent population (5 to 17 years old), and subgroup results are not reported.

Parameter uncertainty

B25. Priority question: A large proportion of the parameters which are considered probabilistic in the model have a assumed an arbitrary 10% variation over the mean parameter value as a measure of uncertainty; these include parameters for which information on the parameter uncertainty is available from the original data sources (e.g. disutilities associated with asthma exacerbations and relative reduction in AA+AR outpatient visits). Please update all assumed SEs within the model for which information over parameter uncertainty is available but was not used.

This has been adjusted in the model.

B26. Priority question: Several parameters in the model sourced from the MT-04 and MT-06 trials have been set up deterministically, despite the company having access to individual patient data (IPD). Please update the model so that for all parameters informed by these trials, parameter uncertainty is duly reflected where information is available.

Only data on the distribution of patients at baseline and end of trial (MT-06)/ACQ visits (MT-04) is available. To implement this probabilistically in the model, this would require sampling of distributions independently at baseline and Year 1, which incorrectly assumes that they are not correlated. As such, this would not be a meaningful exploration of uncertainty. Hence, the company consider the scenario analysis presented on the rhinitis DSS cut-offs sufficient in understanding the impact of variation in the effectiveness of 12 SQ-HDM for the AR model, and the scenario analyses reflecting the results from three non-interventional studies sufficient in

understanding the impact of variation in the effectiveness of 12 SQ-HDM for the AA model.

B27. Some of the economic model parameters for which point estimates from alternative data sources can be selected from drop-down menus have the same standard error regardless across all data source alternatives (e.g., AA+AR, Annual GP visits per disease severity). Please correct this in the model to appropriately reflect the parameter uncertainty in each alternative data source.

Corrected in line with response to B25.

Systematic Literature Reviews

B28. How were the search results for MEDLINE and Embase (p. 33-35, Appendix A, ALK Economics SLR by Initiate) limited to economic evaluations, giving references to any study design search filters that were used?

The searches ran for the 2023 Economics SLR update used the following economic evaluation filters:

- MEDLINE

#	Search string	Rationale
21	exp cost effectiveness analysis/ or exp cost utility analysis/ or exp economic evaluation/ or exp cost-effectiveness model/	To retrieve all articles in the database with subject headings (or terms related to these subject headings) on study designs associated with economic evaluations (as defined in the eligibility criteria)
22	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or unit$ or estimat$ or variable$)).ab.	To retrieve all articles in the database that utilised validated study design filters associated with economic evaluations in their abstracts (https://www.nice.org.uk/guidance/ng50/documents/search-strategies)
23	21 or 22	To ensure that the economic evaluation filter is as broad as possible in restricting search results to articles that report on terms associated with economic evaluations

- Embase

#	Search string	Rationale

22	exp cost effectiveness analysis/ or exp cost utility analysis/ or exp economic evaluation/ or exp cost-effectiveness model/	To retrieve all articles in the database with subject headings (or terms related to these subject headings) on study designs associated with economic evaluations (as defined in the eligibility criteria)
23	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	To retrieve all articles in the database that utilised validated study design filters associated with economic evaluations in their abstracts (https://www.nice.org.uk/guidance/ng50/documents/search-strategies)
24	22 or 23	To ensure that the economic evaluation filter is as broad as possible in restricting search results to articles that report on terms associated with economic evaluations

B29. Please provide the following information which is missing from the search strategies reported in Appendix A of the ALK Utilities SLR document by Initiate and Appendix A of the ALK Cost & Resource SLR document by Initiate:

- The date of the search in MEDLINE and Embase along with the search interface/provider used.

2015 Utilities SLR:

- MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE: OvidSP interface, searches conducted in February 2015
- Embase: OvidSP interface, searches conducted in February 2015

2015 Cost & Resource SLR:

- MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE: OvidSP interface, searches conducted in February 2015
- Embase: OvidSP interface, searches conducted in February 2015

B30. Please provide the following information which is missing from the search strategies reported in Appendix A and Appendix B of the ALK Utilities SLR document

by Initiate, and Appendix A and Appendix B of the ALK Cost & Resource SLR document by Initiate:

- Details of any search filters incorporated into strategies for MEDLINE and Embase. Please include any references for the search filters used.

The strategies for the Utilities and Cost & Resource SLRs were devised using a combination of subject indexing terms and free text search terms in the title, abstract and keyword heading word fields. The search terms were identified through discussion within the research team, scanning background literature, browsing database thesauri and use of the PubMed PubReminer tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi). The strategies excluded some publication types which are unlikely to yield study reports: editorials, news items, comments, letters, and case reports.

Search terms for the resource use concept included cost and resource use terms. The cost terms were based on the filter designed by CRD to identify economic evaluations for inclusion in the NHS Economic Evaluation Database (NHS EED). Resource use terms focussed on non-specific resource use, length of stay and hospitalisation.

In the 2015 Utilities and Cost & Resource SLRs, the search for studies reporting resource use data were limited to studies published from 2000 to date. The search for studies reporting resource use data excluded records which were indexed with subject headings for non-relevant geographical locations, and which were not also indexed with subject headings for relevant geographical locations.

These strategies aimed to identify relevant studies on transition probabilities through a range of approaches. This included searching for study designs of interest, and searching on terms relating to epidemiology, terms relating to the transition between the specific health states of interest (well controlled, poorly controlled, uncontrolled) and terms relating to the specific classification systems of interest (GINA and ARIA).

The terms for identifying RCTs were based on the Cochrane Highly Sensitive Search Strategy filter for identifying randomized trials in MEDLINE: sensitivity-and-precision-maximizing version, 2008 revision, Ovid format (Lefebvre C, Manheimer E, Glanville

J. Chapter 6: Searching for studies. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011): The Cochrane Collaboration; 2011.).

In addition, search filters from SIGN (https://www.sign.ac.uk/what-we-do/methodology/search-filters/) and NICE (https://www.nice.org.uk/guidance/ng50/documents/search-strategies) were incorporated into the search strategies. Where there was absence of validated filters, a pragmatic approach was taken, using terms for key relevant study designs.

B31. The EAG identified two health technology assessments for SQ-HDM with cost-effectiveness evidence potentially relevant to the decision problem in the current appraisal. {National Centre for Pharmacoeconomics Ireland, 2023 #228} {Pharmaceuticals Benefits Advisory Committee, 2016 #227}

- Please clarify whether health technology assessment databases have been searched to inform the systematic literature reviews in the economics section, and if not justify the rationale for this.

To identify economic evaluations relevant to the Economics SLR, the Cochrane Library (including EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>), EconLit, the CEA registry (https://cevr.tuftsmedicalcenter.org/databases/cea-registry) and the National Institute for Health and Care Excellence (NICE) website were searched.

- Please include the two heath technology assessments referenced above in the systematic review of cost-effectiveness studies.

National Centre for Pharmacoeconomics Ireland, 2023 #228: The rapid review identified under HTA ID 23008 which was completed in February 2023 was given the following outcome: A full HTA is recommended to assess the clinical effectiveness and cost effectiveness of HDM allergen extracts compared with the current standard of care. As there is likewise no published, extractable information from this review, it is ineligible for synthesis in the systematic review of economic evaluations (https://www.ncpe.ie/house-dust-mite-allergen-extract-actair-hta-id-23008/).

Pharmaceuticals Benefits Advisory Committee, 2016 #227: The public summary document published online by PBAC does not contain any data extractable information relevant to the SLR eligibility criteria. All key data including costs, cost-effectiveness estimates and economic evaluation results are redacted. This HTA is therefore ineligible for synthesis in the systematic review of economic evaluations (https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-07/files/house-dust-mite-psd-july-2016.docx#:~:text=The%20PBAC%20noted%20that%20for,a%20year%2Dround%20blocked%20nose).

Section C: Textual clarification and additional points

None

Appendices

Appendix A – Additional data requests

See attached file ‘Appendix A – Additional statistical analysis’.

Appendix B – MT-06 post-hoc analysis of mono- and poly-sensitised subjects each month

See attached file ‘Appendix B – MT-06 seasonal and sensitisation subgroup data’.

Appendix C – QoL values from P001

See attached file ‘Appendix C – QoL values from P001’.

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	Allergy UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Allergy UK is the only UK charity that supports all areas of allergic disease, covering respiratory, skin, food, eye, venom, and drug allergies, including anaphylaxis. And we are the only allergy charity with in-house clinical experts in allergy. For thirty years, Allergy UK has been the leading national patient charity for people living with allergies. Our charity was founded by clinicians who recognised the need for an organisation to fill the gap in NHS service provision of primary care across the UK. We believe that those best placed to develop allergy services in the UK are those living with allergies. Two-thirds of our Leadership Team (including our management team and board) have lived experiences of dealing with allergies. The charity is supported through the work of Allergy Research Limited, which is the charity's trading subsidiary. The profits generated by the work of ARL are then funnelled back into the charity. • Endorsement/ARL turnover for 2022/23 - £1,317,306 The British Allergy Foundation also known as Allergy UK (the charitable arm), receives no statutory funding however, but has recently employed a fundraising team to further develop new income streams, to further advance the charity's objectives. The income streams, which are being developed brought in the following amounts in 2022/2023: • Trusts & Foundations - £25k • Individual Giving (One-off and regular) - £25k

	• Annual fundraising campaigns - £4k • Corporate Fundraising (grants and sponsorship) £190k • Gifts in Wills £500 • Major Donor Fundraising £3k • Challenge Events £16k Pharmaceutical companies from which Allergy UK have received funding (grants and sponsorship) over the past 4 years, their amounts and funded projects are as follows: • Abbott - £30k towards dietitian service, dietitian sessions and towards a dietitian salary • Abbvie - £405 sponsorship for Eczema roundtable events, consultation piece • Aimmune - £14,806 sponsorship of a paediatric food allergy masterclass • ALK - £17,772 sponsorship of podcasts for HCPs on anaphylaxis and AAIs, a podcast for patients, digital masterclass on anaphylaxis and AAIs for primary care and pharmacists • LEO Pharma - £2,378 contract to assist with patient survey • Novartis - £23k grant towards E-Booklet and CSU video • Nutricia - £77k sponsorship of Dietitian Service, £4.5k sponsorship of Health Visitor introduction to weaning with Allergies for HCPs and contribution towards Food Allergy Masterclass sponsorship of £8,235, and £4,680 sponsorship of a downloadable cow's milk ladder leaflet • Pfizer – A grant of £9,466 to support Allergy UK with financial support to deliver a project on eczema and allergic skin conditions with the aim of educating healthcare professionals about eczema of educating healthcare professionals about eczema present on different skin types. • Polti - £44,244 sponsorship towards promotion of Lynsey Queen of Clean social media podcast, creation of webpage on respiratory, sponsorship of Allergy UK's Allergy House's Utility Room and dedicated web page on Allergy UKs website, plus an acknowledgement in Allergy UKs Annual report

	• Sanofi – £16,507 Back to basic Eczema for HCP masterclass, plus £375 patient recruitment via Allergy UK's social channels for Sanofi Global Video project • Santen - £350 consultation fee for clinical input • Thermofisher £45k to deliver on projects re: allergic Rhinitis and its impact on asthma, the link between birch trees and allergies and respiratory fruit pollen syndrome • Viatris - £15k sponsorship towards a patient survey reports and review of draft survey questions Allergy UK currently has 30,438 service users registered to our database, which represents an increase of 25% in the past year. Allergy UK's vision is: No one should die from Allergy Allergy UK's mission is: For everyone in the UK to take allergy seriously
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.**	No, Allergy UK has not received any funding from ALK in the past 12 months for any projects.
4c. Do you have any direct or indirect links	No, we do not.

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?	1. Discussions with people who live with the condition 2. Discussions with the people who care for people living with the condition 3. Allergy UKs Nurse Advisor's work interactions with patients/ people who live with the condition and those that care for people living with the condition 4. Allergy UKs Head of Clinical's work interactions with patients/people who live with the condition and those that care for people living with the condition 5. Multiple survey results (referenced below) 6. Independent studies

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?	**We have drawn on existing literature to summarise the experience of patients and carers** • Allergic rhinitis is the most common form of non-infectious rhinitis, affecting between 10-15% of children and 26% of adults in the UK. (GK Scadding et al, 2017). • The percentage of children diagnosed with allergic rhinitis and eczema have both trebled over the last 30 years (Gupta R, 2007) • However, in recent research around 49% of people reported suffering with Hay fever symptoms. (Allergy UK / Kleenex®, 2020). • AR accounts for 16.7 million physician office visits annually (Pawankar R, et al, 2013) • In Europe, the European Community Respiratory Health Survey established the prevalence of AR as being from 4% to 32% (Pawankar R, et al, 2013) • More than 40% of patients with AR have asthma, and more than 80% of asthmatic patients suffer concomitant rhinitis. Also, patients with rhinitis have an increased risk of developing asthma (Pawankar R, et al, 2013) • Up to 57% of adult patients and up to 88% of children with AR have sleep problems, including micro-arousals, leading to daytime fatigue and somnolence, and decreased cognitive functioning (Pawankar R, et al, 2013) • The prevalence of rhinitis symptoms in the International Study on Asthma and Allergies in Childhood (ISAAC) varied between 0.8% and 14.9% in 6–7-year-olds and between 1.4% and 39.7% in 13–14-year-olds. Countries with a very low prevalence include Indonesia, Albania, Romania, Georgia and Greece. • Countries with a very high prevalence include Australia, New Zealand and the United Kingdom (WAO, 2017) • National surveys show prevalence rates of rhinitis of between 5.9% (France) and 29% (United Kingdom) with a mean of 16%. Perennial (persistent) rhinitis is probably more common in adults than in children (WAO, 2017) • A study carried out by Gomez et al (2022) found that school attendance and performance was significantly affected for those with allergic asthma, who also had HDM as a trigger. They also found that school attendance increased following a treatment called Allergen Immunotherapy. You can read more about the treatments for HDM allergy on the Allergy UK websitehttps://www.allergyuk.org/resources/house-dust-mite-allergy-factsheet/

	The following quotes illustrate first-hand the experience of patients and carers • "Living with a House Dust Mite Allergy, means that some days I don't know what I'm going to feel like. Am I gonna feel absolutely fine or coughing, spluttering, coughing, spluttering...?" • "At its worst, the House Dust Mite Allergy will actually stop XXX sleeping through the night, so he'd be extremely fatigued the next morning, and it's difficult for him to try and get through the day at school. He'll be up coughing, a runny nose and sort of runny eyes." • "I wake up the next morning, when I'm actually able to go to sleep, my eyes are just glued shut" • "In the summer months, we do P.E. on the field, but I'm not able to take part and very few people will stay with me and say oh it's just hay fever." • "When we received the House Dust Mite Allergy diagnosis, I'll be honest it was completely overwhelming, because the list of things we had to do, we had to change our daily habits. It means we had a zoo of soft toys on his bed, they had to go, we had to buy all new bedding for dust mite allergy bedding. A new vacuum that was able to pick up any bit of dust in his room, and it does mean that every week, I am cleaning his room two to three times a week just to keep it under control. We have seen an improvement, but it is a lot of work!" • "The treatment I receive is a Cetirizine tablet and metadenethazine nasal spray. They really help, they're really amazing with how they help." • "Thanks to the allergy clinic, that we are part of, xxx was put forward for sublingual immunotherapy for several of his pollen allergies and House Dust Mite allergies. Now this is because he is actually quite severe in terms of his reaction to them. It does impact his daily life. So, they put him forward for this project and he was given the access to it. It does mean it's an extra medication he does have to take every night and there's strict rules to follow but hopefully in three years it will reap the rewards of it." • "It's hard to manage because i need to go to sleep at some point, then I need to have my dinner which means I have to wait ten extra minutes after dinner, then take my SLIT, then half an hour and brush my teeth and go to bed, so it's a busy schedule."

	• "Sometimes, my allergies stop me from doing things. When my dust allergy gets really bad, getting downstairs is a struggle. Sometimes when I get up, it's confusing because I don't know why it's happening. But then I realise it's my allergy and sometimes I get frustrated about that" • "I've had a House Dust Mite Allergy since I was a child, I've had symptoms since I was about 15. It was like having a really bad cold and it went on and on and on for months. Initially it was a lot of nasal symptoms, so i have a nasal spray, then sometimes I get itchy skin. And a rash. My eyes get very watery and I'm always rubbing them. So, I went to the GP, and he diagnosed me the same day with allergies and asthma. He started me on treatment which helped straight away. He followed up with some blood tests. These confirmed I was very allergic to House Dust Mite allergies. But not just House Dust Mite allergies, but other thigs too, so I have an allergy kit bag, which I have on me all the time. Not just if I travel, but at home as well so I can start treatment to deal with the symptoms. • "I've never let it control my life but sometimes it can really affect me." • "I wanted to do some DIY; I even bought a tool belt. It was something I'd wanted to do for quite a while, but sadly that night I ended up in hospital, because of all that exposure to the dust. It was just too much." • "My family also all have asthma and allergies and so we approach housework like a family task, we all help each other." • "I like to do a lot of house cleaning, fresh bedding, damp cloth cleaning and vacuuming really helps a lot, but it can be a lot of work." 'Having struggled for several years with increasing difficulty with my allergies I was eventually considered for the ACARIZAX® treatment and I am now in my 3rd year. The difference this had made to my day-to-day life is immeasurable and I am so grateful to have been offered this treatment. Prior to starting my allergies and associated reactions were virtually year-round with little in the way of respite, the physical symptoms also affected my sleep and in turn my ability to feel like I was functioning during the day and consequently this also affected my mood. Although I am being treated for dust allergy my seasonal rhinitis has, to some degree, improved. The treatment itself is easy to factor into your daily routine'.

Current treatment of the condition in the NHS. What do patients or carers think of current treatments and care available on the NHS?	• Currently if patients experience symptoms of HDM allergy self-treatments are first line, including but not limited to allergy tablets, steroid nasal sprays and eye drops however the cause of the disease is unknown and therefore the change in QOL becomes the new normal. • Many patients do not even know what HDM allergy is and continue to live with this until it becomes severe and chronic, this means not treating the disease at the right time has an impact onto the way it develops. • The impact on QOL is particularly due to the sleep disturbances, uncontrolled asthma and eczema flare ups. • Mild allergy patients can be covered by symptomatic medication alone such as oral/topical antihistamine and/or corticosteroid nasal spray. However, for the moderate to severe allergic patients, symptomatic medication is not enough. They still suffer from significant symptoms despite full coverage with symptomatic medication. • Allergen avoidance is not possible, despite continuously washing bedsheets, thorough house-cleaning etc. On top of this many patients experience side effects to the symptomatic medication such as drowsiness that is a well-known side effect to Antihistamine or local side-effects in the nasal cavity due to constant use of nasal spray as HDM allergy is present all year round. • Current BTS Asthma guidelines not inclusive of checking allergic status, when HDM allergic patients have exacerbation treatment is dominated with doubling steroid dose, not investigating the cause of the disease limits patients access to allergen specific therapy. By only managing patients with steroids, the underlying cause of the disease is not addressed and potential disease modification of the asthma is missed. • The UK is one of the only developed countries (across EU, North America and Asia) that currently does not provide national reimbursement for SQ-HDM SLIT. This provides a significant health disparity for UK patients in relation to access to care when comparing to similar patient populations across the world • Physically: Paediatric population, reduced touchpoints of HCP visits for appointments; Asthma checks, prescriptions for antihistamines, nasal sprays and eye drops as GPs do not routinely prescribe this and this would not be available on repeat medications in primary care. • Sleep quality improved for paeds population leading to less disruption for parents constant wakening in the night due to symptoms getting worse in the bedroom, better quality of sleep for both patient and carer, better sleep outcomes for both groups. • This disease has a detrimental impact on the health-related quality of life of children and adolescents, with negative effects on emotional, physical and social well-being. Studies have even shown that allergic children have lower grades in school then non-allergic children. The SQ-HDM SLIT treatment can reduce this impact which is a relief for carers. • Financially if patient/carer is unable to afford the symptomatic medication OTC/Prescriptions then the burden of the disease significantly increases as such treatments are combination treatments and would incur a charge.

	• Access to care in lower socio-economic areas has poorer health outcomes; HDM manifests in living conditions where improvements in hygiene can impact the disease, air purifiers, washing bedding on hot washes regularly, well-ventilated rooms etc all would not be accessible in such areas. • If patient/carer is unable to afford the symptomatic medication OTC/Prescriptions then the burden of the disease significantly increases as such treatments are combination treatments and would incur a charge. • Heavily populated areas associated with ethnic minorities in council housing with poor living conditions by which this can impact certain ethnic minorities, as living conditions play a significant part in this disease (thinking of council block of flats in deprived areas; London , Birmingham etc) **Patient and carers have told us about** **Lack of availability of HDM SLIT – tablet** "Fortunately, we can afford it, so I took XXX to the States for treatment" **Unaffordable** "If you don't meet the criteria, then you have to pay for it. And not everyone can afford it." **Lack of Provision by the NHS compared to other types of illnesses** "There's so much provision for diabetes, heart disease and cancer, but why so little funding or availability is made available for the treatment of allergies?" **Post Traumatic Stress** 42% of parents caring for a child with food allergy, meet the clinical threshold of Post Traumatic Stress Disorder due to their child's allergies. **Postcode Lottery** "I had to travel 200 miles and back for treatment, in the same day. I was only 16. There was no service provision near me at all."

8. Is there an unmet need for patients with this condition?	• Currently patients suffering with HDM allergy within the UK have limited support/awareness from the NHS. • HDM allergy is not widely recognised or associated with being a condition that affects QOL in the UK, however this is predominantly because the NHS does not routinely test for this. • In order to get a HDM allergy test, a specialist referral is needed to get access to an allergist/ENT this takes on average 1.5 years post pandemic for the initial consultation. • As this is a condition which is currently only recognised in severe cases a lot of patients go under the radar with chronic symptoms for years, thus the QOL impact is profound. • The allergy can and does manifest in children and adults of all ages through eczema, asthma and rhinitis. The severity of the disease dictates how this is treated, eczema treated with emollients and steroids. Asthma treated using steroids, beta agonists (long+short), rhinitis when identified, steroid nasal sprays are offered. Steroids are the cornerstone of HDM allergy therapy with questions around steroid load, long term impacts of steroid use on adrenal axis function to be answered. Steroids do not offer long term treatment they work on the short-term symptoms only. • This leaves patients suffering with this chronic condition without the awareness/access for appropriate therapy. • Current asthma treatments step 1-4 in BTS do not include any form of allergen immunotherapy, unlike GINA, ICGP and Euphoria guidelines where this is included. As a result patients suffering from HDM asthma would not be able to obtain long term, disease modifying control as steroids are not disease modifying. Once patients progress to severe asthma, biologics are introduced which again are a lifetime treatment requiring patients to have injectable treatment for asthma, wherein if SQ HDM SLIT were considered earlier, a shorter disease modifying treatment could be offered.

Advantages & disadvantages of the technology

9. What do patients or carers think are the advantages of the technology?	• Treats the underlying cause of the disease, specific to the nature of the allergy, in a society where everything is tailored specific to needs why should allergy treatments be any different. • "My tip is to always have your allergy kit with you, whether at home or travelling. Sometimes it can come on quite quickly. If you have your kit on you then you're less likely to end up in hot water." • Does not rely on using prolonged steroids, thus long-term impacts of steroids is avoided. On the contrary a reduction in symptom medication is evident in the clinical trials. • Once daily fast dissolving tablet for 3 years is easy to use. • For the symptomatic medication it doesn't always cover the symptoms completely, and it only treat the symptoms when they occur and definitely does not address the cause of the allergic disease. • By providing repeated standardised doses of relevant allergens, AIT induces clinical and immunological tolerance. By addressing the cause of the disease AIT provides disease modification rather than only targeting the symptoms. In contrast to symptomatic medication AIT addresses the cause of allergic disease and thereby halts the progression of disease severity and the development of comorbidities such as asthma or other allergic diseases (which is well recognized risk factors for children with Allergic Rhinitis). Additionally new data suggest that there is also an effect on reducing the number of respiratory infections in children which often leads to hospital visits. • Approval of SQ-HDM SLIT would definitely fulfil an unmet need for HDM allergic patients, since it is a treatment that addresses the cause of the disease. After only 3 years of treatment AIT can provide long-term, sustained symptom control extending beyond the treatment period. Also, it is confirmed that AIT has the potential to alter the disease course. • AIT ensures that patients will have fewer symptoms, less medication use, better quality of life, fewer GP and hospital visits and already after 3 months of treatment benefit from being able to live their life's much more freely from the symptoms that many have been living with for years prior to starting treatment. **Case Study** 'I have been taking Acarizax for 20 months, initiated august 2022, at The RVI in Newcastle, having been diagnosed with multiple allergies (dust, tree, pollen and grass). My symptoms being Allergic asthma, persistent Coughing, difficulty sleeping due to rhinitis, and having to mouth breath, postnasal drip., loss of smell and taste. Also diagnosed with nasal polyposis, with an inverted papilloma removed in October 2021 and then again in March 2024 as it had grown back, further exacerbating my difficulty in breathing at night. Although symptom relief was minimal for the first few months, with Acarizax, symptoms have improved gradually. However, the allergic asthma and coughing has improved significantly and has enabled a significant reduction in inhaler use, resulting in better sleep, and overall better quality of life.

	I have still had episodes where asthma has flared up during peak tree and grass pollen times , when I have needed to attend the local walk in centre for additional steroids and medication, but there is a plan in place with the Newcastle Allergy Team, for me to monitor and keep a dairy of these episodes , should additional treatment be needed for my other allergies at a later date. I have also found the surgery to remove the polyps has significantly improved my breathing, which has in turn improved my sleeping. Recently, my sense of taste and smell have also begun to return (intermittently) which has been fabulous! I feel that the combination of the Acarizax therapy and the removal of my polyps have both contributed to my overall much improved quality of life and look forward to working with the Newcastle Allergy Team to monitor and improve flare ups for my other allergies, which in turn may all help contribute to reducing inflammation which may stop my polyps from growing back again’

10. What do patients or carers think are the disadvantages of the technology?	N/A

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.	N/a

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Treatment should be made available to all geographical areas, not just some postcodes. Treatment should not just be available for the affluent but those living in areas of deprivation and low-income households.

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.	• Allergic Rhinitis and House Dust Mite Allergies can be debilitating and affect the physical and mental health of people living with them at their most chronic • People living with this condition can be unfairly excluded from school or the workplace, impacting on education, household income brackets, as well as the economy • There must be equity in the affordability and widespread availability/access to the SLIT- tablet treatments • SLIT – tablet treatments need to be geographically available and not spread disparately across regional postcodes •

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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]

Patient Organisation Submission

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Anaphylaxis UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are Anaphylaxis UK (formerly Anaphylaxis Campaign prior to July 2022). Anaphylaxis UK is the only UK-wide charity operating solely for the growing numbers of people at risk of serious allergic reactions and anaphylaxis. We've been supporting people living with serious allergies as a charity for 30 years, offering evidence-based information for individuals and their families, for businesses and for schools and other places of education. While there's no treatment or cure for anaphylaxis, we believe that by providing information, training and support, there is a brighter future for people living with serious allergies. Our mission is to create a safer environment for everyone with allergies by working with and offering training for the food industry, schools, pre-schools, colleges, health professionals and others. Most of what we offer is without charge and we rely on the generosity of our supporters to carry out our work.
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.]	Yes, Anaphylaxis UK received £12,380 from ALK for our Bee and Wasp Campaign which ran from May 2023 to September 2023.

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have an active helpline through which the allergic community can talk to us to seek advice about their experiences of living with serious allergies. We have a clinical and scientific panel comprising of consultant allergists, pharmacists, dieticians and nurses who share anonymous insight into their patients experiences of living with allergy which informs the resources and information we have available. Anaphylaxis UK has a Facebook page and is active on a range of social media platforms which enables communication with the allergic community.

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?	Living with the condition • Fatigue • Headaches • Respiratory infections • Congestion • Itchy, runny eyes and if severe, eye swelling, photophobia • Asthma flares • Eczema flares • Ear infections and hearing problems • Sleepless nights Education – Parents have to consider - • Choosing a school for a child with allergies – is the school 'Allergy aware'? • Putting in place an individual healthcare plan for the child. • Have the staff had allergy first aid training? • Does the school undertake an annual allergy risk assessment? • Does the school have policies for children with medical conditions including allergies? Young people living with the condition. • Decrease in parental support for 16–24-year-olds – leaving home for the first-time managing allergy independently • More risk taking in managing their medication – alcohol potentially affecting decisions

	Carers experience • Sleepless nights • Time in hospital • Time off work • Loss of income Adults' Experience of the condition • Time off work/ loss of income/ challenges caring for children if they themselves are unwell / in hospital with asthma flares/ infections. • Also effect on missed school for children and affect on schooling with impaired concentration/learning/affect on exams. • Person affected may have anxiety about being in areas where house dust mite is likely more prevalent- e.g. At school – sitting on carpets (often triggers children), some situations at work which may be unavoidable depending on occupation -e.g. If need to go into other people's houses

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients/Carers report - • Professional knowledge, experience and confidence - lack of understanding in primary care - appropriate referral, treatment, support and education, unaware of availability of immunotherapy treatments. • Can be a long wait to see a specialist and get a diagnosis or follow-up - postcode lottery. • uncertainty about when to use medication. • Concerns about setting up a care plan – care and safety at school. • Lifelong, daily medication • Side effects of medication – such as drowsiness • Compliance difficult with nose sprays and inhalers • Worry about risks of current treatments (steroids) • Carer frustration – treating symptoms but no long-term solution
8. Is there an unmet need for patients with this condition?	Yes, there is an unmet need. There are currently no effective long-term treatments available on the NHS to reduce the severity of an allergic reaction from dust mites. There is a lack of awareness of longer-term solutions within the patient and carer community, and on some occasions, this will lead patients to look for private injections of Kenalog which has significant risks. Families don't have to put up with the symptoms and issues as described in section 7.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients/Carers report that they believe this treatment will - • reduce the burden of managing all the implications of living with allergic rhinitis and allergic asthma as outlined in section 6 above due to decreased risk of an allergic reaction. • Reduce the social and quality of life burdens of living with allergic rhinitis and allergic asthma. • Reduce the need to take lifelong medication. • May have long term benefits such as reducing occurrence of subsequent asthma development.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients/carers report concerns about - • Compliance issues - burden of maintaining the schedule of daily treatment. • Risk of side effects – potential for mild, moderate or severe allergic reactions • Burden of monitoring child for side effects • Psychological effect on child if side effects experienced. • Hospital visits and follow up appointments. • Collecting prescriptions – hospital/GP • Concerns about longevity of results following conclusion of treatment

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.	Patients who might benefit more: • Those with frequent respiratory infections or asthma • Patients experiencing fatigue. • Children and young people frequently missing school/college/work • Families experiencing reduced income due to the impacts of the condition. • People with other chronic conditions where the burden of additional illness/ fatigue may affect their general health. • People on multiple other medicines – interactions with histamines Patients who might benefit less: • Those with milder symptoms may find the side effects of the medications potentially worse and may have less incentive to be compliant with the medication.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	All eligible families should have equal opportunity to access the technology with patient information available in a variety of accessible formats to cater for a diverse range of needs. Other equality issues include: • Language barriers • Access to hospital services and travel • Knowledge of local primary care services • Under 12's • Ability to take time off work/school.

Other issues

13. Are there any other issues that you would like the committee to consider?	Consider that treatment will likely reduce the number of emergency hospital admissions for severe allergic asthma and allergic rhinitis, thus reducing costly emergency care. Other factors to consider: • Who prescribes it and availability • Opportunities for shared care/primary care initiation • Consider of approval of treatment for under 12s

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• This is a much needed and long-awaited technology. • Allergic rhinitis and allergic asthma have a major impact on all aspects of daily life for both patients and carers. • Current treatments only treat symptoms but do not provide a longer-term health solution. • Treatment will alleviate the significant financial burden of living with allergic rhinitis and allergic asthma. • Potential reduction in emergency admissions will reduce NHS burden of treating allergic rhinitis and allergic asthma including emergency care

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Single Technology Appraisal

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- 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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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	Association of Respiratory Nurses (ARNS)
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).	ARNS is a non- profit organisation which acts as a nursing forum to champion respiratory nursing. ARNS is run by nurses and encourages and promotes new respiratory initiatives to improve respiratory care for patients.
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.)	To treat patients with moderate or uncontrolled allergic rhinitis or allergic asthma associated with allergic rhinitis who are allergic to house dust mites. This is aimed at adults age 18-65 and adolescents age 12-17
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.)	Patients getting a greater symptoms relief, possibly a step-down approach to their other usual medications such as steroidal nasal sprays high dose antihistamine and reduced exposure to corticosteroids.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	It depends where the patient is seen and treated. I do not personally in the area or secondary or tertiary care as I work alongside allergy service and severe asthma services where patient may already be on a treatment such as a biologic for allergic asthma Omalizumab. However, there may be unmet needs in other areas such as primary care.

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

9. How is the condition currently treated in the NHS?	Patients can be treated as mentioned above with a variety of treatments such as steroid inhalers for patients with asthma, steroidal nasal sprays , anti-histamines and in severe cases, patients may be seen in allergy for desensitisation therapy or severe asthma centres for Biologics injections such as Omalizumab.
9a. Are any clinical guidelines used in the	There is the BTS/SIGN Guidelines on the management of asthma British Society for Allergy and clinical immunology (BSACI) Allergic Rhinitis (2017)

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.)	I think treatment varies throughout the UK. As mentioned above there was not clear guidance for our Trust which was the reason, I produced our own local pathway for treatment options for treating allergic rhinitis.
9c. What impact would the technology have on the current pathway of care?	Again, it would depend on which pathway and journey the patient is on and which service they are under. They would presumably need to already be under a secondary specialist service as I can imagine it would come with cost implications therefore sit nearer the end of the treatment pathway as more of a final resort to control syptoms.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	I don't know
10a. How does healthcare resource use differ between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	I would suggest in specialist services such as allergy and asthma clinics.
10c. What investment is needed to introduce the technology? (For example,	There would need to be more extensive information, such as possible side effects, dosing regime, comparison data again current available treatment. Cost effectiveness details of the treatment and patient benefit. Training for health care professionals in the first instance to be able to help patients make informed decisions.

for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	At the moment it would be hard to say as more information is required.
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?	Again, would need more information.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I presume that with a cut off age of 65 that it suggests that patients above this age would not do as well. I think patient who have a element of infective disease may not respond as well.

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	It appears it would be easier than some treatments such as injectable biologics and easier for patients to self-administer.

treatments needed, additional clinical requirements, factors 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?	I presume some form of assessment would be needed to monitor progress with treatment and evaluate treatment outcomes. For example, patient questionnaires. Possibly blood test evaluation such as allergy screen, IGE and RAST to House dust mite pre and post treatment to see if the levels reduce. In services such as asthma FeNO is a useful tool to use pre and post 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?	
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?	

16a. Is the technology a 'step-change' in the management of the condition?	I think it would be considered more of a step-up change or as add on last resort treatment.
16b. Does the use of the technology address any particular unmet need of the patient population?	Not that I'm aware of.
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?	Unable to comment without further information on side effects to the patient.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Information unavailable
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	With regards to measuring outcome in allergic rhinitis I think one of most important outcome is severity of symptoms and again would suggest to use patient questionnaires pre and post treatment. I agree with the outcome measurements for patients with allergic asthma. I think reduction in inhaled/ oral corticosteroids and reduced exacerbations are most important. I would suggest alongside lung

	function to monitor and record FeNO. Adverse effects should also be monitored for the allergic asthma. Further clarification is needed to identify if all the outcome measures are considered in both the allergic rhinitis only and the allergic rhinitis with allergic asthma cohort.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Data not available
18d. Are there any adverse effects that were not apparent in clinical 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?	

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	I think it depends, if patients need to be referred for example to a tertiary centre to receive this treatment there maybe issues with patients' accessibility. Again, it depends on eligibility criteria also.
21b. Consider whether these issues are different from issues with current care and why.	I do not feel this is different to current care.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• New treatment for allergic rhinitis and associated allergic asthma. • More clarification needed to patient benefit compared to current treatments available and cost effectiveness. • Clarification needed on the evaluation and monitoring of treatment. • Clinically significant response needs to be identified to show success or failure of treatment. • Consider FeNO as a measurement tool and symptom-based questionnaire to evaluate treatment.

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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.

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 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Thoracic Society
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 or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	British Thoracic Society is a charity.
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.)	This is unclear from the scope document what the aim of the treatment is.
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.)	1. Reduction in asthma exacerbations compared to the previous year 2. Improvement in asthma control and asthma-related quality of life 3. Reduction in health care utilisation (without stopping inhaled steroids)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes

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

9. How is the condition currently treated in the NHS?	Inhaled steroids, topical nasal steroids, antihistamines For patients with severe asthma (frequent exacerbations needing oral steroids despite high dose inhaled steroid therapy), biologics are considered. However, in this patient group, house dust mite related exacerbations are uncommon.

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	British Thoracic Society Guidelines BSACI
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.)	No
9c. What impact would the technology have on the current pathway of care?	Unclear as currently there is no data to show that it will be clinically beneficial in asthma
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Unclear as the clinical evidence is needed regarding the appropriate patient group, cost effective analyses are needed as well.
10a. How does healthcare resource use differ between the technology and current care?	We do not currently use HDL SLT in asthma
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Once the evidence supporting its use is available and the cost effectiveness analyses performed, I suspect it will be delivered in specialist clinics.
10c. What investment is needed to introduce the technology? (For example,	unclear

for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	No; not based on the currently available evidence
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?	unclear
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	unknown

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	See above- more data is needed to demonstrate efficacy

treatments needed, additional clinical requirements, factors 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?	Can only answer this once there is more evidence to show its efficacy and cost effectiveness in asthma
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?	See above
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?	See above
16a. Is the technology a 'step-change' in the	No

management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	
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?	

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	There is only a single trial; more evidence is needed
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The trial measured exacerbations once inhaled steroids were reduced and then stopped. We would not recommend stopping inhaled steroids in a patient who has asthma- this is outside standard guidance and can result in asthma death. Trials should measure exacerbations needing oral steroids, health care utilisation, asthma control and quality of life on treatment

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I am unaware
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I am unaware
20. How do data on real-world experience compare with the trial data?	I am unaware as this treatment is not routinely used in the Uk and therefore we do not have any real-world evidence

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.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Currently there is only one clinical trial that showed it may be of benefit- but when ICS dose was reduced/ stopped • In clinical practice we would not stop inhaled steroids • More evidence is needed on clinical efficacy and cos-effectiveness • Trials should measure exacerbations needing oral steroids, health care utilisation, asthma control and quality of life on treatment

Thank you for your time.

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Your privacy

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Single Technology Appraisal

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Royal College of Physicians (RCP)
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? A specialist in the clinical evidence base for this condition or technology? Other (please specify):
5a. Brief description of the organisation (including who funds it).	Royal College of Physicians (RCP)
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.)	The main aim of treatment for asthma is to prevent progression of asthma by treating airways inflammation and preventing the development of fixed airways obstruction secondary to airways remodelling. The main aim of treatment for allergic rhinitis is to provide symptomatic relief when conventional treatment for allergic rhinitis has failed.
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.)	Asthma: 1. A minimum improvement of at least 0.5 of the Asthma Control Questionnaire; or 2. A minimum improvement of at least 3 of the Asthma Control Test; or 3. Reduction in asthma exacerbations (There is no valid Minimal clinically important difference for this). A reduction in annual exacerbation rate or in the risk of having a severe asthma-related event ranging from 20–40% for a given asthma treatment regimen and/or intervention is considered clinically relevant in RCTs; or 4. Significant reduction in the number of courses of oral steroids taken a year; or 5. Significant reduction in escalation of treatment to the use of biologicals, immunosuppressive agents or low dose corticosteroid for control of asthma Allergic rhinitis 1. A minimum improvement of at least 0.25 - 0.50 of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The majority of treatment for asthma is currently targeted towards patients who have severe asthma. With regards to the mortality of patients with asthma, a significant proportion of them have mild to moderate asthma. The mild nature of their disease effects compliance to inhaled corticosteroid treatment which is necessary to reduce airways inflammation and disease progression. A treatment which could be taken for 3 to 5 years which has continued effects for a further 3 to 5 years after cessation of treatment, is beneficial in this cohort as it would prevent life threatening exacerbations in patients who are poorly compliant on inhaled medications. A treatment for asthma which prevents the escalation of treatment to the use of biologicals, immunosuppressive agents or low dose corticosteroid for control of asthma would be beneficial from the point of view of reduced sequalae of these treatments as well as cost for the NHS for stepping up to these treatment regimes. Non-sedative antihistamines used to treat allergic rhinitis commonly have side effects of reduced attention and drowsiness though significantly reduced compared to sedative antihistamines. This has an impact on work and school performance. A treatment which could spare the use of non-sedative antihistamines would improve work and school performance. Uncontrolled Allergic Rhinitis has a significant morbidity however this is poorly captured by the Global Quality of life questionnaires such as the SF-36 and EQ-5D. Patients who are on maximal conventional treatment who have significant symptoms would benefit from aeroallergen desensitization as this would reduce their mobility from uncontrolled allergic rhinitis.

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

9. How is the condition currently treated in the NHS?	Asthma is treated in a step wise manner with escalation of treatment levels from low dose inhaled corticosteroids, combination inhaled long-acting beta 2 agonist with inhaled corticosteroids, oral prednisolone/biological therapies/immunosuppressive drugs. Allergic rhinitis is treated with a combination of oral antihistamines, intranasal antihistamines, intranasal corticosteroids, Leukotriene Receptor Antagonist, and topical ocular antihistamines.
9a. Are any clinical guidelines used in the	For Asthma there is the NICE Guideline - Asthma: diagnosis, monitoring and chronic asthma management; BTS/SIGN British Guideline on the Management of Asthma, the Global Initiative for Asthma guidelines as well as the EAACI Guidelines on Allergen Immunotherapy: House dust mite-driven allergic asthma

treatment of the condition, and if so, which?	For Allergic rhinitis there is the BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised Edition 2017; First edition 2007) as well as the EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis.
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.)	The pathway of care is well defined by the guidelines. However access to allergen immunotherapy for allergic rhinitis is limited due to limited access to funding for treatment as well as limited centres in England which provide this service. The use of allergen immunotherapy for asthma is in the Global Initiative for Asthma guidelines as well as the EAACI Guidelines on Allergen Immunotherapy: House dust mite-driven allergic asthma. However this has yet to be translated to national guidelines and so access to this is limited.
9c. What impact would the technology have on the current pathway of care?	This technology could improve long term treatment outcomes of patients with mild asthma. It could also prevent the escalation of treatment to the use of biologicals, immunosuppressive agents or low dose corticosteroid for control of asthma would be beneficial from the point of view of reduced sequalae of these treatments as well as cost for the NHS for stepping up to these treatment regimes
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is currently being used for treatment of allergic rhinitis, and this is accessed via referrals by General Practitioners to Allergy Clinics. The technology is rarely being used for treatment of asthma in England and is usually used via a referral from a Respiratory Physician to an Allergy Clinic to start the use of this technology for treatment of asthma. This is due to the discrepancy between the use of this technology for treatment of asthma between national guidelines with European and Global guidelines for the treatment of asthma. This technology is suitable to be used as an add-on treatment for mild asthma or to prevent escalation of treatment to biologicals, immunosuppressive agents or low dose corticosteroid.
10a. How does healthcare resource use differ between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example,	This technology should be initiated in Secondary Care Allergy Clinics where there is currently experience in managing any complications which could arise from the initiation of aeroallergen desensitization. Following

primary or secondary care, specialist clinics.)	initiation, General Practitioners could issue repeat prescriptions with support for patient care and remote monitoring provided by Secondary Care Allergy Clinics.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The majority of Allergy Clinics already provide aeroallergen and bee/wasp venom desensitization services. In view of this it is unlikely that new investment is needed to introduce the technology. If investment is required staff training is the only cost incurred as the technology should not require investment in equipment or facilities.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, we expect the technology to provide clinically meaningful benefits to the care of both patients who have asthma and allergic rhinitis, compared with current care.
11a. Do you expect the technology to increase length of life more than current care?	The technology is not expected to increase the length of life, however it may potentially have an effect on the mortality of patients with mild asthma.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, we expect the technology to increase health-related quality of life more than current care in particular for patients with Allergic Rhinitis and Mild Asthma. However, the current Global Quality of life questionnaires such as the SF-36 and EQ-5D do not accurately capture the improvements in health-related quality of life for these patient cohorts.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	We are unaware of any groups of people for whom the technology would be more or less effective (or appropriate) than the general population.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or	The technology will be easier to use for patients and healthcare professionals. The technology is a sublingual tablet and is therefore easier to administer and use compared to inhalers, intranasal sprays or biologics/immunosuppressant drugs which are usually given by subcutaneous injections. The technology is

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.)	usually well tolerated and the only concomitant treatment which may be required is oral non-sedative antihistamines which are used to treat side effects of the technology which would usually spontaneously resolve with continued treatment.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The rules for starting the treatment should be in accordance with the recommendations of the national and international guidelines for aeroallergen desensitization treatment for allergic rhinitis and asthma. The rules for stopping treatment should be as follows “If no improvement is observed during the first year of treatment with the technology there is no indication for continuing 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?	The use of the technology could result in a substantial benefit in productivity, performance and occupational safety for patients who are taking non-sedative antihistamines, due to the side effects of non-sedative antihistamines of reduced attention and drowsiness though significantly reduced compared to sedative antihistamines.
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	Yes, we consider that the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits. This impact would be particularly seen in patients who have mild asthma who have poor compliance with their inhaled treatment, particularly since the treatment efficacy of the technology is well described to extend for years after cessation of treatment.

way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	Yes, the technology is a 'step-change' in the management of mild to moderate asthma. This is because the technology aims to immunomodulate and increase regulatory T cells to treat house dust mite driven allergic rhinitis and asthma.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, the technology addresses an unmet need in patients who have allergic rhinitis, whose symptoms are uncontrolled with conventional treatment.
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 side effects of the technology is usually controlled with oral non-sedative antihistamines. With continued use of the technology these side effects usually resolve spontaneously without any further need for oral non-sedative antihistamines.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Aeroallergen desensitization is not used routinely in current UK clinical practice for treatment of patients with asthma. The clinical trails on the technology reflect current UK clinical practice for treatment of allergic rhinitis.
18a. If not, how could the results be extrapolated to the UK setting?	The asthma patient cohorts in the clinical trails for the technology are also found in the UK, and in view of this the data can be readily extrapolated to the UK setting.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	For asthma the most important outcomes are exacerbations of asthma, asthma control, and reduced steroid requirement. For allergic rhinitis he most important outcome is Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical 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?	
20. How do data on real-world experience compare with the trial data?	

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	We do not expect there to be any potential equality issues when considering this treatment.
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• The technology addresses an unmet need in patients who have allergic rhinitis and mild asthma. • The technology is immunomodulatory and have sustained effects which last for years after cessation of treatment. • Global Quality of life questionnaires such as the SF-36 and EQ-5D poorly capture improvements in quality of life in this patient cohort. • The technology is a 'step-change' in the management of mild to moderate asthma. • The use of the technology could result in a substantial benefit in productivity, performance and occupational safety for patients who are taking non-sedative antihistamines.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Your privacy

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Single Technology Appraisal

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Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **26 March 2024**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, 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 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.

NICE National Institute for Health and Care Excellence

Part 1: Treating and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Shuaib Nasser
2. Name of organisation	Cambridge University Hospital NHS Foundation Trust
3. Job title or position	Consultant Respiratory Physician and Allergist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with allergic rhinitis and allergic asthma caused by house dust mites? ☐ A specialist in the clinical evidence base for allergic rhinitis and allergic asthma caused by house dust mites or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it – I have not seen it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
8. **What is the main aim of treatment for allergic rhinitis and allergic asthma caused by house dust mites** (For example, to stop progression, to improve	To induce immune tolerance to HDM and thereby reduce future symptoms and requirements for standard medications

mobility, to cure the condition, or prevent progression or disability)	
9. 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 asthma reduction in exacerbations, reduced inhaled or oral corticosteroids, improvements in lung function For rhinitis a reduction in symptoms – blockage, sneezing, rhinorrhoea etc and reduced requirements for standard medications
10. In your view, is there an unmet need for patients and healthcare professionals in allergic rhinitis and allergic asthma caused by house dust mites ?	This is an innovative product – first in class and to the UK market designed to reduce future requirements for therapy in patients allergic to HDM – as this is an allergen difficult to avoid - yes there is an unmet need
11. How is allergic rhinitis and allergic asthma caused by house dust mites currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	Very badly as it is not easy to avoid HDM Therefore, using antihistamines, oral and topical/inhaled corticosteroids, omalizumab BSACI guidelines for rhinitis and also immunotherapy The treatment would be used by allergists, ENT doctors and respiratory physicians in patients with persistent allergic symptoms despite standard treatments and before using omalizumab
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Used in few patients for allergic rhinitis when standard treatments are ineffective but not for asthma specialist care primarily in allergy clinics or in severe asthma clinics who are able to correctly identify that HDM allergy is the driver for symptoms. Treatment pathway is very simple and requires a single outpatient appointment monitoring the patient for 1 hour after administration of the first dose. First month's supply prescribed by specialist and subsequent prescriptions by GP

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes NO Yes with a long time horizon and reduction in usual treatments
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Those with HDM allergic sensitisation and refractory rhinitis +/- asthma
15. 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)	Treatment pathway is very simple and requires a single outpatient appointment monitoring the patient for 1 hour after administration of the first dose. First month's supply prescribed by specialist and subsequent prescriptions by GP. Follow up usually in secondary care If effective, then continue after first year
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	For asthma spirometry, FeNO, exacerbations, medication use For rhinitis use of other meds and symptoms
17. 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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	Use of concomitant medications Long term benefit Side effects of topical/oral corticosteroids

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. 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? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The technology is innovative and a step-change but has to be used in allergic patients in whom the main driver for their asthma or rhinitis is HDM This treatment will modulate allergic sensitivity to HDM and hence provide disease modifying therapy unlike any current treatments including biologics
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Few SE Expected oral swelling in first month which is generally a good sign There is ongoing concern about eosinophilic oesophagitis on which jury is still out
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The trials have tried to demonstrate a reduction in usual medications for asthma and rhinitis Immune deviation is very likely reflective of reduced allergic sensitivity and we can assume provides long term relief as in other immunotherapy treatments eg for grass pollen cf S Durham et al NEJM NO
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	NO
22. How do data on real-world experience compare with the trial data?	If patients are selected by experienced allergists then RWE is excellent

23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	N/A

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

This in an innovative treatment – first to market

Provides disease modifying reduction in allergic sensitivity to HDM

Relatively easy to use with established pathways in both allergy and asthma clinics

Safe and relatively free of side effects

Potential to reduce the adverse effects of oral/topical corticosteroids

Should be cost effective eg in comparison to omalizumab

Thank you for your time.

Your privacy

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Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

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

Information on completing this form

In part 1 we are asking you about living with allergic rhinitis and allergic asthma caused by house dust mites or caring for a patient with allergic rhinitis and allergic asthma caused by house dust mites The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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. Please type information directly into the form.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **26 March 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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Patient expert statement

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

Part 1: Living with this condition or caring for a patient with allergic rhinitis and allergic asthma caused by house dust mites

Table 1 About you, allergic rhinitis and allergic asthma caused by house dust mites current treatments and equality

1. Your name	Amena Warner
2. Are you (please tick all that apply)	☐ A patient with allergic rhinitis and allergic asthma caused by house dust mites ? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with allergic rhinitis and allergic asthma caused by house dust mites ? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Allergy UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience

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	☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I was previously a Clinical Nurse Specialist in Immunology & Allergy and saw many patients with HDM allergy in my time in practice also from Allergy UK's perspective of Our service users and what other practitioners have told me about their patients experiences ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with allergic rhinitis and allergic asthma caused by house dust mites **If you are a carer (for someone with allergic rhinitis and allergic asthma caused by house dust mites) please share your experience of caring for them**	N/A
7a. What do you think of the current treatments and care available for allergic rhinitis and allergic asthma caused by house dust mites on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**Many patients try to manage their symptoms for a long time before seeking help often thinking it's a cold that won't go away. They try different OTC medication themselves may ask a pharmacist, then in desperation go to the GP. Very few GP's have experience in allergy and even less verse with allergy testing, so misdiagnosis and mismanagement is rife. Those that are pointed to antihistamines are often taking sedating ones and many are reluctant to use steroid nasal sprays regularly or for any length of time due to 'steroid phobia'. They desperately try to find information and manage their symptoms that often worsen with time and can lead to night time cough and asthma. As HDM progresses often the picture we see is one of asthma exacerbations, hospitalisations, reduced QOL and the knock on effect that has on the individual and their immediate family or house sharers. An asthma attack can**

	be a life threatening event where they can be 'blue lighted' into resuscitation, linked up to monitors and very traumatic experience for them and their loved ones.
8. If there are disadvantages for patients of current NHS treatments for allergic rhinitis and allergic asthma caused by house dust mites (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Current medication for HDM allergy is either OTC or GP prescribed and needs to be taken life long, not always adequately controlling symptoms, can be very costly, even on prescription unless exempt, that cost has to be considered over the life course for the patient. To me as an allergy professional HDM allergy is one of the worst chronic allergy conditions for a patient as patients rarely get any recognition for the impact this has on them and their families. It is so wonderful that research has been thoroughly done, in terms of efficacy and safety, to get a treatment to be licensed and hopefully to be more widely used to address HDM allergy.
9a. If there are advantages of allergic rhinitis and allergic asthma caused by house dust mites over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does allergic rhinitis and allergic asthma caused by house dust mites help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**House dust mite allergy gives all year round symptoms, year in year out with no prospect of resolution unless the course of the immunological pathway is changed. (There has been good evidence that Immunotherapy does this for many years now. Research also shows that it needs to be a 3 year course of immunotherapy treatment to get long lasting benefits).** **Current treatment regimes are house dust mite avoidance measures(It can't be HDM eradication measures as it is impossible to do this) These are lengthy and costly. Then there is antihistamines, steroid nasal sprays, nasal douching and anti-leukotrienes. A common one prescribed, Montelukast, has been associated with causing suicidal ideations and there have been a number of deaths from this. This has been used for both adults and children.** **Asthma exacerbations often result in oral steroid prescribing which has dangerous side effect when used frequently, prolonged or in high doses. With some people developing steroid induced psychosis.** **HDM SLIT on the other hand does not have this side effect profile. It is closely monitored by experienced HCP's over the 3 year treatment period and side effects are usually immediate and treatable.**

10. If there are disadvantages of allergic rhinitis and allergic asthma caused by house dust mites over current treatments on the NHS please describe these. For example, are there any risks with SQ HDM SLIT? If you are concerned about any potential side effects you have heard about, please describe them and explain why	HDM SLIT can cause symptoms such as itchy mouth and tongue with some people experiencing itchy throat with cough or a feeling of swelling. This is why the first dose of any SLIT treatment is given in hospital so the patient can be monitored and any symptoms can be explained to the patient as either usual and expected or something they need to worry about and get help/treat etc. Severe reactions are very rare, but patients do need to be informed what to do if ever they happen. This also helps empower the patient and in my opinion helps with compliance of treatment.
11. Are there any groups of patients who might benefit more from SQ HDM SLIT or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	The groups of patients that would benefit are those that have tried all the OTC anti-allergy medication and those that have seen their GP and Allergy specialist with no resolution of symptoms, even though complying with these antiallergy regimes ie correct procedure of administering a nasal steroid spray. Those that would be able to comply with a 3 year course of treatment taken every day for that time. (so those that do not have mental capacity or to be able to give informed consent would need to be excluded) Those that are showing early signs of asthma symptoms (especially children) as a result of proven HDM allergy as this may be able to prevent a life course of asthma problems to occur.
12. Are there any potential equality issues that should be taken into account when considering allergic rhinitis and allergic asthma caused by house dust mites and SQ HDM SLIT Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	Language barriers in understanding the treatment which may lead to compliance issues. Disability, if people cannot open treatment packaging and do not have others to help as it can be difficult for them. Hopefully this could be adjusted for. Access to treatment. Very few Allergy centres doing immunotherapy country wide, with large geographical variation in provision, ie postcode lottery GP's with little allergy knowledge not referring patients that potentially fit the criteria for HDM SLIT. Cut off age for Immunotherapy (often referred to as age 70) From my knowledge and experience most allergists/immunologists would not start immunotherapy treatment in pregnancy.

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Immunotherapy is currently the only disease modifying treatment we have for allergy, as it induces a level of tolerance,
- Using a licensed product for house dust mite allergy is preferable to using an unlicensed product which has not had the same rigor applied.
- HDM Allergy is a chronic condition which has lasting QOL impacts, including asthma exacerbations from uncontrolled rhinitis, leading to hospitalisations and potentially death.
- Changing or modifying the disease course can improve symptom control (often resolution) and improve QOL for the patient, carers and family.
- A SLIT treatment where only the first dose is needed to be given in hospital for safety reasons, and the rest of the course administered at home, reduces time off work and school as well as the costs associated with travelling to hospital for treatment for the patient. For the healthcare system it can reduce time and money spent on hospitalisations from asthma exacerbations, visits to GP and walk in centres for symptom control as well as medication costs.

Thank you for your time.

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Patient expert statement

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CONFIDENTIAL UNTIL PUBLISHED
External Assessment Group Report
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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Rider on responsibility for report

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Contributions of authors

Mark Corbett wrote the critique of the decision problem and contributed to the critiques of the systematic review and clinical effectiveness evidence. Thai Han Phung critiqued the CS and wrote section 4.2.8 of the report. He also validated the model and performed the economic analyses. Sumayya Anwer contributed to the critiques of the decision problem, clinical effectiveness evidence and meta-analyses. Shainur Premji critiqued the CS and wrote sections 4.1, 4.2.1 to 4.2.5, 4.2.7 and 5 of the report. She also validated the model and performed the economic analyses. Yiwen Liu contributed to the critique of methods of review (section 3.1), results of the trials (section 3.2.2), summary of observational studies (section 3.2.3), and adverse events (section 3.2.4). Sarah Nevitt contributed to the clinical evidence review and commented on drafts of the report. Melissa Harden wrote the critique of the search strategies and provided editorial support. Ana Duarte contributed to sections 1, 4, 5 and 6 of the report. She also critiqued the CS and provided expert advice on the economic analyses and the report as a whole, writing and commenting on drafts. Sofia Dias was project lead, supported the critical appraisal of the evidence and commented on drafts of the report. Pedro Saramago Goncalves, critiqued the CS and performed the economic analyses, provided advice, wrote and commented on drafts of the report as a whole, led the overall economic sections and takes overall responsibility for the report as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been [redacted]

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List of abbreviations

AA	Allergic asthma
ACQ	Asthma control questionnaire
AE	Adverse event
AHQ	Asthma health questionnaire
AIT	Allergy Immunotherapy Tablet
AQLQ	Asthma quality of life questionnaire
AR	Allergic rhinitis
ARC	Allergic rhinoconjunctivitis
ARD	Allergic respiratory disease
ARIA	Allergic rhinitis and its impact on asthma
ASaT	All-subjects-as-treated
BMI	Body mass index
BSACI	British Society for Allergy and Clinical Immunology
BTS	the British Thoracic Society
CHE	Centre for Health Economics
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CS	Company submission
DMS	Daily medication score
DSA	Deterministic sensitivity analysis
DSS	Daily symptom score
DU	Development unit
EAG	External Assessment Group
EAR	External Assessment Report
EQ-5D	EuroQoL 5-dimensions
EQ-5D VAS	EuroQoL 5-dimensions - visual analogue scale
eMIT	Electronic market information tool
FAS	Full analysis set
FAS-MI	Full analysis set with multiple imputation
FEV	Forced expiratory volume
GINA	Global initiative for asthma
GLMM	Generalised linear mixed effect model
GP	General practitioner
HCRU	Healthcare resource use
HDM	House dust mites
HES	Hospital Statistic Episodes
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroids
ICU	Intensive Care Unit
IgE	Immunoglobin E
IMT	Investigational medicinal product

ITT	Intention to treat
JRQLQ	Japanese allergic rhinitis quality of life questionnaire
LABA	Long-acting β_2-agonists
LAMA	Long-Acting Muscarinic Antagonists
LOCF	Last observation carried forward
LTRA	Leukotriene Receptor Antagonists
LYG	Life year gain
MA	Marketing authorisation
MAOI	Monoamine oxidase inhibitor
MI	Multiple imputation
MID	Minimal important difference
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net Monetary Benefit
NPCE	National Centre for Pharmacoeconomics
OC	Observed cases
ONS	Office for National Statistics
OR	Odds ratio
PBAC	Pharmaceutical Benefits Advisory Committee
PEF	Peak expiratory flow
PP	Per protocol
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	the Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RoB	Risk of bias
ROBINS-I	Risk of bias in non-randomised studies - interventions
RQLQ	Rhinitis quality of life questionnaire
SABA	Short-acting β_2-agonists
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36	Short form (36) health survey
SLIT	Sublingual immunotherapy
SLR	Systematic literature review
SOC	Standard of care
SOP	Standard operating procedure
SQ	Standardised quality
ST	Symptomatic treatment
STA	Single technical appraisal
TA	Technology appraisal
TCRS	Total combined rhinitis score
TEAE	Treatment emergent adverse event
TRAE	Treatment related adverse event

WTP	Willingness-to-pay

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 Summary of EAG's key issues

Key issue number	Summary of issue	Report sections
1	Prohibition of established clinical management treatments which are routinely used in the NHS	2.2, 3.2.1
2	Clinical relevance of the magnitude of the efficacy estimates of 12 SQ-HDM	3.2.2.2, 3.2.2.3
3	Numerous important methodological limitations seen across the 12 SQ-HDM trials	3.2.1
4	The AA+AR model structure does not appropriately reflect the clinical management of asthma which, in clinical practice, involves a stepwise approach to assessing, treating, and monitoring patients' asthma control.	4.2.2
5	AR adolescent subgroup: The EAG considers that the generalisation of cost-effectiveness findings over 12 SQ-HDM from AR adults to AR adolescents to be uncertain.	4.2.3, 4.2.7.2
6	Evidence used to inform short-term effectiveness evidence and its parameterisation in the AA+AR and AR models are uncertain.	4.2.6.1
7	For both AA+AR and AR models, medium to long-term effectiveness estimates are based only on assumptions.	4.2.6.2
8	Evidence used to inform the AA+AR population effectiveness on asthma exacerbations is not reflective of clinical practice.	4.2.6.3
9	A treatment-specific approach to HRQoL was used in the company's base case, which does not align with the model structures developed for AA+AR and AR, respectively.	4.2.7.2
10	Treatment costs in both the AA+AR and the AR models are uncertain.	4.2.8.5
11	Management costs in both the AA+AR and the AR models are uncertain.	4.2.8.6

AA: Allergic Asthma; AR: allergic rhinitis; HRQoL: Health-related quality of life

For the allergic asthma and allergic rhinitis (AA+AR) model, the key differences between the company's preferred assumptions and the EAG's preferred assumptions are: (i) the use of the MT-04

trial[1, 2] maintenance phase to inform short-term effectiveness parameterisation; (ii) use of alternative medium to long-term effectiveness estimates informed by empirical evidence and expert opinion; (iii) using health-state specific utilities and relevant utility source (Briggs et al., 2021[3]); (iv) use of only relevant biologic treatments (omalizumab and tezepelumab); (v) use of the MT-04 trial[1, 2] trial maintenance phase to estimate the treatment effect of 12 SQ-HDM in reducing primary care visits (7.35% relative reduction); and (vi) assuming that the treatment effect of 12 SQ-HDM in reducing secondary care visits is equivalent to the primary care relative reduction.

For the AR model, the key differences between the company's preferred assumptions and the EAG's preferred assumptions are: (i) use of alternative medium to long-term effectiveness assumptions; (ii) using health state-specific utilities derived from the MT-06[4, 5] trial; and (iii) assuming that the treatment effect of 12 SQ-HDM in reducing secondary care visits is equivalent to the primary care relative reduction (a 4.92% relative reduction).

Where the company has not presented robust evidence to support their assumptions, the EAG has performed further scenario analysis over the EAG's preferred base case, exploring alternatives to those assumptions given the level of evidence available and as informed by clinical advice to the EAG.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Applying higher utility estimates to patients treated with the technology compared to the standard of care.

Overall, the technology is modelled to affect costs by:

- Its higher treatment and administration costs compared to standard of care for both AA+AR and AR models.
- The assumptions around the standard of care treatment costs for both AA+AR and AR models.
- The assumptions around the primary and secondary care costs for both AA+AR and AR models.
- The assumptions around exacerbations for the AA+AR model.

The modelling assumptions that have the greatest effect on the ICER are:

- Alternative assumptions to the medium to long-term effectiveness of 12 SQ-HDM and standard of care in both AA+AR and AR models.
- The approach to deriving utilities in both AA+AR and AR models.
- The assumptions around the effect of 12 SQ-HDM in reducing primary and secondary care visits.

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Prohibition of established clinical management treatments which are routinely used in the NHS

Report section	2.2, 3.2.1
Description of issue and why the EAG has identified it as important	All five 12 SQ-HDM trials reported in the company submission for the AA+AR and AA populations prohibited the use of many treatments which are routinely used in the NHS. The EAG considers that patients in the 12 SQ-HDM pivotal trials therefore received lower levels of standard of care than would be seen in patients in NHS practice. Assuming 12 SQ-HDM has some efficacy, we would expect that more of these treatments would have been used in the placebo group. Therefore, it is likely that the trial results are an over-estimate of the treatment effect expected to be seen in an NHS cohort.
What alternative approach has the EAG suggested?	None available given current evidence.
What is the expected effect on the cost-effectiveness estimates?	The treatment effect with standard care would be expected to increase, with associated increase in the ICER, however, the magnitude is uncertain.
What additional evidence or analyses might help to resolve this key issue?	No further relevant studies are available to address this issue.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 Clinical relevance of the magnitude of the efficacy estimates of 12 SQ-HDM

Report section	3.2.2.2, 3.2.2.3
Description of issue and why the EAG has identified it as important	The EAG considers that the trial data demonstrate that 12 SQ-HDM has very little effect on allergic asthma and a minimal effect on allergic rhinitis. AA+AR population (2 trials): The trial methods evaluating efficacy on asthma exacerbations are too different from NHS practice to be of value in this appraisal (see Issues 1 and 3). Asthma control questionnaire score improvements with 12 SQ-

	HDM were either not statistically significant or not clinically significant. 12 SQ-HDM did not produce statistically significant improvements in measures of health-related quality of life nor in measures of lung function. AR population (3 trials): Although statistically significant improvements in allergic rhinitis symptoms were reported, they appear to be of borderline clinical significance, despite the impact of biases which likely favour the 12 SQ-HDM groups (see Issues 1 and 3). No clinically significant improvements were seen in health-related quality of life measures and no effect was seen on complications of rhinitis (such as sinusitis). Additionally, the typical trial durations of around 12-18 months meant that the studies did not evaluate the effects of receiving three years of treatment (the recommended immunotherapy treatment duration), nor whether durable efficacy was seen after 12 SQ-HDM cessation.
What alternative approach has the EAG suggested?	N/A
What is the expected effect on the cost-effectiveness estimates?	The impact on the cost-effectiveness estimates is unknown.
What additional evidence or analyses might help to resolve this key issue?	N/A

Issue 3 Numerous important methodological limitations seen across the 12 SQ-HDM trials

Report section	3.2.1
Description of issue and why the EAG has identified it as important	The many design and methodological limitations in the pivotal trials means that their results should not be considered as reliable estimates of the 12 SQ-HDM treatment effects which would be expected to be seen in the NHS setting. The EAG considers that these issues mean that the trial results over-estimate the efficacy of 12 SQ-HDM, even though it does not appear to be very efficacious (see Issue 2). Two methodological limitations were identified in all five trials: the prohibition of many treatments routinely used in the NHS (see Issue 1) and the use of primary efficacy assessment periods outside of the major pollen season. Other issues identified included (but were not limited to): the alteration of usual medication prior to randomisation; periods of protocol-mandated reductions, then complete withdrawal, of inhaled corticosteroids; the exclusion of patients based on symptom control scores who would nevertheless be eligible for 12 SQ-HDM treatment (in the NHS); and methods of handling missing outcome data which appeared likely to bias analyses.
What alternative approach has the EAG suggested?	The EAG extracted results from the trial periods with the least amount of bias, where these were available, and presented alternative analyses.

What is the expected effect on the cost-effectiveness estimates?	The relative effect of 12 SQ-HDM compared to standard care would be expected to decrease, with associated increase in the ICER, however, the magnitude is uncertain.
What additional evidence or analyses might help to resolve this key issue?	The EAG reviewed the company's submitted evidence from observational studies but these did little to help to resolve this issue.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 4: AA+AR model structure

Report section	4.2.2
Description of issue and why the EAG has identified it as important	The AR+AA population model structure consisted of three health states reflecting different levels of asthma control. ACQ data from the MT-04 trial[1, 2] trial was mapped to Global Initiative for Asthma (GINA) 2010 criteria[6] to classify asthma control in line with the modelled health states. The AA+AR model imperfectly reflects asthma management, which, in clinical practice, involves a stepwise approach to assessing, treating, and monitoring patients' asthma control. The GINA guidelines recommend that treatment is stepped-up when symptoms persist and stepped down when symptoms are well controlled for 3 months. The EAG considers that the AA+AR model structure may not be suitable for decision making.
What alternative approach has the EAG suggested?	For the AA+AR model to appropriately reflect asthma management and the stepping up/down in treatment according to patients' asthma control, the model structure should explicitly account for asthma disease progression over treatment steps, as modelled, for example, in the Parra-Padilla et al., 2021[7] study.
What is the expected effect on the cost-effectiveness estimates?	The impact on the cost-effectiveness estimates is unknown.
What additional evidence or analyses might help to resolve this key issue?	External evidence to the company's trial (MT-04 trial[1, 2]) could be sought to complement it to adequately reflect asthma management in this population.

Issue 5: AR adolescent subgroup

Report section	4.2.3, 4.2.7.2
Description of issue and why the EAG has identified it as important	12 SQ-HDM is indicated in adolescents (12-17 years) and adults (18-65 years) with persistent moderate-to-severe house dust mite allergic rhinitis. The AR model was populated with MT-06[4, 5] trial evidence in adults, which was generalised to adolescents, implicitly assuming that no difference in effectiveness exists between the two subgroups. The company suggests that effectiveness evidence from P001[8, 9] and TO-203-32[10, 11] trials show similar efficacy across the two subpopulations. However, P001[8, 9] Health-related quality of life (HRQoL) data suggests greater benefits for the adolescent's

	subpopulation compared with adults - although the EAG notes that it is unclear whether these HRQoL findings are reliable. The company performed a scenario analysis assuming the starting age in the model to be 12 years, but, as this analysis does not include any empirical evidence specific to the adolescent subgroup, the EAG does not consider it to be appropriate. The EAG considers that the generalisation of cost-effectiveness findings over 12 SQ-HDM from AR adults to AR adolescents to be uncertain.
What alternative approach has the EAG suggested?	The EAG believes that the company could have used the identified evidence on the adolescent's subgroup to parameterise the AR model and obtain subgroup specific cost-effectiveness estimates, if an alternative model parameterisation had been used.
What is the expected effect on the cost-effectiveness estimates?	The cost-effectiveness estimates for the AR adolescent subpopulation are unknown.
What additional evidence or analyses might help to resolve this key issue?	Further AR adolescent effectiveness, HRQoL and resource use evidence could enhance the evidence base for this subpopulation and enable a full implementation of a cost-effectiveness analysis of 12 SQ-HDM over this patient subgroup.

Issue 6: Short-term effectiveness in the AA+AR and AR models

Report section	4.2.6.1
Description of issue and why the EAG has identified it as important	The short-term effectiveness parameterisation proposed by the company for AA+AR and AR models is not reflective of the progression in disease severity and the stepping up/down in treatments as observed in clinical practice. Furthermore, the use of an unadjusted post-hoc analysis to inform the AA+AR and AR models' natural history and short-term treatment effectiveness, i.e., the distribution of patients across asthma control levels and rhinitis severity levels, adds considerable uncertainty. For the AA+AR model, the use of period 2 only (maintenance phase) or periods 2 and 3 (maintenance and inhaled corticosteroids [ICS] reduction phase) of the MT-04 trial[1, 2] trial to inform the AA+AR short-term effectiveness is not reflective of clinical practice as, if asthma is uncontrolled, patients would not be maintained in their current treatment(s) and would not have an ICS reduction or withdrawal. Uncertainty in the transition probabilities in the first cycle of both the AA+AR and the AR models was also not considered.
What alternative approach has the EAG suggested?	The non-adjusted post-hoc approach developed by the company to parameterise short-term effectiveness is considered inappropriate, however, in the absence of a better alternative approach available within the timelines of the current appraisal, the EAG is obliged to use it. The EAG implemented changes to the AA+AR and AR models so that these reflect the uncertainty in the short-term effectiveness evidence, under assumptions. The EAG has fundamental concerns relating to the use of MT-04 trial[1, 2] to inform the current decision problem for the AA+AR population. Nonetheless, in the absence of better evidence and acknowledging that the MT-04 trial[1, 2] trial may be the best evidence

	available, the EAG considered its use for the AA+AR model, although restricting its use to the maintenance phase (period 2 of the trial), as in previous economic analyses.
What is the expected effect on the cost-effectiveness estimates?	No sizeable impact on total costs and total QALYs for both AA+AR and AR models.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that a modelling approach to effectiveness that reflects the progression in disease severity and the stepping up/down in treatment, as observed in clinical practice, would be the most appropriate (see Issue 4).

Issue 7: Medium to long-term effectiveness in the AA+AR and AR models

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	For both AA+AR and AR models, the company assumed improvements in health for 12 SQ-HDM from 2 to 10 years. The EAG considers these assumptions not to be supported by published evidence. The company assumed also that treatment waning would be initiated in year 15 of the model and that by year 20, 80% of the patients in the 12 SQ-HDM treatment arm would match the distribution of patients in the standard of care arm. The EAG believes that any long-term effectiveness assumptions beyond 9 years are subjective and very uncertain, and that no evidence exists beyond 20 years.
What alternative approach has the EAG suggested?	Available evidence supports a sustained effect of 12 SQ-HDM from 2 to 10 years, not an increase in effect as assumed by the company. Thus, the EAG proposed in a scenario a stable effect of 12 SQ-HDM over this period for both populations. The EAG considers that evidence for both populations beyond 10 years is too uncertain to be considered in the economic modelling. Thus, the EAG considered a scenario where post-10 years patients in the 12 SQ-HDM treatment match the effectiveness of standard of care. This scenario is part of the EAG preferred assumptions for both AA+AR and AR models. Additional analysis using alternative medium to long-term effectiveness assumptions have been explored over the EAG base case.
What is the expected effect on the cost-effectiveness estimates?	The use of alternative medium to long-term effectiveness assumptions imply an increase in 12 SQ-HDM total costs for both models mainly due to secondary care costs matching standard of care costs post-10 years. These alternative assumptions also imply a slight decrease in 12 SQ-HDM total QALYs for both models, as slightly fewer patients transition to better health states.
What additional evidence or analyses might help to resolve this key issue?	Medium to long-term effectiveness evidence from well-designed randomised controlled trials (RCTs) for both 12 SQ-HDM and standard of care in AA+AR and AR populations.

Issue 8: Asthma exacerbations in the AA+AR model

Report section	4.2.6.3
Description of issue and why the EAG has identified it as important	Evidence from the MT-04 trial[1, 2] trial used to inform the AA+AR effectiveness on asthma exacerbations 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 trial would not be expected in the NHS. The company's assumptions that the risk of an exacerbation is independent of asthma control level and that exacerbations do not affect subsequent health state membership are not clinically supported.
What alternative approach has the EAG suggested?	The EAG identified a study that suggests asthma control questionnaire (ACQ) scores are a good predictor of future risk of asthma exacerbations. The MT-04 trial[1, 2] trial did not collect evidence on the occurrence of asthma exacerbations in period 2. The EAG considers that the ACQ evidence indicating similar levels of asthma control between 12 SQ-HDM and placebo over this period suggests that the 12 SQ-HDM treatment effect on exacerbations is negligible in period 2 of MT-04 trial.[1, 2] However, the EAG considers that the existing uncertainty on these parameters should be explored further. The EAG did not identify external evidence which could be used to inform asthma exacerbation probabilities in the AA+AR model within the time constraints of this assessment but notes that the company did not report any systematic approach to identify such as evidence. Clinical opinion to the EAG in TA880[12] noted that while exacerbations can happen in any health state, the risk of having an exacerbation will differ according to the level of asthma control, with higher risk of an exacerbation in uncontrolled than controlled asthma. The clinical adviser to the EAG also considered that it is more likely for patients to return to an uncontrolled asthma health state than to controlled asthma after an exacerbation. The EAG considered a scenario considering a null probability of asthma exacerbations across levels of asthma control in each arm. This scenario implies null exacerbation related costs and disutilities.
What is the expected effect on the cost-effectiveness estimates?	The impact of the company's assumptions on the relationship between the occurrence of exacerbations and the level of asthma control on the estimates of cost-effectiveness is unknow. The scenario of null exacerbation probabilities implied a decrease in total costs and a slight increase in total QALYs for both intervention and standard of care. Minor changes to Net Monetary Benefit (NMB) were observed, with 12 SQ-HDM still dominant over standard of care.
What additional evidence or analyses might help to resolve this key issue?	A systematic review of the literature may identify external evidence that would enable the exploration of the uncertainty on exacerbation probabilities and of the 12 SQ-HDM treatment effect on asthma exacerbations.

Issue 9: Approach to HRQoL

Report section	4.2.7.2
Description of issue and why the EAG has identified it as important	The treatment-specific approach to utility estimation does not align with the health state modelling structure proposed by the company. Furthermore, in the AA+AR model, the treatment-specific approach utilises HRQoL estimates derived from the SF-36 data collected in MT-04 trial[1, 2].
What alternative approach has the EAG suggested?	The EAG's suggests the use a health-state valuation of HRQoL, as it aligns with the health state AA+AR model structure. For the AA+AR model, the EAG suggests the use the health utilities derived from Briggs et al., 2021[3] that mapped AQLQ data to EQ-5D-3L, as this approach adheres to the NICE reference case. These scenarios have been considered in the EAG preferred set of assumptions.
What is the expected effect on the cost-effectiveness estimates?	The suggested changes to the HRQoL by considering health-state specific utilities and relevant utility sources implied changes to estimated total QALYs, substantially reducing incremental QALYs in the AA+AR model and more than halving incremental QALYs in the AR model.
What additional evidence or analyses might help to resolve this key issue?	None

Issue 10: Treatment costs

Report section	4.2.8.5
Description of issue and why the EAG has identified it as important	The EAG has several concerns relating to how the company has estimated the costs of treatments in both the AA+AR and the AR models. The EAG considers that the company's modelling approach in the AA+AR model does not allow the impact of 12 SQ-HDM on the consumption of standard of care pharmacotherapy due to improved asthma control to be appropriately captured. In the AR model, the EAG considers that the generalisability of standard of care medication from the MT-06[4, 5] trial to UK clinical practice is uncertain. Furthermore, in the AA+AR model, the EAG questions the company's interpretation of clinical guidance to inform standard of care treatment composition, which the EAG believes may have led to an overestimation of costs. The EAG also considers it inappropriate to include costs of biologic treatments that are not reflective of UK clinical practice. The 22.5% reduction in biologics adjustment made for step 5 for 12 SQ-HDM (relative to standard of care) was elicited via clinical experts and is considered uncertain, uncertainty which was not appropriately reflected in the model. Finally, the EAG considers that the differences in costs of standard of care between AA+AR model health states relies on a strong and implausible assumption that relative increases in ICS dose between levels of control directly translate to a proportional increase in costs across all standard of care asthma medications.

What alternative approach has the EAG suggested?	The EAG recommends that the list of biologics used in step 5 is restricted to relevant biologics to this decision problem, that is, omalizumab and tezepelumab. This has been considered as a scenario and is part of the EAG set of preferred assumptions for the AA+AR model. The EAG also suggests disregarding the assumption of cost weighting based on ICS dose increases across levels of control.
What is the expected effect on the cost-effectiveness estimates?	Using only relevant biologic treatments did not have a sizeable impact on total costs and total QALYs for the AA+AR model. Removing the ICS-based cost weighting did not have a sizeable impact on total costs and total QALYs for the AA+AR model.
What additional evidence or analyses might help to resolve this key issue?	Clinical consensus should be sought over what is the optimal clinical guidance and/or standard of care treatment composition.

Issue 11: Management costs

Report section	4.2.8.6
Description of issue and why the EAG has identified it as important	The company imposed several assumptions to the management cost estimation in both AA+AR and AR models. The EAG considers the annual GP visits for AA+AR by asthma control levels and for AR by severity levels to be uncertain. Evidence used to inform primary care costs has limitations and is poorly aligned with both models. The three-stage calculation procedure to estimate primary care costs for standard of care in the AA+AR population is particularly complex and relies on strong assumptions around the distribution of patients across treatment steps and the weighting based on ICS reduction. Also, the relative reductions in GP visits associated with 12 SQ-HDM in the AA+AR and AR populations are uncertain as these have been derived from the MT-04 trial[1, 2] and MT-06[4, 5] trials, respectively. This may have contributed to an overestimation of primary care cost savings associated with 12 SQ-HDM. Similarly, the EAG considers the annual secondary care visits for AA+AR and AR estimated by the company to be uncertain as it questioned the applicability of the Hospital Statistic Episodes (HES) data analysis for AR and AR+AR HDM. Also, the relative reductions in annual outpatient visits associated with 12 SQ-HDM in the AA+AR and AR populations are uncertain, as these are based in the MT-04 trial[1, 2] trial and a before and after study by El-Qutob et al., 2016,[13] respectively. The management costs are a key driver of the cost-effectiveness results in both models. The costs of asthma exacerbations may not be reflective of exacerbation management in the NHS, and the cost of severe asthma exacerbations may have been overestimated, favouring the cost-effectiveness of 12 SQ-HDM compared to the standard of care. Furthermore, the costs of exacerbations may also already have been accounted for to some extent in other cost categories.

What alternative approach has the EAG suggested?	For consistency with the short-term effectiveness assumptions, for the AA+AR model the EAG recommends using the relative reduction associated with 12 SQ-HDM derived from MT-04 trial[1, 2] from the maintenance phase covering weeks 4 to 9, excluding randomisation. This assumption is part of the EAG base case in the AA+AR model. In the absence of better evidence, in both AA+AR and AR models, the EAG used the estimates for the treatment effect of 12 SQ-HDM in reducing secondary care visits to be equivalent to the primary care relative reduction, respectively. The EAG considers this scenario to be part of the EAG preferred set of assumptions in both the AA+AR and the AR model.
What is the expected effect on the cost-effectiveness estimates?	Using the relative reduction associated with 12 SQ-HDM derived from MT-04 trial[1, 2] from the maintenance phase did not imply a sizeable impact on total costs and total QALYs for the AA+AR model. Using the estimates for the treatment effect of 12 SQ-HDM in reducing secondary care visits to be equivalent to the primary care relative reduction, respectively, substantially increased 12 SQ-HDM total costs.
What additional evidence or analyses might help to resolve this key issue?	High quality data on primary and secondary care usage for 12 SQ-HDM and standard of care by disease severity and for both AA+AR and AR populations.

1.6 Other key issues: summary of the EAG's view

None.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Table 2 Deterministic cost-effectiveness results for the EAG's preferred AA+AR model assumptions

Preferred assumption	Total Costs	Total QALYs	Incr. cost	Incr. QALYs	Cumulative ICER £/QALY	Section in EAG report
1. Company's updated base case						
Standard of care	[redacted]	[redacted]				5.1
12 SQ-HDM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
2. Company's corrected base case						
Standard of care	[redacted]	[redacted]				6.1
12 SQ-HDM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
3. Analysis 2 + MT-04 maintenance phase to inform short-term effectiveness						
Standard of care	[redacted]	[redacted]				4.2.6.1
12 SQ-HDM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
4. Analysis 3 + evidence based medium to long-term assumptions						
Standard of care	[redacted]	[redacted]				4.2.6.2
12 SQ-HDM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
5. Analysis 4 + health state specific utilities sourced from Briggs et al., 2021						4.2.7.2

Standard of care	[redacted]					
12 SQ-HDM	[redacted]					
6. Analysis 5 + using only relevant biologic treatments						4.2.8.3
Standard of care	[redacted]					
12 SQ-HDM	[redacted]					
7. Analysis 6 + estimate for the treatment effect of 12 SQ-HDM in reducing primary care visits derived from MT-04 maintenance phase (7.35% relative reduction)						4.2.8.3
Standard of care	[redacted]					
12 SQ-HDM	[redacted]					
8. <u>EAG base case:</u> Analysis 7 + estimate for the treatment effect of 12 SQ-HDM in reducing secondary care visits equivalent to the primary care relative reduction						4.2.8.3
Standard of care	[redacted]					
12 SQ-HDM	[redacted]					

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

Table 3 Deterministic cost-effectiveness results for the EAG's preferred AR model assumptions

Preferred assumption	Total Costs	Total QALYs	Incr. cost	Incr. QALYs	Cumulative ICER £/QALY	Section in EAG report
1. Company's updated base case						5.1
Standard of care	[redacted]					
12 SQ-HDM	[redacted]					
2. Company's corrected base case						6.1
Standard of care	[redacted]					
12 SQ-HDM	[redacted]					
3. Analysis 2 + evidence based medium to long-term assumptions						4.2.6.2
Standard of care	[redacted]					
12 SQ-HDM	[redacted]					
4. Analysis 3 + health state specific utilities from MT-06						4.2.7.2
Standard of care	[redacted]					
12 SQ-HDM	[redacted]					
5. <u>EAG base case:</u> Analysis 4 + alternative estimate for the treatment effect of 12 SQ-HDM in reducing secondary care visits (4.92% relative reduction)						4.2.8.3
Standard of care	[redacted]					
12 SQ-HDM	[redacted]					

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

Modelling inconsistencies identified and corrected by the EAG are described in section 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see section 6.2.

EXTERNAL ASSESSMENT GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report presents a critique of ALK-Abello's company submission (CS) to NICE on the clinical- and cost-effectiveness of 12 SQ-HDM for treating allergic rhinitis (AR) and allergic asthma (AA) caused by house dust mites (HDM).

12 SQ-HDM is an allergy immunotherapy containing allergen extract from the house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* which aims to modify immune responses to house dust mite allergens. It is thought to work via the repeated administration of allergens to induce a switch from an allergic response to a tolerance-building immune response. It is indicated in adolescents (12-17 years) and adults (18-65 years) with persistent moderate-to-severe house dust mite allergic rhinitis, despite use of symptom-relieving medication, and also in adults with house dust mite allergic asthma not well-controlled by inhaled corticosteroids and associated with mild-to-severe house dust mite allergic rhinitis. Patients must have been diagnosed by clinical history and a positive test for house dust mite sensitisation (skin prick test and/or specific IgE).

2.2 Background

Allergic asthma population

Treatments for allergic asthma include inhaled short or long-acting beta-2 agonists, low dose inhaled corticosteroids (ICS), and leukotriene antagonists. If asthma is uncontrolled on these regimens, consideration should be given to referral for specialist care where they may also receive daily steroid tablets or other treatments. The company's modelling approach was based on the GINA[6] guidelines; the EAG's clinical adviser stated that the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN)[14] and NICE[15] guidelines are also used in clinical practice and that differences exist between the guidelines. In the GINA guidelines, a stepwise treatment approach is recommended in which patients whose asthma is not well-controlled on a particular treatment first have their adherence, inhaler technique and comorbidities checked, before considering a different medication in the same step, or before stepping up (see Figure 3 of the CS for details of treatments used in each step). Stepping down of treatment should be considered once good asthma control has been achieved and maintained for three months.

The company submission stated that 12 SQ-HDM is intended to be an addition to the formulary, rather than a replacement for an existing drug in the treatment pathway. In response to EAG clarification question 2, to clarify the positioning of SQ-HDM in the treatment pathway, the company

noted that 12 SQ-HDM's marketing authorisation (MA) does not state that all other relevant treatments must have been exhausted. The company reiterated their positioning as an additional therapy, adding that this positioning does not require patients to be on any specific treatment dosage (e.g. low, medium, or high dose ICS), rather patients are eligible if asthma is categorised as 'not well controlled', despite treatment with ICS, so the positioning aligns with steps 2, 3, and 4 of the GINA guidance.

The company stated that 12 SQ-HDM would not be an option for severe asthma as an alternative to biologics, as this would be beyond the marketing authorisation for 12 SQ-HDM. Omalizumab is indicated for severe allergic asthma and requires patients with forced expiratory volume in the first second (FEV1) <80% of predicted value, and patients must have multiple documented severe exacerbations despite high-dose ICS and long-acting β_2-agonists (LABA). This conflicts to a large extent with the marketing authorisation for 12 SQ-HDM whereby patients cannot have a FEV1 <70% of predicted value at initiation of treatment and cannot have experienced a severe asthma exacerbation within the three months prior to initiation of treatment. The company further clarified that 12 SQ-HDM would be given at an earlier treatment stage compared to biologics and was not expected to replace biologics. NICE TA278[16] recommends omalizumab for treating severe persistent confirmed allergic Immunoglobin E (IgE)-mediated asthma in people aged 6 years and older who need continuous or frequent treatment with oral corticosteroids (defined as four or more courses in the previous year). NICE TA880[12] recommends tezepelumab as an option for severe asthma in people 12 years and over, when treatment with high-dose inhaled corticosteroids plus another maintenance treatment has not worked well enough.

The EAG notes that the company's proposal that 12 SQ-HDM is intended to be an addition to the formulary, rather than a replacement for an existing drug, conflicts with several aspects of the pivotal trials' methods, including i) the changing of existing treatment before randomisation in the MT-04 (asthma) trial, ii) the prohibition of many treatments used as part of standard care, and iii) the use of fixed protocol driven ICS reduction/withdrawal periods in MT-04. These issues are discussed further in section 3.2.1.

Allergic rhinitis population

Pharmacological treatment for allergic rhinitis may include antihistamines, topical nasal corticosteroids and leukotriene receptor antagonists. For more severe allergic rhinitis, which does not respond to usual therapy, immunotherapy may be considered. The company submission refers to the current British Society of Allergy and Clinical Immunology (BSACI) guidelines (see Figure 2 of the CS), which states, like the GINA guidance for asthma, that a stepwise approach to treatment should be undertaken. The company recommends that 12 SQ-HDM be added as an additional step in the management of allergic rhinitis.

2.3 Critique of company's definition of decision problem

Table 1 of the CS presents the decision problem, including a description of the final scope issued by NICE, the decision problem addressed within the submission and the rationale for any differences between the two. This information, along with the EAG comments on the rationale provided, is presented in Table 4.

EAG comments

Population

The EAG notes that the populations recruited to the allergic asthma trials were restricted by asthma control questionnaire (ACQ) score, which would not be expected to happen in the NHS as such restrictions are not part of the marketing authorisation (section 3.2.1).

Comparators

The NICE scope did not expand on the comparator details of 'Established clinical management' (ECM). The EAG notes that the use of the following concomitant therapies was prohibited in both the 12 SQ-HDM pivotal trials (i.e. the MT-04 'MITRA' allergic asthma trial and the MT-06 allergic rhinitis trial): glucocorticoids, nedocromil/cromolyn sodium, leukotriene antagonists, synthase inhibitors, LABA, LAMA (long-acting muscarinic antagonists), MAOIs (monoamine oxidase inhibitors), pizotifene, theophylline, beta blockers, tricyclic antidepressants or antipsychotic with antihistaminic effects. Also, antihistamines other than desloratadine and azelastine were prohibited in trial MT-06. The EAG's clinical adviser considered most of these, except for anti-depressants and beta blockers, to be widely used options in the NHS for treating adolescent patients with moderate-to-severe allergic rhinitis and allergic asthma not well-controlled by inhaled corticosteroids. Given the stepwise approach to treatment recommended in the GINA guidelines, the EAG considers that patients in the 12 SQ-HDM pivotal trials received both lower levels of standard of care and had much less flexibility in terms of treatment management than would be seen in patients in NHS practice.

Outcomes

For AR, the NICE scope lists complications of AR (such as sinusitis or middle ear infections) as a relevant outcome but these were not reported in the CS. Following a clarification question on this, the company implied that these outcomes were only reported in the trials as treatment related adverse events (TRAEs) and that neither sinusitis nor middle ear infections were identified as common TRAEs in the MT-06, P001, and TO-203-32 trials. The EAG notes that these events are more likely to be viewed by patients as being disease symptoms, rather than TRAEs, and that they are important outcomes to evaluate and discuss in the submission. The CS also did not report data on lung function outcomes, which are listed in the scope; the EAG therefore sought lung function data from the MT-04 clinical study report (section 3.2.2.2).

For the AA+AR population the EAG considers the outcome *time to first moderate or severe asthma exacerbation after ICS reduction* to be restrictive in the way it was evaluated in the asthma trials. In practice not all patients would have their ICS dose reduced (especially so for the placebo/supportive care) but rather managed in a stepwise approach based on GINA guidance. The results for this outcome therefore have limited applicability to a clinical setting. Also, severity of rhinitis symptoms and complications of allergic rhinitis are listed as outcomes though they do not appear to have been evaluated in the AA+AR trials.

Table 4 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People aged 18 to 65 years with house dust mite sensitisation with persistent moderate-to-severe house dust mite allergic rhinitis despite use of symptom-relieving medication, or allergic asthma not well-controlled by inhaled corticosteroids and associated with mild-to-severe allergic rhinitis. People aged 12 to 17 years with house dust mite sensitisation with persistent moderate-to-severe house dust mite allergic rhinitis despite use of symptom-relieving medication	As per NICE final scope	N/A	The EAG notes that the populations recruited to the allergic asthma trials were restricted by ACQ score which would not happen in the NHS (section 3.2.1).
Intervention	SQ-HDM SLIT as an add-on to standard therapy	12 SQ-HDM	Intervention aligned with NICE final scope	Some of the company's observational studies were not based on 12 SQ-HDM, but on other types of immunotherapy (section 3.2.3).
Comparator(s)	Established clinical management (ECM) without SQ-HDM SLIT	SOC AA+AR SOC AR	Comparator aligned with NICE final scope. Established clinical management efficacy is represented by the placebo arms of the clinical trials.	The EAG notes that the use of numerous concomitant therapies, which are usually available in the NHS, were prohibited in the 12 SQ-HDM trials and considers that trial ECM is a poor representation of NHS ECM. This is an important limitation of the evidence-base (section 3.2.1).
Outcomes	For house dust mite sensitisation with persistent moderate-to-severe house dust mite allergic rhinitis despite use of symptom-relieving medications, the outcome measures to be considered include: Severity of rhinitis symptoms, Complications of allergic rhinitis (such as sinusitis or middle ear infections), Rhinitis medication use, Adverse effects of treatment, Health-related quality of life. For house dust mite sensitisation with allergic asthma that is not well-controlled by inhaled corticosteroids and associated with mild-to-severe allergic rhinitis, the outcome measures include: Use of ICS, Use of rescue medication, Time to first moderate or severe asthma exacerbation after ICS reduction, Reduction	As per NICE final scope	N/A	The EAG considers the outcome *time to first moderate or severe asthma exacerbation after ICS reduction* to be restrictive and unrepresentative of NHS practice in the way it was evaluated in the asthma trials. In practice not all patients would have their ICS dose reduced (especially so for placebo/ECM) but rather managed using a stepwise approach based on GINA guidance. The EAG found complications of AR (such as sinusitis or middle ear infections) and lung function outcomes to be absent from the CS – data on these outcomes were therefore sought by the EAG.

	of the risk of an asthma exacerbation, Lung function, Severity of rhinitis symptoms, Complications of allergic rhinitis (such as sinusitis or middle ear infections), Adverse effects of treatment, Health-related quality of life, Overall survival.			For the AA+AR population, severity of rhinitis symptoms and complications of allergic rhinitis are listed as outcomes, although they do not appear to have been evaluated in the AA+AR trials.
Special considerations including issues related to equity or equality	None stated	Considerations related to access to specialist services for allergic respiratory disease patients	Despite the large burden of allergic respiratory disease (ARD) for both patients and the NHS, there is a lack of accessible and well-resourced specialist services for ARD patients. As the first dose of 12 SQ-HDM is administered in secondary care, this may be considered to represent a barrier to some patients for whom allergy services are less accessible	No comment.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted two systematic literature reviews (SLR); an original one in 2015, and an updated SLR in 2023 to identify any additional studies published. Details of the SLRs are reported in Appendix D of the CS. A non-systematic review was also conducted to identify real-world evidence on long-term efficacy.

3.1.1 Searches

The search strategies to identify randomised controlled trials (RCTs) of allergy immunotherapy for patients with HDM allergic rhinitis or HDM allergic asthma were included in Appendix A and B of a report by Initiate Consultancy Ltd.[17] Searches were carried out in January 2015 with an update search undertaken in March 2023.

Several weaknesses were identified with the search approach taken which may have affected optimal retrieval of all relevant RCTs. These are presented in Table 5.

Table 5 EAG appraisal of evidence identification

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	PARTLY	Some information about the searches and search strategies were missing from the submission. This was mostly provided in the company response to the clarification questions, however the search strategies for Embase and the Cochrane Library used for the original 2015 review were not supplied.
Were appropriate sources searched?	PARTLY	Published studies were sought from the key sources of healthcare literature –MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR). Several trial registers were searched to identify unpublished studies. However, the company did not carry out any supplementary searches of relevant conference proceedings. Limited searching for previous systematic reviews. As the search of Embase and MEDLNE was restricted to RCTs only, these searches may have missed relevant systematic reviews. Databases of systematic reviews such as Epistimonikos were not searched. The HTA database and the INAHTA database were not searched to inform the clinical effectiveness review. Both databases are key sources for identifying health technology assessments from national and international HTA agencies. Supplementary searching of individual HTA agency websites was not carried out.
Was the timespan of the searches appropriate?	YES	Database inception to 1st March 2023.
Were appropriate parts of the PICOS included in the search strategies?	YES	Population (HDM allergic rhinitis OR HDM allergic asthma) AND Intervention (allergy immunotherapy) AND Study design (RCTs).

Were appropriate search terms used?	PARTLY	Terms for the intervention included textword and subject headings for immunotherapy only. The brand name (Acarizax) and abbreviations (e.g. SQ HDM SLIT, 12 SQ HDM) for the intervention were missing from the search strategies.
Were any search restrictions applied appropriate?	PARTLY	Searches for the 2023 update were not limited by language, therefore studies in any language published from 2015 onwards would have been identified by the searches. However, it is unclear if the original 2015 searches were all limited to English language studies only. An English language limit was applied in MEDLINE however the strategies for Embase and the Cochrane Library were not supplied by the company therefore they could not be checked. A publication date limit of 2015 onwards was used in the 2023 update searches. This would not have identified studies with a publication year prior to 2015 but only available in the databases from 2015 onwards. An incorrect human limit in the search strategy for Embase was noted by the company in their response to the clarification questions. Therefore, the EAG could not be sure that animal studies were removed correctly from the Embase search.
Were any search filters used validated and referenced?	NO	Searches were restricted to RCTs in MEDLINE and Embase. However, the RCT search filter used in MEDLINE was not validated or referenced. The search filter used in Embase was not validated however the company did supply a reference to a search strategy designed to identify RCTs for a cirrhosis guideline. Therefore, it is possible that relevant RCTs could have been missed. Validated RCT search filters with clearly reported performance data for both MEDLINE and Embase are available and would have been more appropriate to use for this SLR to identify all relevant RCTs.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Searches for the non-systematic review of real-world evidence

The company carried out a non-systematic review of real-world evidence to identify any studies with long-term efficacy data for 12 SQ HDM. PubMed and two trial registers were searched, though the search strategies were missing from the original submission. Brief details on search methods were provided in the company response to the clarification questions, including a search strategy for PubMed. Search strategies were not provided for the two trial registers so could not be checked by the EAG.

The PubMed strategy combined terms for post-marketing or observational study designs with terms for 9 brand names for 12 SQ HDM or other company non-HDM allergy immunotherapy tablet (AIT) products (grazax, itulazax, ragwizax, acarizax, grastek, itulatek, ragwitek, miticure, and odactra). A date limit of 1st January 2006 to 15th July 2023 was applied.

As these searches were designed to identify studies for a non-systematic review, they were not fully comprehensive and therefore less likely to have retrieved all observational studies with efficacy data for 12 SQ HDM.

3.1.2 Inclusion criteria

The eligibility criteria for inclusion in the SLR on clinical efficacy are reported in Table 1 in Appendix D of the CS (ALK Clinical SLR). The eligibility criteria were broader than the decision problem addressed in the CS. In the original SLR, the patient population included children; this was amended in the updated SLR and included adult patients (18+) with HDM sensitisation AA or AR, or adolescents (12-17 years) or adults (18+) with HDM AR. There was no upper age limit (65 years as indicated in the NICE scope) and no restrictions to include "persistent moderate-to-severe house dust mite allergic rhinitis despite use of symptom-relieving medication, or allergic asthma not well-controlled by inhaled corticosteroids and associated with mid-to-severe allergic rhinitis" (defined in the NICE scope and license). The intervention of interest included all allergy immunotherapy, the comparators were any treatment, and a broad range of outcomes were listed for AA and AR studies. Only RCTs were eligible for inclusion, and only those reported in the English language were included. In the updated SLR, safety outcomes were also included.

Study selection was undertaken independently by two reviewers, and disagreements were resolved by a third independent reviewer. A list of excluded studies with reasons for exclusion from the updated SLR only is included in Appendix D. A total of 42 studies were identified from the original SLR, and an additional 36 studies from the updated SLR, although only 13 studies were included in the CS, as the other studies included immunotherapy other than 12 SQ-HDM. Of these, 5 were identified as pivotal phase 3 clinical trials that provided relevant clinical evidence in the CS.

3.1.3 Critique of data extraction

Data extraction methods were reported in Appendix D (ALK Clinical SLR section 2.3.2) of the CS. Data were extracted by a single reviewer and validated by a second reviewer, with any disagreements resolved through consensus with a third reviewer. A wide range of data were extracted on study-related characteristics, participant characteristics, intervention, comparator, outcomes, results, and conclusions.

Information on the design and methods of the 5 pivotal trials were presented in the CS (section B.2.3, B.2.4.1). Results from each individual trial and subgroup analysis were presented in section B.2.6 and B.2.7 of the CS. Only data relating to the efficacy assessment period was presented in the CS, and additional tables and figures in appendices were not attached. Access to all tables and figures listed, particularly data relating to the treatment maintenance period, were requested by the EAG and provided by the company at the clarification stage.

3.1.4 Quality assessment

A summary of the quality assessment of the 5 pivotal trials is presented in Table 45 of the CS, and a more detailed quality assessment is included in Appendix P in the CS. The company used the Cochrane Risk of Bias (RoB) tool to appraise the trials, and further re-appraised the studies using the more recent RoB 2 tool,[18] with results provided by the company at the clarification stage; the latter assessments contained only risk of bias judgements (i.e. without details or justifications of how judgements were arrived at).

Four trials (MT-04, MT-06, P001, TO-203-31) were rated as having low risk of bias on the randomisation process, and TO-203-32 was rated as unclear due to a lack of reporting on the allocation sequence. The EAG identified a notable imbalance in the numbers randomised in MT-06 (n=318 for 12 SQ-HDM vs n=338 for placebo), despite the use of block randomisation. Further details on the randomisation and allocation concealment processes were requested by the EAG at the clarification stage (question A15). However, the company's response did not resolve the uncertainty about whether allocation concealment methods were adequate for trials MT-04 and MT-06. Although the EAG has some concerns about these methods, these are allayed to some extent by the absence of any potentially important imbalances in key patient characteristics at baseline between treatment groups in these two trials.

Although the P001 trial had a higher rate of withdrawals and drop-outs in the 12 SQ-HDM group (n=179/740 withdrew) compared to the placebo group (n=128/741 withdrew) the company's assessment was that there were 'no unexpected imbalances in drop-outs between groups. The EAG considers this trial to be at high risk of bias due to missing outcome data given that this imbalance is largely driven by withdrawals due to adverse events (many more in the 12 SQ-HDM group) coupled with the use of only observed data in the efficacy analyses. The EAG also has some concerns about attrition bias for MT-04 and MT-06, where last observation carried forward was used to impute missing data for several outcomes. Other EAG concerns included amendments to outcome measures, and the lack of a formal assessment regarding the applicability of trial results to the NHS setting. Many applicability concerns were identified by the EAG, including the protocol mandated reduction in ICS in MT-04, restrictions on concomitant medications which are commonly used in practice, and the restriction to the timing of the primary efficacy assessment to be between October and March, outside the major pollen season, rather than year-round assessment. These are discussed further in (section 3.2.1).

A risk of bias assessment for the REACT (real-world) study was requested by the EAG and provided by the company using the ROBINS-I tool at the clarification stage, which is discussed further in section 3.2.3.

3.1.5 Evidence synthesis

Results from the two AA and AR trials (MT-04, TO-203-31), and the three AR trials (MT-06, P001, TO-203-32) were pooled in separate meta-analyses in the CS (section B.2.8). No indirect comparisons with other currently recommended treatments were provided by the company.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

The company included 5 phase 3 clinical trials: MT-04 and TO-203-31 for the AA+AR population, and MT-06, P001 and TO-203-32 for the AR population. MT-04, MT-06, P001 and TO-203-31 each consisted of 3 distinct trial periods, and TO-203-32 consisted of 2 trial periods (see Table 6 for further details on terminology used to describe trial periods in MT-04 and MT-06). The primary efficacy assessment period considered by the company was period 3 in the MT-04, MT-06 and TO-203-31 trials, and the last 8 weeks in the P001 and TO-203-32 trials.

The primary outcome in the AA+AR population was time to first moderate or severe asthma exacerbation during period 3 (ICS reduction/withdrawal), and in the AR population was rhinitis symptoms (total combined rhinitis score [TCRS]) during the efficacy assessment period (period 3 or last 8 weeks of treatment).

Table 6 Terminology used to describe the trial treatment periods in the two pivotal trials used in the cost-effectiveness analyses

	MT-04 (AA+AR)	**MT-06 (AR)**
Period 1	**Screening** (lasts 5-7 weeks, up to the point of randomisation)	**Baseline** (lasts 15 days, up to the point of randomisation)
Period 2	**Treatment maintenance** *Period 2A* lasts 7-12 months following randomisation, followed by *period 2B* which lasts 4 weeks.	**Treatment maintenance** Lasts 10 months following randomisation
Period 3	**ICS reduction and efficacy assessment** *Period 3A*: ICS 50% dose reduction for 3 months *Period 3B*: 100% ICS dose reduction* for 3 months	**Efficacy assessment** Lasts 2 months

* Only for participants who did not experience an asthma exacerbation during Period 3A

3.2.1 Critical appraisal of the 12 SQ-HDM trials

The EAG identified many important methodological limitations across the 12 SQ-HDM RCTs. These are summarised in Table 7 and mostly relate to issues which the EAG consider are likely to have important implications on the applicability of the trial results to the NHS setting. The EAG considers

that these issues mean that the trial results over-estimate the efficacy of 12 SQ-HDM, even though it does not appear to be very efficacious (sections 3.2.2.2 and 3.2.2.3).

Table 7 Key methodological issues across the randomised trials

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

A: Issue related to applicability to NHS setting issue, ACQ: Asthma control questionnaire, ICS: Inhaled Corticosteroids, LOCF: Last observation carried forward, NA: Not applicable, NE: Not evaluated by EAG, RoB: Risk of bias issue.
*Sensitivity analyses used multiple imputation, last observation carried forward, and longitudinal data analysis model

Use of concomitant treatments

The EAG's main concern with the applicability of the trial results to the NHS setting was the prohibition of concomitant medications which are available and frequently used in the NHS. This issue occurred in all five trials. Trial protocols only allowed a selection of concomitant treatments to be used. The extent of the restrictions in trials MT-04 and MT-06 (which were used in the cost-effectiveness modelling) are summarised in Table 8.

For MT-04, the EAG's clinical adviser thought that many patients may use LABA at baseline and the changing of steady pre-trial asthma treatment was not desirable, since it may result in a loss of control

of symptoms in the short-term. For MT-06, the EAG's adviser thought that NHS patients would require more treatment for conjunctivitis symptoms than is detailed in Table 8 and that for rhinitis symptoms NHS patients may need oral antihistamine tablets ***and*** a nasal corticosteroid spray. For both MT-04 and MT-06 the EAG's adviser considered that most of the prohibited treatments listed in Table 8 may be used in the NHS setting. In the AA+AR trials, concomitant treatment given in both the intervention and control arms was not adjusted by stepping treatment up or down according to required level of asthma control, to the extent expected to be seen in an NHS setting.

For trial MT-04, the EAG also has serious concerns about the applicability (to NHS practice) of the use of trial protocol-mandated inhaled corticosteroids reduction and withdrawal phases in period 3. This involved a 50% reduction (in period 3A), then withdrawal (in period 3B) of inhaled corticosteroids. These methods do not reflect NHS practice, particularly so for patients who were receiving placebo. The EAG considers that these methods are inadequate for evaluating the effect of 12 SQ-HDM on asthma exacerbations and that the exacerbations results data are unreliable.

Table 8 Concomitant treatment restrictions in the 12 SQ-HDM pivotal RCTs (MT-04 and MT-06)

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

Outcome assessment

In all trials, the primary efficacy assessment period was outside of the major pollen season. The EAG considers that this restricted approach to evaluating outcomes was especially problematic in trial MT-04 because asthma exacerbations were only evaluated outside of the major pollen season. The EAG's clinical adviser would have preferred to have seen efficacy data from timepoints including the pollen season.

The trial MT-04 protocol specified that, during period 3A (ICS reduction), patients who had more than three exacerbations should be discontinued from the trial, as should patients who had an exacerbation during period 3B (ICS withdrawal). This has the effect of restricting the collection of

outcome data in patients who are prone to having multiple exacerbations. Similarly, in AA+AR trial TO-203-31, patients had their trial treatment discontinued if they had an ACQ>1.5 at the start of efficacy assessment period.

Approach to handling missing outcome data

Although three trials (including MT-04 and MT-06) used appropriate methods (multiple imputation methods) to minimise the effect of possible bias arising from missing outcome data on primary outcomes, less robust methods (such as last observation carried forward (LOCF) or the use of only observed data) were used for secondary outcomes. Given both the proportion of participants who had missing data in the trials (Table 9), and the imbalances across treatment groups in some trials in the number withdrawing due to adverse events, the EAG considers that most outcomes for trials MT-04 and P001 are at high risk of bias due to missing outcome data.

Table 9 Participants with missing outcome data across the 12 SQ HDM RCTs

	AR trials						AA trials			
	MT-06		P001		TO-203-32		MT-04		TO-203-31	
	12 SQ	Pla	12 SQ	Pla	12 SQ	Pla	12 SQ	Pla	12 SQ	Pla
N randomised	318	338	741	741	314	319	282	277	276[a]	274[a]
N missing during period 2	NA	NA	NA	NA	NA	NA	34	20	38[b]	28[b]
N entered period 3	NA	NA	NA	NA	NA	NA	248	257	238	246
N missing during period 3	NA	NA	NA	NA	NA	NA	43	48	11	9
Total N (%) with missing data	34 (11)	42 (12)	179 (24)	128 (17)	33 (11)	34 (11)	77 (27)	68 (25)	49 (18)	37 (14)

[a]Excluding duplicate enrolment (n=1): 1 subject was enrolled and assigned to both placebo and 12 SQ groups. [b]Including those with ACQ>1.5 at first day of period 3 (12 SQ: n=8; placebo: n=6). N Number of participants, NA Not available

Selection of trial population – trial eligibility criteria

In MT-04 trial (AR+AA population) one of the inclusion criteria was having an ACQ score of between 1.0 and 1.5 at randomisation. The study's protocol states that "*Some subjects use LABA instead of SABA. In such cases the subject's ACQ score may be artificially low and result in the subject failing to meet the criterion of having an ACQ of at least 1.0. In order to have the ACQ filled in as intended, LABA should be switched to SABA before scoring the ACQ and hence the ACQ may be deferred to visit 2 (the visit before randomisation)".* An important implication of this is that some patients with well-controlled asthma using a LABA, will have had to significantly alter their usual treatment in order to meet the criterion on asthma not being well controlled. Given that these patients already had well-controlled asthma before participating in the trial, it may be easier to treat them with SQ-HDM SLIT than it would be to treat the population seen in the NHS, whose asthma would not be well-controlled taking usual care treatments. At the other end of the ACQ score range used for this eligibility criterion, the exclusion of patients with an ACQ>1.5 would also not be reflective of NHS

practice (as they would still be eligible to receive SQ-HDM SLIT, based on its marketing authorisation) and patients with higher ACQ scores might be harder to treat.

Both the AA+AR trials, and the TO-203-32 AR trial, only randomised patients who had been adequately compliant with completing the trial electronic diary systems in the run up to the randomisation visit; the compliance rate must have been ≥ 80%. These patients may be different to patients who were excluded for inadequate diary compliance (e.g. they may also be more compliant with taking the trial treatments), which raises concerns about the applicability of the populations in these three trials.

Different definitions of the primary outcome measure in trial MT-04

The company did not define the primary outcome consistently in trial MT-04. In the two earliest versions (September 2011 and October 2011) of the trial's entry on the clinicaltrials.gov trial registry website (reference NCT01433523), the company stated that the primary outcome was the reduction of risk of an asthma exacerbation, defined as the number of exacerbations in the SQ-HDM SLIT group compared to the number of exacerbations in the placebo group. However, in later clinicaltrials.gov entries, and in the trial's protocol (dated 12 April 2010), the company identified the primary outcome as being time to first (moderate or severe) asthma exacerbation measured in days from the start of period 3 (ICS reduction/withdrawal). The significance and implications of these definition differences is unclear, but they are a concern, given that this is the primary outcome for trial MT-04.

3.2.2 Results of the 12 SQ-HDM trials

Given the methodological issues associated with trial results reported in the efficacy assessment trial periods (outlined in section 3.2.1), data from period 2 (or the period prior to the efficacy assessment period) for all five pivotal trials (AA+AR and AR trials) were requested from the company at the clarification stage, so that results across periods could be compared. These results were provided in the company's response to question A5. Results are summarised in Table 10 and Table 12. Where only raw means and standard deviations (SD) were provided by the company, the EAG calculated the mean difference (calculated as the mean of 12 SQ-HDM minus the mean of placebo) and 95% confidence interval (CI) using Welch's two-sample t-test in R ("BSDA" package).[19]

3.2.2.1 Baseline characteristics

Overall, few differences in baseline characteristics were observed between treatment groups across the five trials (CS Tables 15-16, 20-21, 26-27, 31-32, 35-36). The average age ranged from 27 (TO-203-32) to 38 years (TO-203-31), although P001 included adolescents (12 to <18 years: n=189) as well as adults (≥18 years: n=1293). TO-203-31 reported more males in the placebo group (54.4%) compared to the 12 SQ-HDM group (47.1%) (CS Table 31), whereas a similar proportion was observed between treatment groups in the other four trials. The distribution of participants with mono-

sensitisation or poly-sensitisation was also similar across treatment groups, with the majority of participants being poly-sensitised, although TO-203-31 reported a higher proportion of participants who were mono-sensitised in the placebo group (17.2%) compared to the 12 SQ-HDM group (11.2%) at baseline (CS Table 32). There were no differences in asthma or rhinitis symptoms, lung function, or disease duration between treatment groups across all five trials, where reported, although the average length of disease varied between trials (from 8 to 9 years in MT-06 to 19 years in P001). Smoking history and quality of life were additionally reported at baseline in the MT-04 and MT-06 trials, with no differences between treatment groups.

3.2.2.2 Results of the AA+AR trials

Asthma exacerbations and symptoms

The two AA and AR trials (MT-04 and TO-203-31) reported time to first moderate or severe asthma exacerbation during period 3 as the primary outcome. The MT-04 trial reported a risk reduction of 31% (full analysis set with multiple imputation, calculated as 1 minus the hazard ratio [HR]: 0.69 [0.50, 0.96]) in the 12 SQ-HDM group compared to the placebo group (CS Table 46).

The TO-203-31 trial reported no significant differences (CS Table 52), which may be due to differences in Japanese guidelines compared to the GINA guidelines (resulting in a high proportion of patients with well-controlled asthma according to the GINA at baseline). When a subgroup analysis was performed by including only subjects who required SABA at baseline (to better align with GINA guidelines), a similar risk reduction was found in the 12 SQ-HDM group compared to placebo (HR: 0.71 [0.49, 1.02]) (CS page 124).

Both trials also recorded asthma symptoms usinacross both period 2 and period 3 using full analysis set (FAS) with available observed data (complete cases) (see Table 10). Across both trials, larger mean differences were observed between the groups during period 3 compared to period 2, although the only statistically significant finding came from the TO-203-31 trial during period 3, which showed that the 12 SQ-HDM group scored on average 0.11, 95% CI (0.01, 0.20), points higher on the ACQ compared to the placebo group. This was not considered clinically meaningful, given the minimal important difference (MID) of 0.5 reported in the literature.[20] As only complete cases were used, different numbers of patients were included in each analysis; caution is therefore needed when interpreting and comparing findings from period 2 and period 3, particularly in period 3 where a substantial proportion of patients had missing data, which is unlikely to be missing at random due to reasons such as adverse events (AEs), asthma exacerbation, or lack of efficacy.

The MT-04 trial also reported data on the level of asthma control according to the GINA guidelines, where patients were categorised into well-controlled, partially controlled, or uncontrolled asthma (Table 11). A comparison of data from the last visit in periods 2 (visit 8) and 3 (visit 13) found that a

higher proportion of patients in the 12 SQ-HDM group were classified as well-controlled in period 3 (31.5%) compared to period 2 (14.8%). However, similar improvement was also seen in the placebo group between the two periods (visit 8: 16%; visit 13: 26%). The proportion of patients with uncontrolled asthma changed from 26.4% and 22.3% in period 2 (visit 8) to 19.2% and 21.2% in period 3 (visit 13) in the 12 SQ-HDM and placebo group, respectively. Again, these findings should be interpreted with caution as only a complete case analysis was used, therefore the total number of patients included at each visit differed and the results may be biased (sections 3.1.4 and 3.2.1).

Health-related quality of life

Both trials assessed quality of life (QoL) (Table 10): MT-04 used the asthma quality of life questionnaire (AQLQ), and TO-203-31 used the asthma health questionnaire-Japan (AHQ-Japan). None of the findings were statistically significant or clinically meaningful (less than the MID of 0.5).[21]

Lung Function

Although listed as an outcome in NICE's scope, the CS did not report lung function results data. The EAG examined the MT-04 clinical study report (CSR) and found that no statistically significant differences, when comparing 12 SQ-HDM with placebo, were evident for PEF (peak expiratory flow) and FEV_1 (forced expiratory volume in 1 second); see Figure 1, taken from the MT-04 CSR.

Figure 1 Mean change from baseline in percentage predicted FEV_1 in trial MT-04 (from CSR Panel 9-28)

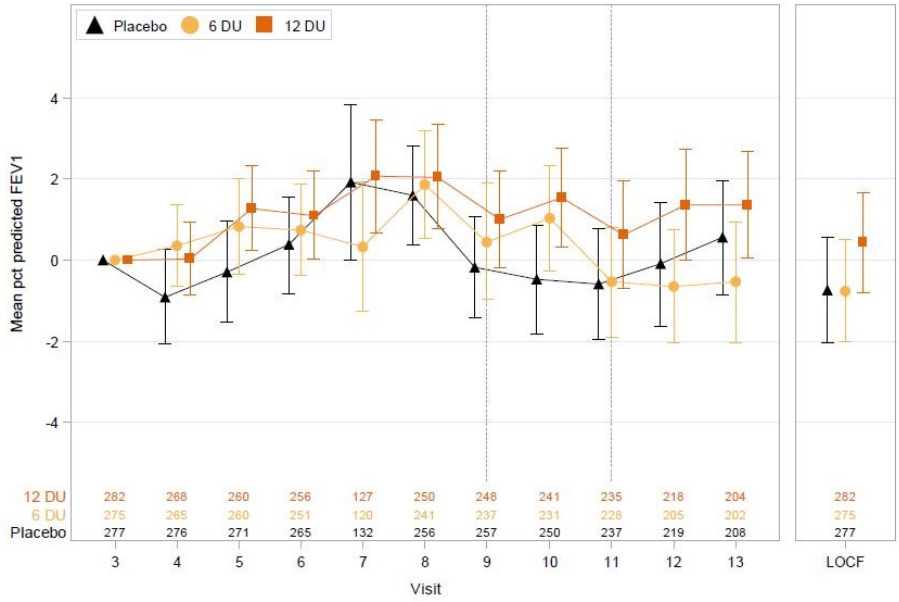


Table 10 AA+AR trials - comparison of asthma symptoms and quality of life outcomes between period 2 and period 3

Asthma population		Period 2						Period 3		
		12 SQ-HDM	*Placebo*	*Mean difference (95% CI)*	*12 SQ-HDM*	*Placebo*	*Mean difference (95% CI)*	*12 SQ-HDM*	*Placebo*	*Mean difference (95% CI)*
MT-04		**Visit 6**			**Visit 8**			**Visit 13**		
ACQ (FAS)	**MID**	N=256	N=265		N=250	N=256		N=204	N=208	
Mean score (SD)	0.5[20]	1.00 (0.70)	1.00 (0.66)	0.00 (-0.12, 0.12)a	0.99 (0.66)	0.95 (0.66)	0.04 (-0.08, 0.16)a	0.75 (0.62)	0.87 (0.68)	-0.12 (-0.25, 0.01)a
Change from baseline (SD)		-0.22 (0.68)	-0.23 (0.63)	0.01 (-0.10, 0.12)a	-0.24 (0.65)	-0.28 (0.63)	0.04 (-0.07, 0.15)a	-0.47 (0.60)	-0.36 (0.67)	-0,11 (-0.23, 0.01)a
AQLQ (FAS)										
Mean score (SD)	0.5[21]	5.88 (0.84)	5.88 (0.81)	0.00 (-0.14, 0.14)a	6.02 (0.73)	5.91 (0.82)	0.11 (-0.03, 0.25)a	6.26 (0.71)	6.14 (0.76)b	0.12 (-0.02, 0.26)a
Change from baseline (SD)		0.40 (0.74)	0.33 (0.72)	0.07 (-0.06, 0.20)a	0.52 (0.77)	0.38 (0.71)	0.14 (0.01, 0.27)a	0.75 (0.89)	0.59 (0.78)b	0.16 (-0.00, 0.32)a
TO-203-31		**Visit 10**			**Visit 17**			**Visit 24**		
ACQ (FAS)	**MID**	N=257	N=267		N=249	N=256		N=123	N=127	
Mean score (SD)	0.5[20]	0.94 (0.52)	0.92 (0.56)	0.01 (-0.09, 0.10)	0.85 (0.47)	0.81 (0.53)	0.03 (-0.05, 0.11)	0.62 (0.44)	0.50 (0.38)	0.11 (0.01, 0.20)
AHQ-Japan (FAS), M (SD)	NR				NR					
Asthmatic symptoms		0.67 (0.51)	0.69 (0.54)	-0.02 (-0.11, 0.07)a				0.37 (0.34)	0.36 (0.36)	0.01 (-0.08, 0.10)a
Emotions		0.33 (0.41)	0.32 (0.44)	0.01 (-0.06, 0.08)a				0.17 (0.28)	0.17 (0.39)	0.00 (-0.08, 0.08)a
Daily Activity		0.25 (0.44)	0.29 (0.51)	-0.04 (-0.12, 0.04)a				0.09 (0.23)	0.14 (0.38)	-0.05 (-0.13, 0.03)a
Factors which worsened symptoms		0.61 (0.58)	0.59 (0.58)	0.02 (-0.08, 0.12)a				0.28 (0.39)	0.23 (0.34)	0.05 (-0.04, 0.14)a
Social activity		0.28 (0.41)	0.29 (0.49)	-0.01 (-0.09, 0.07)a				0.17 (0.34)	0.18 (0.45)	-0.01 (-0.11, 0.09)a

Asthma population		Period 2						Period 3		
		12 SQ-HDM	*Placebo*	*Mean difference (95% CI)*	*12 SQ-HDM*	*Placebo*	*Mean difference (95% CI)*	*12 SQ-HDM*	*Placebo*	*Mean difference (95% CI)*
Economic		0.57 (0.80)	0.55 (0.88)	0.02 (-0.12, 0.16)a				0.46 (0.82)	0.28 (0.58)	0.18 (0.00, 0.36)+

ACQ=asthma control questionnaire; AHQ=asthma health questionnaire; AQLQ=asthma quality of life questionnaire; CI=confidence interval; FAS=full analysis set; MID=minimal important difference (smallest difference in score which the patient perceives as beneficial); NR=not reported; SD=standard deviation.

MT-04: visit 6=treatment maintenance (approximately 20 weeks after randomisation), visit 8=treatment maintenance/start of period 2B, visit 13=end of trial; TO-203-31: visit 10=ICS maintenance period (approximately 24 weeks from study treatment), visit 17=ICS maintenance period (final observation period before ICS reduction), visit 24=completion of study treatment.

[a] Calculated by the EAG using Welch two sample t-test in R using the "BSDA" package,[19] using mean and SD provided; [b]n=209.

Sources: MT-04 Appendices Tables 3.14-3.15 (pages 865-870) and 3.17-3.18 (pages 890-894); TO-203-31 CSR and Appendices Tables 14.2.7.8 (pages 372-373) and 14.2.8.34 (pages 476-480).

Table 11 Comparison of asthma control (GINA) outcomes between period 1, 2 and 3

MT-04	Period 1		Period 2				Period 3					
	Visit 3 (Baseline)		Visit 6		Visit 8		Visit 9		Visit 11		Visit 13	
	12 SQ-HDM	*Placebo*	*12 SQ-HDM*	*Placebo*	*12 SQ-HDM*	*Placebo*	*12 SQ-HDM*	*Placebo*	*12 SQ-HDM*	*Placebo*	*12 SQ-HDM*	*Placebo*
GINA control (FAS)	n=282	n=277	n=256	n=265	n=250	n=256	n=247a	n=257	n=234a	n=237	n=203[a]	n=208
Controlled (%)[b]	0 (0.0%)	0 (0.0%)	40 (15.6%)	45 (17.0%)	37 (14.8%)	41 (16.0%)	41 (16.6%)	39 (15.2%)	55 (23.5%)	49 (20.7%)	64 (31.5%)	54 (26.0%)
Partially (%)[b]	200 (70.9%)	200 (72.2%)	141 (55.1%)	152 (57.4%)	147 (58.8%)	158 (61.7%)	149 (60.3%)	152 (59.1%)	124 (53.0%)	129 (54.4%)	100 (49.3%)	110 (52.9%)
Uncontrolled (%)[b]	82 (29.1%)	77 (27.8%)	75 (29.3%)	68 (25.7%)	66 (26.4%)	57 (22.3%)	57 (23.1%)	66 (25.7%)	55 (23.5%)	59 (24.9%)	39 (19.2%)	44 (21.2%)

FAS=full analysis set; NA=not applicable; visit 3 = randomisation; visit 6=treatment maintenance (approximately 20 weeks after randomisation), visit 8=treatment maintenance/start of period 2B, visit 9=ICS reduction/start of period 3A, visit 11=ICS withdrawal/start of period 3B, visit 13=end of trial.

[a]Does not include 1 participant with missing data, as reported in MT-04 additional appendices Table 8.1. [b]Percentage was calculated by the EAG from the total number of subjects with events (in contrast to results provided by the company, which calculated the percentage in FAS).
Source: MT-04 additional appendices Table 8.1 (pages 2-3).

3.2.2.3 Results of the AR trials

Rhinitis symptoms

The three AR trials (MT-06, P001, TO-203-32) recorded rhinitis symptoms using the TCRS (see Table 12 for more details).

The MT-06 reported TCRS across both period 2 (FAS using complete cases) and period 3 (FAS-multiple imputation: FAS-MI), and mean differences with 95% CI were provided by the company (calculated as the mean of placebo minus the mean of 12 SQ-HDM, but converted by the EAG as 12 SQ-HDM minus placebo for consistency with other results). Statistically significant mean differences between the groups were observed during period 2 (visit 5: -1.41 [-2.14, -0.68]; visit 6: -1.22 [-1.99, -0.46]) and period 3 (visit 7-8: -1.09 [-1.84, -0.35]), which suggest that the placebo group reported worse symptoms on average compared to the 12 SQ-HDM group at all three visits. However, the number of patients included in period 2 and period 3 differed due to the use of complete cases in period 2 and FAS-MI in period 3. The period 3 results therefore have better internal validity than the period 2 results. The World Allergy Organisation has suggested that the MID should be at least 20% improvement between the active and placebo group.[22] These effect sizes from both period 2 and 3 were less than 20% of the relative difference from placebo, and therefore are not considered clinically meaningful.

The TO-203-32 trial (using complete cases) also showed significant mean differences on the TCRS between the two groups during the efficacy assessment period (visit 10-12: -0.80 [-1.30, -0.30]) and at the previous visit (visit 9: -0.68 [-1.21, -0.15]). Like the MT-06 trial, these suggest the placebo group reported worse symptoms compared to the 12 SQ-HDM group, although only complete cases were used, which may lead to bias due to missing data. These differences were nevertheless smaller than the MID of 20% relative difference and therefore not considered clinically meaningful.

The P001 trial only reported TCRS averaged across visit 10 and 11 during the efficacy assessment period (period 3) using complete cases, with patients in the placebo group scoring significantly higher on the TCRS compared to the 12 SQ-HDM group (-0.82 [-1.24, -0.40]). However, this analysis only included complete cases, therefore results are likely to be biased due to the high rates of discontinuation (mainly from adverse events) in the trial; furthermore, the effect estimate did not exceed the MID (20% relative difference between active and placebo) and may therefore not be considered clinically meaningful. P001 performed subgroup analyses by age, as it included a sample of adolescents as well as adults. Using complete cases from the efficacy assessment period only, it reported a slightly larger difference on the TCRS in the adolescent subgroup (ages 12 to <18: -1.0 [-2.0, -0.1], 22.4% relative difference), which exceeded the threshold for MID, compared to the adult

subgroup (ages 18 to <50: -0.9 [-1.3, -0.4], 19.2% relative difference; 50 to <65: -0.4 [-1.5, 0.7], 12.3% relative difference), which did not exceed the threshold for MID (CS Figure 20).

Health-related quality of life

All three AR trials assessed health-related quality of life (analysed using complete cases) using different instruments: MT-06 and TO-203-32 used the rhinitis quality of life questionnaire (RQLQ) or the Japanese version (JRQLQ), and P001 used EuroQol Group's 5-dimension questionnaire visual analogue scale (EQ-5D VAS) (see Table 12). Similar results were reported across different visits in the MT-06 and TO-203-32 trials: in MT-06, the placebo group scored significantly higher on RQLQ during period 2 and 3 compared to the 12 SQ-HDM group (mean difference [95% CI]: period 2 visit 5: 0.27 [0.06, 0.48]; period 3 visit 7-8: 0.21 [0.02, 0.39]). This was below the previously reported MID of 0.5,[23] and therefore was not considered as clinically meaningful.

In TO-203-32, results were presented for each of the six domains of JRQLQ separately. Some statistically significant mean differences were found on daily life, sleep, body, and psycho-life domains; some differences were slightly larger at later visits (visit 12) compared to earlier visits (visit 8), whereas others were similar across visits, although the mean differences were generally small (0.1-0.2). The MID for the overall scale has been previously reported to be 8.2, or 0.5 for each item;[24] data for the overall scale or individual items were not reported, although, as mean differences for each domain were less than 0.5, the EAG did not consider these to be clinically meaningful. Lastly, for P001, although a larger mean difference was observed during the efficacy assessment period (visit 11: -0.70 [-2.70, 1.30]) compared to previous visits (visit 10: 0.00 [-2.04, 2.04]; visit 6: 0.20 [-1.20, 1.60]), none of the findings were statistically significant or clinically meaningful (using the previously reported MID of 6.5-8).[25, 26]

Complications of allergic rhinitis

The company's response to the EAG's first clarification question revealed that in the MT-06 trial, sinusitis was not reported as a complication of AR but as a treatment-emergent adverse event, occurring in 6 (2%) placebo patients, and 4 (1%) 12 SQ-HDM patients. In the P001 trial, sinusitis was reported as a specific adverse event in 27 (3.7%) of placebo patients, and 30 (4%) of 12 SQ-HDM patients. For the TO-203-32 trial, acute sinusitis was reported as a common adverse event in 18 (5.6%) of placebo patients, and 15 (4.8%) of 12 SQ-HDM patients. The EAG therefore concludes that there is currently no evidence available to support the proposition that 12 SQ-HDM can significantly reduce the incidence of sinusitis.

Table 12 AR trials - comparison of rhinitis symptoms and quality of life outcomes between period 2 and period 3

Rhinitis population		***12 SQ-HDM***	***Placebo***	***Mean difference (95% CI)***	***12 SQ-HDM***	***Placebo***	***Mean difference (95% CI)***	***12 SQ-HDM***	***Placebo***	***Mean difference (95% CI)***
MT-06		**Period 2**						**Period 3**		
		Visit 5 (complete cases)			**Visit 6 (complete cases)**			**Visit 7-8 (FAS-MI)**		
TCRS (FAS)	**MID**	N=279	N=303	-1.41 (-2.14, -0.68)a	N=281	N=295	-1.22 (-1.99, -0.46)a	N=318	N=338	-1.09 (-1.84, -0.35)a
Mean score (95% CI)	20% relative difference [22]	7.22 (6.71, 7.73)	8.63 (8.11, 9.15)		7.24 (6.71, 7.77)	8.46 (7.91, 9.02)		5.71 (5.40, 6.02)	6.81 (6.48, 7.13)	
Rhinitis DSS		3.56 (3.30, 3.83)	4.21 (3.95, 4.47)	-0.65 (-1.02, -0.27)a	3.62 (3.36, 3.88)	4.08 (3.81, 4.35)	-0.46 (-0.84, -0.09)a	2.84 (2.73, 2.96)	3.31 (3.20, 3.43)	-0.47 (-0.82, -0.11)a
Rhinitis DMS		3.65 (3.30, 4.00)	4.42 (4.05, 4.79)	-0.77 (-1.28, -0.25)a	3.62 (3.24, 4.01)	4.38 (3.97, 4.80)	-0.76 (-1.33, -0.20)a	2.32 (2.17, 2.48)	2.86 (2.68, 3.05)	-0.54 (-1.07, -0.01)a
RQLQ (FAS)[a]	0.5[23]	N=216	N=239	-0.27 (-0.48, -0.06)a	N=217	N=231	-0.20 (-0.40, 0.01)a	N=229	N=240	-0.21 (-0.39, -0.02)a
Mean score (95% CI)		1.50 (1.35, 1.65)	1.78 (1.63, 1.92)		1.50 (1.36, 1.64)	1.70 (1.55, 1.85)		1.41 (1.28, 1.54)b	1.61 (1.48, 1.75)b	
P001		**Period 3 (complete cases)**								
		Visit 6			**Visit 10-11 (averaged between visits)**					
TCRS (FAS)	**MID**	NR			*N=566*	*N=620*	-0.82 (-1.24, -0.40)[a]			
Mean score (SD)	20% relative difference [22]				*4.67* (3.55)	*5.49* (3.82)				
		Visit 6			**Visit 10**			**Visit 11**		
EQ-5D VAS (FAS)	6.9 (6.5-8)[25, 26]	N=648	N=705	0.20 (-1.20, 1.60)c	N=350	N=381	0.00 (-2.04, 2.04)c	N=392	N=378	-0.70 (-2.70, 1.30)c
Mean score (SD)		82.9 (12.96)	82.7 (13.36)		82.4 (14.18)	82.4 (13.93)		82.1 (13.92)	82.8 (14.28)	
TO-203-32		**Period 2 (complete cases)**								
		Visit 8			**Visit 9**			**Primary evaluation period (visit 10-12)**		

Rhinitis population		***12 SQ-HDM***	***Placebo***	***Mean difference (95% CI)***	***12 SQ-HDM***	***Placebo***	***Mean difference (95% CI)***	***12 SQ-HDM***	***Placebo***	***Mean difference (95% CI)***
TCRS (ITT)	**MID**	N=288	N=294	-0.32 (-0.88, 0.24)c	N=282	N=293	-0.68 (-1.21, -0.15)c	N=281	N=286	-0.80 (-1.30, -0.30)c
Mean score (SD)	20% relative difference [22]	6.06 (3.60)	6.38 (3.21)		4.98 (3.22)	5.66 (3.26)		4.73 (3.04)	5.53 (3.07)	
Rhinitis DSS		5.38 (2.63)	5.75 (2.36)	-0.37 (-0.78, 0.04)c	4.61 (2.62)	5.17 (2.56)	-0.56 (-0.98, -0.14)c	4.40 (2.58)	5.07 (2.42)	-0.67 (-1.08, -0.26)c
Rhinitis DMS		0.67 (1.67)	0.63 (1.55)	0.04 (-0.22, 0.30)c	0.37 (1.23)	0.49 (1.35)	-0.12 (-0.33, 0.09)c	0.34 (0.96)	0.46 (1.24)	-0.12 (-0.30, 0.06)c
JRQLQ (FAS), mean (SD)	**MID**	**Visit 8**			**Visit 10**			**Visit 12**		
	8.2 (0.5 per item) overall [24]	N=281	N=285		N=281	N=285		N=281	N=285	
Daily life		1.0 (0.9)	1.2 (1.0)	-0.20 (-0.36, -0.04)c	0.7 (0.8)	0.9 (0.9)	-0.20 (-0.34, -0.06)c	0.8 (0.9)	0.9 (0.9)	-0.10 (-0.25, 0.05)c
Outdoor		0.8 (0.9)	0.9 (1.0)	-0.10 (-0.26, 0.06)c	0.5 (0.8)	0.6 (0.9)	-0.10 (-0.24, 0.04)c	0.5 (0.8)	0.6 (0.8)	-0.10 (-0.23, 0.03)c
Social		0.7 (0.9)	0.8 (0.9)	-0.10 (-0.25, 0.05)c	0.5 (0.8)	0.6 (0.8)	-0.10 (-0.23, 0.03)c	0.5 (0.8)	0.6 (0.8)	-0.10 (-0.23, 0.03)c
Sleep		1.0 (1.2)	1.2 (1.1)	-0.20 (-0.39, -0.01)c	0.8 (1.0)	1.0 (1.0)	-0.20 (-0.37, -0.03)c	0.7 (1.0)	1.0 (1.0)	-0.30 (-0.47, -0.13)c
Body		1.1 (1.1)	1.3 (1.0)	-0.20 (-0.37, -0.03)c	0.9 (1.0)	1.0 (1.0)	-0.10 (-0.27, 0.07)c	0.8 (1.0)	1.0 (1.0)	-0.20 (-0.37, -0.03)c
Psycho-life		0.8 (1.0)	0.9 (0.9)	-0.10 (-0.26, 0.06)c	0.6 (0.8)	0.8 (0.9)	-0.20 (-0.34, -0.06)c	0.6 (0.8)	0.7 (0.8)	-0.10 (-0.23, 0.03)c

AS=allergy specific; CI=confidence interval; FAS=full analysis set; FAS-MI=full analysis set-multiple imputation; DMS=daily medication score; DSS=daily symptom score; EQ-5D VAS=EuroQol Group's 5-dimension questionnaire visual analogue scale; ITT=intent-to-treat; JRQLQ=Japanese allergic rhinitis standard quality of life questionnaire; MID=minimal important difference (smallest difference in score which the patient perceives as beneficial); SD=standard deviation; RQLQ=rhinitis quality of life questionnaire; TCRS=total combined rhinitis score.

MT-06: visit 5=treatment maintenance phase (approximately 24 weeks from randomisation), visit 6=treatment maintenance phase (approximately 34 weeks from randomisation), visit 7-8=efficacy assessment period to end of trial (last 8 weeks of treatment); P001: visit 6=treatment phase (week 4), visit 10=treatment phase (week 27-44), visit 11=treatment phase (week 35-52), visit 10-11=efficacy assessment period; TO-203-32: visit 8=treatment period (28 weeks of administration), visit 9=treatment period (36 weeks of administration), visit 10=treatment period/start of primary efficacy evaluation period (44 weeks of administration), visit 12=primary efficacy evaluation period (52 weeks of administration).

[a]Mean difference and 95% CI originally reported by the company as placebo-active, the EAG converted these to active-placebo for consistency with other results; [b]Results from complete cases; [c]Mean difference calculated by the EAG as active-placebo, 95% CI calculated using Welch two sample t-test in R using the "BSDA" package.[19]

Sources: MT-06 Appendices Tables 6.10-6.12 (pages 782-789), 6.17 (pages 797-799), 9.1.1 (page 864), 9.2.1 (page 868), 9.3.1 (page 870); P001 CSR and Appendices 14.2.3.7 (pages 280-284) and Table 14.2.1.3.1 (page 306); TO-203-32 CSR and Appendices Tables 14.2.4.1-14.2.4.3 (pages 243, 245, 247), 14.2.5.25 (pages 310-315).

3.2.3 Observational studies of 12 SQ-HDM

CARIOCA Study

The CARIOCA study[27] is a one-year longitudinal study conducted in France. The study's primary objective was to investigate the safety and tolerability of SQ-HDM, and its secondary objectives were to describe rhinitis and asthma symptoms at baseline and change over time. Of the 1526 patients enrolled, 1483 were included in the primary analysis, and 858 completed the study (at visit 4). The company reported findings from their secondary objectives in the CS, with the distribution of asthma control at baseline (visit 1) being 54% well controlled, 28% partially controlled, and 18% uncontrolled. The high proportion of patients with well controlled asthma at baseline suggest a population with milder disease than those specified in the NICE scope (moderate to severe). In the CS, the company further stated that asthma control improved to 81% well-controlled, 14% partially controlled, and 5% uncontrolled at the end of the study. However, these did not correspond with results reported in published references of the CARIOCA study. In the paper by Demoly et al., 2022,[27] levels of asthma control were only reported for subjects at baseline, not at the end of the study. The EAG identified a recent paper[28] which reported levels of asthma control at each visit although different levels of asthma control were reported at the end of the study compared to the CS (54% well controlled, 30% partially controlled, 16% uncontrolled), which suggest that contrary to the CS, levels of asthma control did not change substantially between baseline and end of study (see Table 13 for a comparison of results between different sources). The EAG could not verify results provided in the CS; all publications were conducted by researchers who are employees or received personal fees from the company (i.e. had conflict of interests), and the population included many patients with mild disease, therefore, results of this study may not be applicable to the NHS setting.

Table 13 Comparison of asthma control according to GINA among patients on 12 SQ-HDM in the CARIOCA study between different sources

	CS (pg36)		**Demoly 2022[27]**		**Jaffuel 2023[28]**	
	V1	**V4**	**V1**	**V4**	**V1**	**V4**
Total N	***NR***	***NR***	***494***	***NR***	***494***	***269***
Well-controlled, n (%)	NR (54%)	NR (81%)	266 (54%)	NR	266 (54%)	146 (54%)
Partly controlled, n (%)	NR (28%)	NR (14%)	138 (28%)		138 (28%)	81 (30%)
Uncontrolled, n (%)	NR (18%)	NR (5%)	90 (18%)		90 (18%)	42 (16%)

V1=start of study; V4=end of study (12 months after V1); NR=not reported.

Reiber et al. 2021

A longitudinal observational study on the safety and tolerability of SQ-HDM was conducted in Germany over 1 year.[29] Although the primary objective of this study was to investigate adverse

events, clinical symptoms were also collected at baseline and at the end of the study. A total of 1525 patients were analysed: 1096 with AR (without AA) and 429 with AA (of which 424 had AR and AA, and 5 AA only). The median treatment period was 301 days; all patients received SQ-HDM but were prescribed for different periods initially (30 or 90 tablets).

The level of asthma control at baseline was assessed as well-controlled in 37% of patients, partly controlled in 41%, and uncontrolled in 22%; at the last visit the levels were reported as being 78%, 15% and 6%, respectively. These data were based on results from 369 patients, although 429 asthma patients were recruited. No details were provided on how missing data were handled; it seems these patients were excluded from the analyses so the results are likely to be over-estimates. Data on safety and tolerability showed that 32% of patients experienced AEs, which is much lower than the rate reported in the pivotal trials. Despite this, the rate of discontinuation due to AEs was higher in this study (13%) compared to the pivotal trials (1-10%).

Patient eligibility for the study was stated as being based on the 12 SQ-HDM marketing authorisation i.e. for AA it was patients whose allergic asthma was not well-controlled by inhaled corticosteroids, yet 37% of patients had well-controlled asthma at baseline. Only 69% of the asthma subgroup had received inhaled corticosteroids in previous 12 months. The recruited population therefore did not appear to match that specified in the license or the NICE scope i.e., it appears that a cohort with milder disease was recruited compared to the population expected to receive treatment in the NHS. Two authors were also employees of the company, indicating a serious conflict of interests. Given this, and that this is an uncontrolled, unblinded study, there is also a high risk that performance bias (in how patients were cared for) and detection bias (in how outcomes were assessed) may have affected the results. In light of these important limitations, the results of this study should not be considered as being relevant or applicable to the NHS setting.

Sidenius et al. 2021

A study by Sidenius et al., 2021,[30] conducted in Denmark and Sweden recruited 198 patients: 115 (58%) had AR without asthma and 83 (42%) had both AR and AA; 84% of patients completed the study. The aim of the study was to evaluate safety and tolerability, with the symptoms and medication use outcomes being exploratory. Patients were followed up only twice after treatment initiation, at months 1 and 12. At baseline, 52% of patients had well-controlled asthma in the AA+AR subgroup, and 11% of the AR patients had no or mild symptoms. 21 (32%) patients achieved an improvement of asthma control of at least one step from visit 1 to visit 3, p=0.013. ICS and SABA use were reduced from visit 1 to visit 3 by 20% (p=0.013) and 23% (p=0.004), respectively. Two of the four authors are employees of the company (so have important conflict of interests). The small sample size, uncontrolled design, important author conflicts of interest, and the recruitment of so many patients

with well-controlled asthma mean the results of this study should not be considered as being reliable, nor applicable to the NHS setting.

The REACT study

The medium to long-term effectiveness assumptions used in the cost-effectiveness modelling in both the AA+AR and AR populations were based on results from the propensity score matched REACT study, which is a retrospective cohort study on the long-term effectiveness of allergen immunotherapy (AIT) over 9 years using health insurance data from Germany.[31] To be included in REACT, patients had to have AR with or without asthma. AR patients treated with AIT (n=46,024) were matched with a control group not treated with an AIT (n=46,024); 14,614 patients in each group had pre-existing asthma. Patients were retrospectively followed up for up to 9 years, though year 9 data were available only for 1846 patients per group. The primary outcome, as stated in the protocol, was the number of patients with AR prescriptions by each follow-up year and the number of prescriptions by AR drug class. Secondary outcomes were the number of patients with asthma prescriptions and the number of prescriptions by asthma drug class, the number of pre-existing asthma patients by asthma treatment step and with a change in asthma treatment step from pre-index to follow up year, and several outcomes on asthma exacerbations and worsening/improving of asthma. Analyses based on changes from the pre-index year to individual post-index years were also undertaken.

For the primary outcome, a statistically significantly larger proportion of AIT-treated patients, than control group patients, received at least one AR prescription during years 1–4; the proportions were very similar across groups for years 5-9. In the pre-existing asthma cohort, there were no significant differences between groups except for years 4, 5 and 6, where fewer AIT patients had asthma prescriptions. When comparisons were made with pre-index year data, both the AIT and control groups had reductions in AR prescriptions per subject across years, with effect sizes ranging from −0·14 to −0·65 and −0·16 to −0·52 for AIT-treated subjects and control subjects, respectively. For the pre-existing asthma cohort, the effect sizes ranged from −0·36 to −1·11 and −0·25 to −1·06 for AIT-treated subjects and control subjects, respectively. The AIT group had significantly greater likelihood of stepping down asthma treatment and a significantly greater reduction in severe asthma exacerbations.

In a clarification question (A12) the company was asked to appraise this study for risk of bias; the company stated that the study was judged to generally be of a low risk of bias and is therefore relevant to the submission. However, no details were provided to justify the domain and overall risk of bias judgements. The low risk of bias judgement presented by the company contradicts the study protocol which states that "*despite the planned matching, there still is a high risk of cofounding and bias occurring due to great heterogeneity*." As noted in the study's protocol, a further limitation of the study is that the "*databases do not provide data on symptoms, and much of the symptomatic*

medication use for allergic rhinitis is over the counter, i.e. without prescriptions. Consequently, only prescriptions are recorded and can be used as a proxy for asthma treatment steps and treatment effects".

Other limitations of the study relate to the population and interventions studied. Although the study included patients with allergic asthma, patients with non-allergic asthma or unspecified asthma were also included. Children were also included in the study, and patients only had to have a confirmed AR diagnosis before or during the retrospective study follow up period, i.e. not necessarily at the start.

More than half the patients had had no AR prescriptions in the pre-index year. The EAG's adviser stated that for AR of the severity she would plan to start HDM immunotherapy, all patients will have had regular prescribed treatment. Less than 20% of patients were taking an AIT for a house dust mite allergy (most were taking AITs for grass or tree allergies) so around 80% of AIT patients received SCIT treatment (i.e. subcutaneous delivery), with the remainder taking SLIT AITs. Differences in changes from pre-index year in AR prescriptions in the SLIT-tablet subgroup were less pronounced (compared to the full cohort results) with the effect appearing to plateau after year 2 (supplementary materials Figure S13).[31] SCIT treatments must be administrated at a medical office, so the level of medical attention given to the AIT group may have been greater than for the control group. Therefore, the populations and AIT interventions used in this study have limited applicability to those stated in the NICE scope. Furthermore, the study was funded by the company and some of the authors were company employees so there were important conflicts of interest to consider.

In summary, this study demonstrated a lack of significant effects for key outcomes and modest effects for other outcomes, which combined with the methodological issues identified by the EAG, raise concerns on the reliability of the results and applicability of this study to the NHS setting.

Marogna et al. 2010

A study on the long-term effectiveness of SLIT (though not 12 SQ-HDM) was conducted by an independent group of researchers.[32] This was a prospective study over 15 years which included patients with mono-sensitisation to HDM and allergic rhinitis lasting at least 2 years with or without asthma. No details were provided on the inclusion criteria in terms of the severity of rhinitis symptoms, and as the GINA guidelines did not exist at the start of this study, patients were enrolled if their asthma was episodic with normal FEV. Participants were assigned to a control group (n=21) or one of the three SLIT groups with varying treatment durations (3 years: n=19; 4 years: n=21; 5 years: n=17).

Assignment to the control or SLIT group depended on patients' preference, whereas among those receiving SLIT, the duration of treatment was assigned according to birth dates. A comparison of

baseline characteristics showed little difference in symptom scores between the groups, however, those receiving SLIT for 5 years had higher lung function compared to the other groups at baseline, and those receiving SLIT for 3 and 5 years had higher levels of nasal eosinophil counts (an indication of nasal inflammation for the diagnosis of allergic rhinitis) compared to the control group and those receiving SLIT for 4 years at baseline. Symptoms were recorded yearly between September and February, rather than year-round assessment, which the EAG has previously noted is also a limitation in the five pivotal trials.

The results showed that those who received SLIT for 3 or 4 years had a significant improvement in their symptoms compared to the control group from the first year, whereas for those who received SLIT for 5 years, improvement was only seen from the second year, although this may be due to the imbalance in baseline characteristics between the groups. The effectiveness of SLIT (defined as symptom score being less than 50% of baseline value) in the 3-year group persisted for an additional 6 years at the end of treatment, whereas for those who received SLIT for 4 or 5 years, the effect persisted for an additional 7 years, with the authors concluding that a 4-year course was the most optimal choice.

The symptoms score calculated in this study were different to the assessment used in the pivotal trials (i.e., TCRS), although the definition of clinical effectiveness as being below 50% of baseline scores is much higher than the MID of 20% relative difference as recommended by the World Allergy Organisation.[22] Methodological issues identified by the EAG which raise concerns about the applicability and reliability of this study include: the small sample size, use of quasi-randomisation to assign groups, use of SLIT-solution instead of 12 SQ-HDM, a lack of information on symptom severity in the included population, and the inclusion of only mono-sensitised patients.

3.2.4 Adverse events

The company performed safety analyses and reported AEs for the 12 SQ-HDM and placebo groups across all 5 pivotal trials (CS Tables 58-63). Safety analyses in the MT-04, MT-06, and TO-203-31 trials used the FAS datasets; P001 included all randomised subjects who received at least 1 dose; and TO-203-32 included all subjects who were randomised (see Table 14 for number of subjects with AEs across all trials). Adverse events were unsolicited (open-ended questioning without specifying individual AEs) in all trials apart from P001, which actively solicited AEs from subjects (collected specific AEs via structured questionnaire). AEs were assessed as mild, moderate or severe, and serious adverse event (SAE) was defined according to the ICH Harmonised Tripartite Guidelines E2A Step 5 as causing death, being life-threatening, requiring hospitalisation, persistent or significant disability or incapacity, congenital anomaly or birth defect, or was judged medically important. Details for AEs provided by the company are summarised below.

3.2.4.1 Prevalence, onset, and duration of AEs

The prevalence of AEs was high across all 5 trials, and those in the 12 SQ-HDM group reported more AEs (range: 67-96%) compared to the placebo group (range: 46-89%) (Table 14). More than half of AEs reported in the 12 SQ-HDM group were treatment related adverse events (TRAEs). TO-203-31 reported the largest number of subjects experiencing AEs among both the 12 SQ-HDM and placebo groups, while MT-06 reported the lowest. Some of the most common AEs in the 12 SQ-HDM group were: throat irritation (18-80%), oral pruritis (20-74%), ear pruritis (10-61%), oral discomfort (0.5-31%), and oedema mouth (0.3-24%). Although TO-203-31 had the highest rate of AEs overall, P001 showed the highest rate on specific AEs, in particular throat irritation (80%), oral pruritis (74%), and ear pruritis (61%), which may be due to the study actively soliciting specific AEs from subjects.

The median onset and duration of AEs differed between groups and the type of AEs experienced. The majority of AEs reported in the 12 SQ-HDM group had a median time to onset of 0-14 days, and in the placebo group this was 1-305 days. The majority of AEs reported were resolved between a median of 1-107 days in the 12 SQ-HDM group, and between a median of 1-184 days in the placebo group. The range was large for most of the AEs reported (from 1 day to over a year), suggesting high variability in time to first onset and resolution (median and range for commonly reported AEs can be found in Table 14).

3.2.4.2 SAEs and discontinuation

Most AEs reported across the trials were assessed as mild or moderate, with 1-7% of AEs considered severe in all trials apart from TO-203-32, where no AEs were considered severe. SAEs were generally low across the 5 trials, with the highest reported in the TO-203-32 trial (4%) and the placebo group of MT-04 (4%). No SAEs were reported in the 12 SQ-HDM group in the MT-06 trial, and 2% of subjects treated had SAEs in the MT-04, P001, and TO-203-32 trials. No deaths were reported across all trials, and one case of anaphylactic reaction was reported in MT-06 (12 SQ-HDM group) and TO-203-32 (placebo group). AEs led to a higher proportion of subjects receiving 12 SQ-HDM to discontinue from the trial in P001 (10%) and MT-04 (9%), compared to TO-203-31 (5%), MT-06 (4%), and TO-203-32 (1%), and a small proportion of subjects in the placebo group also discontinued due to AEs (2-3%) (see Table 14 for more details).

Table 14 Summary of adverse events across trials

	AA+AR				AR					
	MT-04		**TO-203-31**		**MT-06**		**P001**		**TO-203-32**	
	12 SQ-HDM	**Placebo**	**12 SQ-HDM**	**Placebo**	**12 SQ-HDM**	**Placebo**	**12 SQ-HDM**	**Placebo**	**12 SQ-HDM**	**Placebo**
N	***282***	***277***	***276***	***274***	***318***	***338***	***743***	***738***	***314***	***319***
All AEs	222 (79%)	174 (63%)	266 (96%)	243 (89%)[a]	213 (67%)	154 (46%)	676 (91%)	539 (73%)	284 (94%)	256 (80%)
All TRAEs	130 (46%)	48 (17%)	185 (67%)	72 (26%)	167 (53%)	50 (15%)	624 (84%)	301 (41%)	200 (64%)	54 (17%)
Severity										
Mild	181 (64%)	137 (49%)	175 (63%)	168 (61%)	184 (58%)	119 (35%)	361 (49%)b	281 (38%)b	254 (81%)	232 (73%)
Moderate	125 (44%)	92 (33%)	87 (32%)	73 (27%)	78 (25%)	56 (17%)	262 (35%)b	220 (30%)b	30 (10%)	24 (8%)
Severe	20 (7%)	14 (5%)	4 (1%)	2 (<1%)	7 (2%)	10 (3%)	48 (6%)b	36 (5%)b	0 (0%)	0 (0%)
Seriousness										
SAEs	7 (2%)	11 (4%)	10 (4%)	11 (4%)	0 (0%)	8 (2%)	11 (2%)	7 (1%)	5 (2%)	3 (<1%)
Non-SAE	221(78%)	173 (62%)	NR		213 (67%)	151 (45%)	NR		NR	
Discontinuation										
Yes	25 (9%)	8 (3%)	14 (5%)	7 (3%)	13 (4%)	7 (2%)	73 (10%)	18 (3%)[c]	4 (1%)	6 (2%)
No	213 (76%)	171 (62%)	NR		207 (65%)	151 (45%)	NR		NR	
Common TRAEs										
Throat irritation	27 (21%)	4 (8%)	33 (18%)	2 (3%)	47 (28%)	12 (24%)	498 (80%)	162 (54%)	37 (19%)	3 (6%)
First onset (days), median (range)	1 (1-348)	29 (1-210)	0 (0-125)	11.5 (7-16)	1 (1-244)	2 (1-267)	1 (1-223)	2 (1-134)	1 (0-17)	5 (0-28)
Resolution (days), median (range)	11 (1-275)	31 (3-146)	84 (1-526)	12 (4-20)	9 (1-360)	9 (1-377)	1 (1-370)	1 (1-280)	81 (1-379)	36 (1-169)
Oral pruritis	55 (42%)	8 (17%)	37 (20%)	5 (7%)	66 (40%)	8 (16%)	463 (74%)	105 (35%)	55 (28%)	4 (7%)
First onset (days), median (range)	1 (1-37)	1 (1-2)	4 (0-224)	14 (0-166)	1 (1-72)	1 (1-30)	1 (1-85)	2 (1-225)	8 (0-59)	0.5 (0-14)
Resolution (days), median (range)	6 (1-532)	10 (1-464)	57 (1-540)	15 (1-43)	6 (1-288)	3 (1-115)	1 (1-374)	1 (1-280)	71 (1-359)	13 (1-19)
Oedema mouth	28 (22%)	0 (%)	40 (22%)	3 (4%)	29 (17%)	1 (2%)	2 (0.3%)	0 (0%)	47 (24%)	0 (%)
First onset (days), median (range)	1.5 (1-229)	NA	14 (0-227)	154 (17-166)	2 (1-241)	3 (3-3)	NR		11 (0-58)	NA
Resolution (days), median (range)	19 (1-367)		38 (1-448)	7 (3-11)	27.5 (1-174)	3 (3-3)			68 (1-377)	

	AA+AR				AR					
	MT-04		TO-203-31		MT-06		P001		TO-203-32	
	12 SQ-HDM	Placebo	12 SQ-HDM	Placebo	12 SQ-HDM	Placebo	12 SQ-HDM	Placebo	12 SQ-HDM	Placebo
N	*282*	*277*	*276*	*274*	*318*	*338*	*743*	*738*	*314*	*319*
Ear pruritis	11 (8%)	2 (4%)	25 (14%)	1 (1%)	16 (10%)	1 (2%)	378 (61%)	84 (28%)	27 (14%)	1 (2%)
First onset (days), median (range)	1 (1-367)	36.5 (1-72)	5 (0-119)	305 (305-305)	1 (1-15)	1 (1-1)	1 (1-30)	4.5 (1-190)	6 (0-56)	14 (14-14)
Resolution (days), median (range)	6 (1-48)	9 (1-17)	107 (3-474)	184 (184-4184)	14 (1-222)	2 (1-3)	1 (1-375)	1 (1-313)	55 (3-370)	15 (15-15)
Oral discomfort	4 (1%)	2 (<1%)	57 (31%)	11 (15%)	9 (5%)	0 (0%)	4 (0.5%)	0 (0%)	31 (16%)	3 (6%)
First onset (days), median (range)	NR		7 (0-260)	0 (0-7)	1 (1-1)	NA	NR		8 (0-280)	7 (0-16)
Resolution (days), median (range)			53 (1-450)	25 (1-543)	1 (1-200)				84 (1-365)	1 (1-8)

AA=allergic asthma; AR=allergic rhinitis; AE=adverse event; NA=not applicable; NR=not reported; SAE=serious adverse event; TRAE=treatment related adverse event

[a]CS Table 62 reported different number of total AEs (n=246) compared to Appendices Table 14.3.1.16 (pg 705) (n=243); [b]Percentage calculated by the EAG from the total number of treated subjects; [c]CS Table 60 reported different number of discontinuation (n=19) compared to Appendices Table 10-2 (page 69) (n=18).

Sources: MT-04: CS (Table 58), Appendices Tables 6.8 (page 1069), 6.16 (page 1088), 6.18 (page 1101); MT-06: CS (Table 59), Appendices Tables 4.15 (page 731) and 4.17 (page 741); P001: CS (Table 60), CSR and Appendices Tables 12-10 (page 110), 12-12 (page 113), 14.3.2.1 (page 454), 14.3.2.3 (page 469); TO-203-31: CS (Table 62), CSR and Appendices Table 14.3.1.16 (page 705); TO-203-32: CS (Table 63), CSR and Appendices Table 14.3.1.16 (page 582).

3.3 Additional work on clinical effectiveness undertaken by the EAG

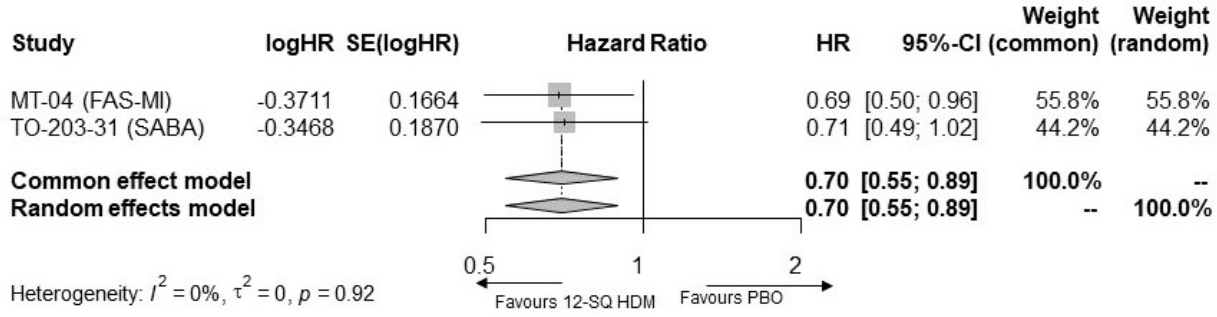
For primary outcomes the EAG performed additional meta-analyses using the FAS-MI population datasets, where available, as the meta-analyses presented in the CS (Figures 22 and 24) did not utilise the multiple imputation datasets. The EAG also wanted to explore to what extent results for other outcomes remained consistent if different datasets or timepoints were used (Table 10 and Table 12). The EAG meta-analyses were conducted using the *meta* package (version 6.5-0) [33] in R (Version 4.3.2). [34]

3.3.1 AA+AR trials

Analysis 1: Results on time to first asthma exacerbation in Period 3 pooling the MT-04 (FAS-MI population) and TO-203-31 (SABA subgroup) studies

The results of the EAG's analysis are presented in Figure 2. There was no evidence of statistical heterogeneity between the two trials (I^2=0%). The estimate for the pooled treatment effect for the EAG fixed-effect model (HR 0.70, 95% CI: 0.55 to 0.89) favours 12 SQ-HDM over placebo and is consistent with the results presented by the company (HR 0.68, 95% CI: 0.53 to 0.88; CS, Figure 22). However, for the reasons described in 3.2.1, the EAG considers these estimates, as well as those presented in the CS, to be biased in favour of 12 SQ-HDM, and to have limited applicability to the NHS context.

Figure 2 Meta-analysis showing the hazard ratio for time to first asthma exacerbation in the 12 SQ-HDM versus placebo AA+AR trials

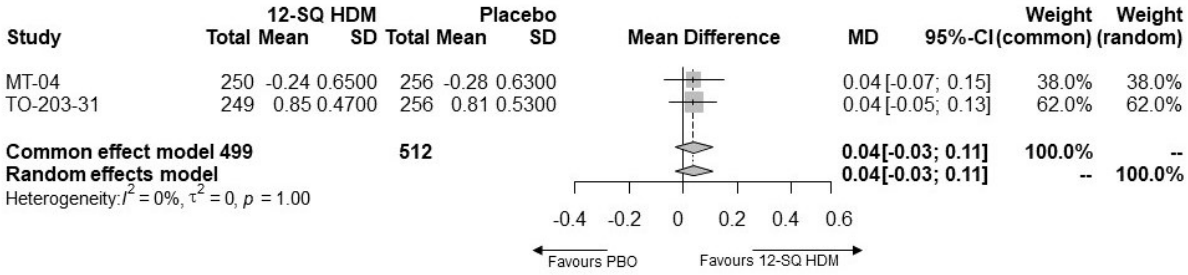


Analysis 2: Results on ACQ change from baseline in Period 2 pooling the MT-04 (FAS population) and TO-203-31 (FAS population) studies.

Given the EAG's concerns with the validity of the period 3 exacerbation data and given there were no time to asthma exacerbation data available for period 2, the EAG conducted a meta-analysis on change from baseline in ACQ to explore the effectiveness of 12 SQ-HDM compared to placebo

during period 2 (Figure 3). No statistical heterogeneity was observed between the two studies (I^2=0%). There was no statistically significant difference between the interventions, with the mean difference (0.04, 95% CI -0.03 to 0.11) also falling a long way short of the published minimal important difference of 0.5 for ACQ.[20]

Figure 3. Meta-analysis showing ACQ change from baseline in 12 SQ-HDM versus placebo in period 2



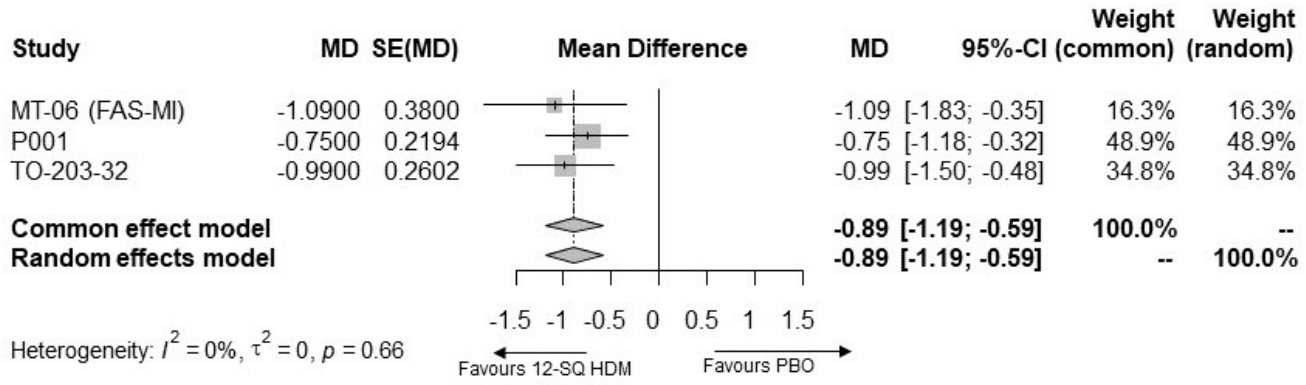
3.3.2 AR trials

Analysis 1: Results on the mean difference in average TCRS, measured in the last 8 weeks of treatment, pooling the MT-06 (FAS-MI population), TO-203-32 (FAS population) and P001 (FAS population) studies

In the CSR for MT-06, the company noted that although the efficacy evaluation period for the trial was referred to as the last 8 weeks of treatment, it was actually the duration between visits 7 and 8, which is approximately 8 weeks and could vary between patients.

The results of the EAG's analysis for TCRS reported in the AR trials are presented in Figure 4. There was no evidence of statistical heterogeneity between the three trials (I^2 = 0%). The estimate for the pooled treatment effect for the EAG fixed-effect model (MD -0.89, 95% CI: -1.19 to -0.59) favours 12 SQ-HDM over placebo and is consistent with the results presented by the company (MD -0.91, 95% CI: -1.21 to -0.61; CS, Figure 24). However, both the EAG and company results are not considered clinically meaningful, given that none of individual trials met the MID (20% relative difference between active and placebo).[22] These meta-analysis results may also be over-estimates, given that only observed data were available for trials P001 and TO-203-32 and given the imbalance in withdrawals in P001 (section 3.1.4).

Figure 4. Meta-analysis showing mean difference (MD) in average TCRS in 12 SQ-HDM versus placebo in AR patients



3.4 Conclusions of the clinical effectiveness section

The evidence presented on the efficacy and safety of 12 SQ-HDM was based on the results of five randomised trials: three focussed on patients with HDM allergic rhinitis and two focussed on patients with HDM allergic asthma. The design and methodological approaches used in the trials mean their results should not be considered as reliable estimates of the 12 SQ-HDM treatment effects expected to be seen in the NHS setting. Numerous limitations were identified which are likely to have biased results in favour of 12 SQ-HDM. Two methodological limitations were identified in all five trials: the prohibition of many treatments routinely used in the NHS and the use of primary efficacy assessment periods outside of the major pollen season. Other issues identified included (but were not limited to): the alteration of usual medication prior to randomisation; periods of protocol-mandated reductions, then complete withdrawal, of inhaled corticosteroids; the exclusion of patients based on symptom control scores who would nevertheless be eligible for 12 SQ-HDM treatment (in the NHS); and methods of handling missing outcome data which appeared likely to bias analyses.

The trial methods relating to efficacy on asthma exacerbations are considered to be too different from NHS practice to be of value in this appraisal. For the other outcomes, the results from the two allergic asthma trials showed that 12 SQ-HDM does not produce statistically significant improvements in measures of health-related quality of life and measures of lung function. A statistically significant improvement in the asthma control questionnaire score was seen in one of the two trials, although this effect was neither clinically significant, nor statistically significant at time points outside of the major pollen season. The efficacy of 12 SQ-HDM was more evident in improving symptoms in allergic rhinitis patients. Nevertheless, although trial results were statistically significant, they appear to be of borderline significance clinically, despite the likely impact of biases favouring the 12 SQ-HDM

groups. Moreover, no clinically significant improvements were seen in health-related quality of life measures and no effect was seen on complications of rhinitis (such as sinusitis).

A further limitation of the evidence-base is that the typical trial durations of around 12-18 months meant that the studies did not evaluate the effects of receiving three years of treatment (the immunotherapy treatment duration recommended in the ARIA guidelines), nor whether durable efficacy was seen after 12 SQ-HDM cessation. Although the company also submitted results of observational studies on HDM SLIT to support their efficacy claims, these studies also had important methodological limitations and most also included authors who were employed by the company (i.e. with serious conflicts of interest).

12 SQ-HDM appears to have an acceptable and largely manageable safety profile.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company completed an SLR of published cost-effectiveness studies in Spring 2023 and identified 15 studies of 484 potential records (507 with grey literature records included) that reported economic data for AR (n=9), AA (n=2), AR or AA (n=1), AR with or without AA (n=1), AA with or without AR (n=1), or patients with grass pollen or mite allergy (n=1). Of these, the company details for 5 studies (Table 64, p.168 of the CS) that conducted cost-utility analyses. The EAG notes that the studies selected by the company did not fully reflect all relevant cost-utility studies identified in the SLR.

4.1.1 Search strategy

The CS included the searches to identify studies on the cost-effectiveness of treatments for HDM allergic rhinitis or HDM allergic asthma. Full details of the SLR search strategy, study selection process, and results were presented by the company in Appendix G of a report by Initiate Consultancy Ltd.[35] Key databases such as MEDLINE and Embase were searched, together with smaller databases such as NHS EED.

4.1.2 Identified studies

Table 51 in the Appendix provides an overview and data extraction for the studies which the EAG deemed relevant for this decision problem (n=5). These studies are cost-utility analyses that evaluated SCIT, SLIT or both. The EAG acknowledges the limited relevance of the SCIT only studies for this decision problem. Note that this set of studies do not fully coincide with the summary list of studies provided by the company in their submission. The EAG disregarded Bjorstad et al., 2017,[36] as it

compared the costs of SLIT and SCIT for HDM in a cost-minimisation analysis, but considered the study by Bruggenjurgen et al., 2008[37] to be relevant as it conducted a cost-utility analysis.

Bruggenjurgen et al., 2008[37] uses a Markov model to estimate the cost-utility of SCIT in addition to symptomatic treatment (ST) compared with ST alone for treating children aged 6-12 years, adolescents aged 13-18 years, and adults aged 19-65 years with allergic rhinitis and allergic asthma in a German health care setting over a 15-year time horizon. This model involved annual cycles and model parameters were sourced from the literature. Health states were related to both AA and AR: mild allergic rhinitis, moderate to severe allergic rhinitis, moderate to severe allergic rhinitis and mild allergic asthma, moderate to severe allergic rhinitis and moderate to severe allergic asthma, no symptoms, and dead. SCIT in addition to ST was found to be cost-effective with an overall ICER of €19,787 per additional QALY, using a willingness-to-pay (WTP) of €50,000 per QALY gained.

The studies reported by Hahn-Pedersen et al., 2016[38] and Green et al., 2019[39] provided a cost-utility analyses of 12 SQ-HDM versus placebo in patients aged 18+ with AA and AR from Germany, Poland, Czech Republic, and Slovakia. Data from the treatment maintenance period of the MT-04[1, 2] trial was used, with the authors noting that the ICS reduction period was unlikely to represent clinical practice in the settings of interest. Green et al., 2017[40] conducted a cost-utility analysis in patients with HDM induced AR within a German setting, and utilised data from the MT-06[4, 5] trial to estimate cost and effectiveness parameters. All three studies utilised a simple decision-tree modelling approach to extrapolate costs and QALYs accrued within-trial over the modelled time horizons. All three studies were funded by the company and estimated the cost-effectiveness of 12 SQ-HDM versus pharmacotherapy over the time horizon (5 or 9 years). All three studies found 12 SQ-HDM to be more costly and more effective relative to pharmacotherapy. Final ICERs for AA+AR population ranged from €4,041 to €8,814 per QALY gained and of €7,519/QALY gained for the AR population, all considering the SQ-HDM to be cost-effective.

The study by Parra-Padilla et al., 2021[7] used a Markov model structure to conduct a cost-utility of SCIT plus ICS versus ICS alone for paediatric and adult patients with moderately persistent HDM induced AA with or without AR in Columbia, over a 10-year time horizon. The effectiveness of strategies was measured by reductions in medication doses, reflecting potential stepping down of therapies, asthma remission and exacerbation events, incorporating these in the model in 3-monthly cycles. All cost and effectiveness parameters were sourced using the literature. For the AA only population, SCIT plus ICS was more costly (US$828) and more effective (0.37 QALYs) relative to ICS alone, yielding an ICER of US$19,282 per QALY gained. For the AA+AR population, SCIT plus ICS was also more costly (US$673) and more effective (0.41 QALYs gained) relative to ICS alone, yielding an ICER of US$14,028 per additional QALY. SCIT plus ICS was deemed cost-effective for both populations.

4.1.3 Points for critique

The EAG found that the search terms used to limit to economic evaluations were restrictive. Validated economic evaluation search filters, which are more suited to the highly sensitive searching needed for identifying studies for a systematic review, would have been a more appropriate way of limiting retrieval to economic evaluations. In addition, sources of economic evaluations such as the INAHTA database and HTA agency websites were not searched, raising further concerns about the comprehensiveness of these searches. The EAG appraisal of the searches can be found in Table 52 in the Appendix.

The EAG notes that the company indicated in Appendix G of the CS that a quality assessment was completed for the studies that passed full text review using a tool based on the Drummond checklist[41], yet details on this assessment were not provided. The EAG is therefore unable to comment on the overall quality of studies included in the review. The EAG further identified that the search strategy excluded a search of relevant HTA appraisals for AR with or without AA for HDM outside of the UK.

The EAG identified two health technology assessments with cost-effectiveness evidence relevant to the decision problem of the current appraisal. In response to points for clarification, the company noted these assessments were ineligible for inclusion in the current review as there is no published, extractable information. The EAG finds this evidence relevant for the current appraisal and thus considers that the company's cost-effectiveness review was not fully comprehensive. The EAG provides a summary of each assessment here, including key points related to the submitted modelling structure and direction of cost and effectiveness results to the furthest extent possible.

The Pharmaceuticals Benefits Advisory Committee (PBAC) reviewed Actair® allergy immunotherapy relative to placebo in its sublingual form as a last line treatment for adolescent or adult patients (ages 12 and older) with HDM induced moderate to severe AR.[42] While details are not provided, two Markov models were developed, one for adults and one for children, to model annual cycles over a 9-year time horizon. While the model structure is not fully described, some of the health states included immunotherapy with symptomatic treatments, symptomatic treatments alone, and asthma (for the child model only). Model costs and outcomes (valued using rhinitis symptoms adjusted life years, not QALYs) were sourced from a European study (trial V057.07) and transition probabilities were sourced from literature estimates and Australian life tables. The submission assumed a constant treatment effect for all patients regardless of symptom severity. PBAC did not recommend Actair® for HDM induced moderate to severe AR due to insufficient evidence to support clinical and cost-effectiveness.

The National Centre for Pharmacoeconomics (NCPE) Ireland reviewed the company's submission for Acarizax® (12 SQ-HDM' brand name) allergy immunotherapy plus standard of care relative to

standard of care alone for adult patients with HDM induced AA not well controlled by inhaled corticosteroids and associated with mild to severe AR.[43] A *de novo* Markov model was developed over a lifetime time horizon, with health states in line with the current submission. Outcome data was sourced from the MT-04 trial.[1, 2] The NCPE did not recommend 12 SQ-HDM be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. Key issues raised in this submission included the placebo group in the MT-04 trial[1, 2] being unsuitable to adequately represent standard of care for clinical practice due to the reduction and withdrawal of ICS during the efficacy assessment period of the trial, and the lack of evidence on long-term effectiveness given treatment duration in MT-04[1, 2] was shorter than the standard course of allergy immunotherapy treatment (3 years).

From the review of cost-effectiveness studies performed by the EAG, it is clear that no consistent structure has been used to model HDM induced AR or AA+AR. The EAG notes that for asthma, the Parra-Padilla et al., 2021 study[7] explicitly reflected the potential stepping up/down of therapies and exacerbation events in their model structure. Given the fluctuation in asthma control over time, the EAG believes this to be the preferred structure for the AA+AR population as it reflects both the natural history of the disease and the patient care pathway as recommended by clinical guidance.

The EAG also notes that, except for the NCPE submission,[43] none of the identified cost-effectiveness studies modelled a lifetime time horizon (i.e., considering instead horizons between 5 and 15 years) given the lack of data on longer-term effectiveness. It is also unclear to the EAG how previous NICE technology appraisals (TAs) (e.g., TA278[16] in severe allergic asthma) were considered by the company in this submission. In the sections below, we elaborate on these issues.

Issue: The cost-effectiveness review was not fully comprehensive

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

In this section, the EAG summarises and critiques all elements submitted by the company to support their cost-effectiveness results. Areas of uncertainty and/or issues with potential impact on the estimates of cost-effectiveness are emphasised and revisited in section 6.

4.2.1 NICE reference case checklist

Table 15 summarises the EAG's assessment of whether the company's economic evaluation meets NICE's reference case criteria.

Table 15 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS is appropriate.
Perspective on costs	NHS and PSS	The CS is appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS is appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS is appropriate. The time horizon for both AA+AR and AR models was 69 years. While a long time horizon is appropriate, there are significant uncertainties regarding the longer-term effect assumptions which are likely to be higher with longer horizons.
Synthesis of evidence on health effects	Based on systematic review	No pooled effectiveness evidence was used to inform the economic models. For the AA+AR population, evidence from the MT-04 trial in a post-hoc analysis was used to inform the AA+AR model base case. For the AR population, evidence from the MT-06 trial in a post-hoc analysis was used to inform the AR model base case. MT-06 trial evidence in adults was generalised to adolescents (12+), implicitly assuming no difference in effectiveness exists between the two subpopulations.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The CS is partly appropriate. Treatment specific utilities were used for both AA+AR and AR populations. A health state utility approach was considered as scenario analysis. The AA+AR model considers utility scores estimated from the SF-36/SF-6D as no EQ-5D data was collected during MT-04. When applying the health state approach, EQ-5D data was mapped from AQLQ scores. The AR model considers utility scores estimated directly from EQ-5D.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS is appropriate. Utility data was collected from patients.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The CS is appropriate. For both populations a UK tariff was utilised.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The CS is appropriate.

Element of health technology assessment	Reference case	EAG comment on company's submission
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The CS is partly appropriate. The cost perspective is appropriate and the valuation of costs is consistent with the perspective. The selection of evidence to inform costing is not entirely consistent with the model structure. The EAG notes in the relevant sections where costs may not have been appropriately sourced and captured.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is appropriate.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company developed a *de novo* Markov model to assess the cost-effectiveness of 12 SQ-HDM compared with standard of care for treating HDM-induced AA and/or AR. Two separate models were developed.

The AR+AA model structure consisted of a three-state Markov model, encompassing three 'alive' health states: uncontrolled AA, partly controlled AA, and well controlled AA. The company states that these health states reflect the GINA guidelines definition of asthma control.[44] Patients were able to cycle within or between any of the included health states over a lifetime time horizon. A 'death' health state was also included to reflect patients that transition from any health state to death (all cause). Patients could also experience moderate or severe asthma exacerbation events at any time, with disutilities (section 4.2.7) and costs (section 4.2.8) associated with these. For this economic model, ACQ data from the MT-04 trial[1, 2] was mapped to GINA 2010 criteria[6] to classify asthma control in line with the modelled health states (sections 4.2.6 and 4.2.7). AR outcomes were not explicitly modelled for the AA+AR population.

The AR economic model considers 3 mutually exclusive health states relating to mild, medium, and severe AR, and the absorbing death health state. Patients may enter the AR model in the moderate or severe AR health states, being allowed to transition between any health state or stay in their current health state over a lifetime horizon.

Both model structures have annual cycles and a lifetime horizon. The base case estimates total lifetime costs and QALYs for each treatment arm and reports the incremental cost effectiveness ratio (ICER), accordingly. A half-cycle correction is also applied to each model cycle.

4.2.2.1 Points for critique

The EAG notes that of the cost-utility studies identified in the company's SLR (section 4.1.2), Hahn-Pedersen et al., 2016[38] and Green et al., 2019[39] present cost-effectiveness analyses in the AA+AR population using data from the MT-04 trial,[1, 2] and Green et al., 2017[40] presents a cost-effectiveness analysis in the AR population using data from the MT-06 trial.[4, 5] These models were sponsored by the company and all implemented the same simplified decision-tree structure. The EAG considers the structural approach taken by the company in the current submission more complex than what has previously been developed to support decision making. The CS did not provide a critique of the simplified model structure applied in previous models, nor did it provide justification for why a different model structure was commissioned for this submission. Following points for clarification, the company stated that the simplified decision tree structure did not adequately represent the burden of illness related to AR and to AA+AR, respectively. Their preferred approach was therefore to develop a model structure that reflects current clinical practice guidelines for AA and AR in the UK, as they considered these guidelines best capture the underlying biological process of disease. The EAG would like to acknowledge and highlight what has already been noted by Green et al., 2017.[40] While patients suffering from AR [and AA+AR] may commonly experience subtle and varying changes in their overall health, which would indeed be better captured using a more complex modelling approach that allows patients to transition across multiple health states over time, the data captured in MT-06[4, 5] may be insufficient to support accurate estimation of these changes in the overall burden of disease (section 4.2.6). The EAG believes that the same issue applies when using MT-04 evidence to inform the AA+AR model. Further, the EAG notes that to support these more complex model structures, the company had to rely solely on post-hoc analyses of the trial data with strong assumptions, which has several implications (section 4.2.6).

A key weakness of the AA+AR model structure is that it imperfectly reflects asthma management, which in clinical practice involves a stepwise approach to assessing, treating, and monitoring patients' asthma control. As mentioned in section 2.2, the GINA guidelines[6] recommend that treatment is stepped-up when symptoms persist and stepped-down when symptoms are well controlled for 3 months. For this to be captured appropriately, the model structure should explicitly account for asthma disease progression over treatment steps as, for example, in the Parra-Padilla et al., 2021[7] study (section 4.1.2).

The EAG further notes that model cycle lengths (annual) do not enable the model to accurately reflect potential fluctuations in disease severity throughout the year. In their original submission, the company claimed that a shorter cycle length was considered but not implemented given this would lead to unreliable long-term effectiveness, and the CS noted a key limitation of their results was that HRQoL and health resource use would likely be underrepresented. However, during points for

clarification, the company then indicated they did not feel that short-term fluctuations in disease would lead to meaningful differences in HRQoL or heath resource use. The company was unable to provide an updated model structure with 3-month cycle lengths as requested during the points for clarification by the EAG. The EAG is therefore unable to fairly assess the implications of using an annual versus a shorter model cycle, including the potential impact of mapping data from the final efficacy period (between October and March in both MT-04[1, 2] and MT-06[4, 5] trials) to an annual cycle length (section 3.2.1).

Issue: The AA+AR model structure may not be suitable for decision making as it does not reflect options to step up treatment, being fit only for last line of treatment.

Issue: A 1-year cycle length may not fully capture disease severity fluctuations.

4.2.3 Population

The submitted models provide cost effectiveness analyses of a patient population in line with the marketing authorisation for 12 SQ-HDM, which is licensed for the treatment of adults aged 18-65 years with HDM-induced AA not well controlled by ICS and associated with mild to severe HDM-induced AR, and for the treatment of adolescents and adults aged 12-65 years with moderate to severe HDM-induced AR despite the use of symptom-relieving medication. Each patient population was modelled independently in accordance with the NICE final scope.

Table 66 of the CS provides an overview of the baseline model characteristics, which are based on the MT-04[1, 2] and MT-06[4, 5] trials, used in each model, AA+AR and AR respectively.

4.2.3.1 Points for critique

The EAG would like to highlight that the company did not include any adolescent related evidence in the AR model. Clinical advice to the EAG suggests that there may be differences in treatment effectiveness for the adolescent versus adult AR subpopulations, due to hormonal changes. At clarification stage, the company showed evidence from P001[8, 9] and TO-203-32[10, 11] trials, where adults and adolescents both demonstrated a significant improvement in TCRS compared with placebo, regardless of age group, suggesting similar efficacy across the two groups. Nonetheless, the company indicated that it would be impossible to incorporate any point estimates from the P001[8, 9] trial in the cost-effectiveness model for AR. Thus, the EAG is not able to verify what impact the use of the adolescent subgroup evidence, from either the P001[8, 9] or the TO-203-32[10, 11] trials, would have if used to inform the AR economic model. Furthermore, the company provided treatment specific HRQoL data for adolescents aged 12-17 years, from the P001[8, 9] trial, which suggests greater benefits for this subgroup compared with adults. A critique of the P001[8, 9] trial is provided in section 4.2.7.2.

Issue: No adolescent related evidence was used to inform the AR model and evidence from adults is assumed generalisable to the adolescent subpopulation.

4.2.4 Interventions and comparators

The proposed intervention is 12 SQ-HDM, administered sublingually as a tablet daily, in addition to standard clinical management, and comparators include standard clinical management alone for both the AR+AA and AR populations. The EAG notes that omalizumab was excluded as a relevant comparator, as it is indicated for patients with multiple documented severe exacerbations despite high dose ICS-LABA and a FEV1 less than 80% of predicted value.

4.2.4.1 Points for critique:

The EAG notes that the comparator arms in the MT-04[1, 2] and MT-06[4, 5] trials, which were used to support modelling for the AA+AR and AR populations, may not represent established clinical practice in the UK. Please see section 2.3 for further detail.

For the AA+AR population, the EAG notes that in the MT-04 trial[1, 2] comparator arm, pharmacotherapy was constrained to budesonide 400-1200µg and SABA. In UK current clinical practice alternative therapies or add-ons could have been used e.g., higher dose SABA, LAMA, or LTRA, depending on the level of control for asthma, as confirmed by the clinical advisor (section 3.2.1). This was also highlighted as a key issue for the NCPE appraisal (section 4.1.3). Within the cost-effectiveness model, there was no attempt to establish indirect comparisons between 12 SQ-HDM and other step-up strategies for AA+AR. In relation to AR, and during points for clarification, the company was asked to clarify whether 12 SQ-HDM was being submitted for appraisal as a last line therapy. The company indicated it was not.

For the AR population, in the MT-06 trial[5, 45] pharmacotherapy was constrained to budesonide 400µg and SABA for those with asthma. The EAG's clinical advisor further confirmed that in UK current clinical practice, alternative therapies or add-ons would have been used for these patients and the list of allowed concomitant medications is not representative of the UK standard of care (section 3.2.1). During points for clarification, the company was asked to clarify whether 12 SQ-HDM was being submitted for appraisal as a last line therapy. The company indicated it was not.

The EAG further notes that during the clarification stage, the company indicated that the placebo arms in the MT-04[1, 2] and MT-06[5, 45] trials likely experienced improvements in disease severity due to participants' awareness of being part of the study ("Hawthorne effect") and being provided training on how to use their medications. The company further acknowledged that the improvements observed among the placebo arm in both trials are likely not representative of a real-world setting. However,

the EAG notes that in a blinded randomised trial, these effects should also be captured in the intervention arm.

4.2.5 Perspective, time horizon and discounting

In line with NICE reference case criteria, this submission employed a National Health Service and Personal Social Services (NHS & PSS) perspective, with a lifetime time horizon and costs and outcomes discounted annually at 3.5%.

4.2.5.1 Points for Critique

The company's perspective, time horizon and discounting for the economic modelling is aligned with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

This section considers the following aspects of treatment effectiveness for both AA+AR and AR populations: (i) short-term effectiveness evidence, (ii) medium to long-term treatment effectiveness, (iii) asthma exacerbations (AA+AR only), (iv) mortality, (v) treatment discontinuation, and (vi) adverse events.

As previously stated, two state-transition Markov models, one for each licensed population, were presented by the company to calculate lifetime costs and QALYs for treatment with 12 SQ-HDM compared with established clinical management, for simplicity called standard of care from now on. The pivotal trials for each population, MT-06[4, 5] for AR and MT-04[1, 2] for AA+AR, were used to inform the short-term treatment effectiveness of 12 SQ-HDM compared with standard of care, while the medium and long-term treatment effectiveness were mainly anchored on assumptions validated by clinical experts.

As previously highlighted (section 2.3), the EAG has several concerns relating to the pivotal trial informing the AA+AR economic model, MT-04,[1, 2] and its adequacy to inform the current decision problem. In addition, the restrictions imposed in the comparator arm in terms of the pharmacotherapies used and the mandated reduction of ICS in period 3 are not reflective of clinical practice in the UK. While previous economic analyses have used period 2 (maintenance phase) of MT-04[1, 2] to inform treatment effectiveness of AA+AR economic models, the EAG also has fundamental concerns with data from this phase, as uncontrolled patients are maintained on their (constrained) pharmacotherapies, thereby not reflecting the stepping up/down in therapies according to patients' asthma control that is observed in clinical practice. Thus, the EAG believes that evidence from MT-04[1, 2] is of limited use for decision making and of limited relevance to inform the 12 SQ-HDM short-term effectiveness.

Throughout this section, the EAG will highlight relevant external non-randomised real-world evidence identified in the literature which could have been used by the company to better reflect current UK clinical practice for the AA+AR population. A critique of these studies can be found in section 3.2.3.

4.2.6.1 Short-term treatment effectiveness (Year 1 / Cycle 1)

AA+AR population

Evidence from MT-04[1, 2] at baseline and trial end, covering both maintenance and ICS reduction and efficacy assessment phases, was used to inform the cycle 1/year 1 transitions between the well controlled, partly controlled, and uncontrolled AA health states in a post-hoc analysis. The Asthma Control Questionnaire[46] (ACQ) was mapped to GINA 2010 criteria[6] to classify asthma control according to the relevant control-based health states. Table 70 of the CS provides detail on the GINA 2010 criteria[6] for asthma control classification.

The proportion of people in each health state at baseline and at cycle 1/year 1 was determined by the proportion of patients in each health state at the start (baseline) and end of the MT-04 trial,[1, 2] covering both periods 2 (maintenance) and 3 (ICS reduction and efficacy assessment) of the trial. A post-hoc patient-level data analysis was conducted using ACQ data and classifying each patient in terms of their asthma control according to the GINA 2010 criteria.[6] All patients from each arm were classified in terms of their asthma control.

Three non-comparative observational non-UK studies, CARIOCA/Demoly et al., 2022,[27] Reiber et al., 2021,[29] and Sidenius et al., 2021[30] that assessed the benefits, safety profile and tolerability of 12 SQ-HDM were identified by the company as having relevant data on asthma control. The three studies reported asthma symptom control status as assessed according to the GINA criteria[6] and were used as scenario analyses in the company's AR model. As no evidence was available for standard of care in these studies, due to their non-comparative design, the company assumed that asthma control levels at baseline in these studies were reflective of asthma control levels on standard of care at baseline and in year 1, that is, patients would stay in the same asthma control level for the entire year.

The proportion of patients at baseline and end of the MT-04 trial[1, 2] used by the company as base case is presented in Table 71 of the CS, and are reproduced in Table 16, which also shows the asthma control status of patients in the CARIOCA,[27] Reiber et al., 2021[29] and Sidenius et al., 2021[30] observational studies at baseline and Year 1.

Table 16 Distribution of patients for the baseline and year 1 of the MT-04 trial and CARIOCA, Reiber et al., 2021 and Sidenius et al., 2021 observational studies.

Treatments	SOC		12 SQ-HDM	
AA+AR model base case – MT-04[1, 2] baseline and trial end				
Timepoint	**Baseline (n=277) (model start)**	**End of trial (n=208) (cycle 1/year 1)**	**Baseline (n=282) (model start)**	**End of trial (n=203) (cycle 1/year 1)**
Well controlled asthma	0 (0.0%)	54 (26.0%)	0 (0.0%)	64 (31.5%)
Partly controlled asthma	200 (72.2%)	110 (52.9%)	200 (70.9%)	100 (49.3%)
Uncontrolled asthma	77 (27.8%)	44 (21.2%)	82 (29.1%)	39 (19.2%)
AA+AR Scenario analysis using CARIOCA[27] study baseline and Year 1				
Timepoint	**Baseline (n=N/A) (model start)**	**End of trial (n=N/A) (cycle 1/year 1)**	**Baseline (n=494) (model start)**	**End of trial (n=228) (cycle 1/year 1)**
Well controlled asthma	53.8%*	53.8%*	266 (53.8%)	184 (80.7%)
Partly controlled asthma	27.9%*	27.9%*	138 (27.9%)	33 (14.5%)
Uncontrolled asthma	18.2%*	18.2%*	90 (18.2%)	11 (4.8%)
AA+AR Scenario analysis using Reiber et al., 2021[29] study baseline and Year 1				
Timepoint	**Baseline (n=N/A) (model start)**	**End of trial (n=N/A) (cycle 1/year 1)**	**Baseline (n=369) (model start)**	**End of trial (n=369) (cycle 1/year 1)**
Well controlled asthma	36.9%*	36.9%*	36.9%	78.4%
Partly controlled asthma	41.2%*	41.2%*	41.2%	15.4%
Uncontrolled asthma	22.0%*	22.0%*	22.0%	6.2%
AA+AR Scenario analysis using Sidenius et al., 2021[30] study baseline and Year 1				
Timepoint	**Baseline (n=N/A) (model start)**	**End of trial (n=N/A) (cycle 1/year 1)**	**Baseline (n=82) (model start)**	**End of trial (n=67) (cycle 1/year 1)**
Well controlled asthma	52.4%*	52.4%*	43 (52.4%)	42 (62.7%)
Partly controlled asthma	25.6%*	25.6%*	21 (25.6%)	17 (25.4%)
Uncontrolled asthma	22.0%*	22.0%*	18 (22.0%)	8 (11.9%)
Abbreviations: SQ, standardised quality; HDM, house dust mite; SOC, standard of care; AA, allergic asthma; AR, allergic rhinitis; N/A, not applicable.				

Note: Table adapted from Tables 72-74 in the CS; *CARIOCA/ Demoly et al., 2022, Reiber et al., 2021 and Sidenius et al., 2021 are non-comparative observational studies, thus the standard of care distributions across the different levels of asthma control for both baseline and end of trial periods were assumed to be equivalent to the observed distribution at baseline of 12-SQ-HDM.

Points for critique

The company highlights that it followed the GINA 2010 guidelines[6] to classify patients in terms of their asthma control status through patients' ACQ[46] score. The company mentions also that other relevant guidelines exist, namely the NICE[15] and the BTS and Scottish Intercollegiate Guidelines Network (SIGN)[14] guidelines. Previous NICE TAs on asthma (TA479[47], TA565[48], TA751[49] and TA880[12]) structured their Markov models around asthma control and exacerbation events. The health states in these TAs were defined based on the ACQ[46] score in line with the BTS/SIGN[14] guidelines (where patients are classed as having uncontrolled asthma if their ACQ score is ≥1.5, and controlled asthma if ACQ score is <1.5). It is unclear to the EAG why the company opted to be inconsistent with

previous TAs and mapped ACQ[46] scores to GINA criteria[6] rather than directly use ACQ scores to classify patients in terms of the asthma control as per BTS/SIGN[14] guidelines. The EAG notes that for the MT-04 trial one of the eligibility criteria was having an ACQ score 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.

Furthermore, the clinical expert to the EAG mentioned that all these guidelines are commonly used in clinical practice and that fundamental differences exist between them. The EAG was not provided with any rationale for the use of the GINA[6] guidance by the company over and above the use of the NICE[15] or the BTS/SIGN[14] guidelines (section 2.2). The EAG is concerned that differences in how patients may be classified in terms of their asthma control could be generated if guidelines other than GINA[6] would have been used. When questioned at points for clarification, the company stated that it considered the definitions of asthma control and the treatment options for adults and adolescents across all the asthma guidelines to be very similar. The EAG believes that differences exist between the different guidelines, particularly with respect to treatment recommendations at different steps.

Although the EAG has fundamental concerns relating to the use of MT-04 study[1, 2] to inform the current decision problem, acknowledging that this trial may be the best currently available evidence, the EAG highlights several issues relating to how evidence from the MT-04 trial[1, 2] was used by the company to inform the year 1 standard of care and intervention effectiveness in the AA+AR model.

The EAG considers the effectiveness parameterisation proposed by the company through the use of the MT-04 study[1, 2] to not be reflective of the progression in disease severity and the stepping up/down in treatment as observed in clinical practice. For example, Schmitt et al., 2020,[50] a population-based cohort study utilising healthcare data (2005 to 2014) from a statutory health insurance in Germany, where severity of asthma was classified according to the treatment steps recommended by GINA,[6] modelled the progression of disease severity and the effect of allergy immunotherapy on the transitions between the GINA steps using Cox regression models adjusted for age and sex. The EAG believes that the approach taken by Schmitt et al., 2020[50] to estimate treatment effectiveness and asthma disease progression would have been more appropriate than the company's approach. The EAG is unclear why the company has not explored or discussed alternative approaches to modelling disease progression similar to the one presented in Schmitt et al., 2020[50].

An unadjusted post-hoc analysis was performed on data collected in study MT-04[1, 2] at baseline and trial end to inform the effectiveness in year 1/cycle 1 of the AA+AR model for both established clinical therapy and 12 SQ-HDM. The benefits and limitations of post-hoc analyses have been extensively discussed in the statistical literature. One of the key limitations of these unplanned analyses is the danger of identifying (spurious) statistical relationships that suggest cause and effect.

That is, an apparent difference between interventions by way of an unplanned post-hoc analysis may discover nothing more than simple coincidence, with the effects observed being down to pure chance. At points for clarification the company continued to support the approach taken, without acknowledgement of the limitations of such analyses.

Secondly, although the MT-04 trial sample[1, 2] included adults with both HDM allergy–related asthma and HDM allergy–related rhinitis, all outcomes collected within the trial were asthma related. Thus, the EAG questions the effectiveness findings of 12 SQ-HDM and their applicability to any improvement in patients' rhinitis symptoms, in addition or instead of improvements to their asthma symptoms.

The EAG notes that the AA+AR model year 1 effectiveness is populated by findings from period 2 (maintenance phase) and period 3 (ICS reduction/efficacy assessment phase) of the MT-04 trial.[1, 2] The EAG is concerned that neither period 2 or period 3 are reflective of clinical practice in the UK as patients, if uncontrolled, would not be maintained in their current treatment(s) (as per period 2) and would not have an ICS reduction or withdrawal (as per period 3) – see section 3.2.1 for further detail. This has been confirmed by the EAG's clinical expert. Previous economic analyses (e.g., Hanh-Pedersen et al., 2016[38], Green et al., 2017[40], Green et al., 2016[39]) funded by the company have also recognised these issues to some extent and have opted to use the only maintenance period 2 to inform treatment effectiveness within the first year. Thus, the EAG is concerned that the short-term effectiveness parameterisation performed by the company, in addition to being based on a post-hoc analysis, is informed by evidence which has limited generalisability to the UK clinical practice. At points for clarification, the EAG requested the distribution of patients at baseline and end of period 2 (maintenance phase) in the MT-04 trial,[1, 2] at each level of asthma control as described in the GINA 2010 guidance.[6] The company provided the distribution of patients at each timepoint from visit 4 to visit 12. The distributions for baseline and end of trial (period 2 and 3) and baseline to end of maintenance phase (period 2 only) are presented in Table 11 in section 3.2.2. The EAG notes that, compared to the trial end, the proportion of patients in the partly controlled and uncontrolled asthma is higher in the end of period 2. Although of limited use to inform treatment effectiveness, and in the absence of a better alternative, the EAG preference falls on the MT-04[1, 2] maintenance period (period 2) to inform the short-term effectiveness.

From Table 71 of the CS it is the EAG's understanding that complete evidence on the ACQ scores at baseline was available for all 559 patients (standard of care (n=277) and 12 SQ-HDM (n=282), respectively) and was used for the baseline population in the AA+AR economic model. However, end of the trial (visit 13 and, thus, end of efficacy phase / period 3) evidence on the ACQ[46] scores was only available for 441 patients (standard of care (n=208) and 12 SQ-HDM (n=203), respectively), and evidence from this sub-sample was used for trial end in the model. The EAG believes that, for

consistency with the approach taken for the AR model, the same sub-sample of patients should have been used for both baseline and trial end. Moreover, this available case analysis performed by the company may bias estimates if non-respondents systematically differ from the respondents. Similar issues are found when using the end of period 2 (maintenance phase) of the MT-04 trial.[1, 2]

The EAG notes also that clinical findings published by Virchow et al., 2016,[1] show that 68 patients (20 in period 2 and 48 in period 3) in the standard of care arm and 77 patients (34 in period 2 and 43 in period 3) in the 12 SQ-HDM arms were discontinued, with a full analysis of 257 and 248 patients for standard of care and 12 SQ-HDM, respectively. The number of patients per arm published by Virchow et al., 2016[1] do not coincide with those presented by the company. Thus, the EAG is concerned with how the distribution of patients at MT-04[1, 2] baseline and trial end were estimated; no clarity or justification was provided on the approach(es) taken to consider patients that dropped-out and/or were censored within the relevant periods. At points for clarification the company indicated that the last observation carried forward (LOCF) method was used to manage missing data, though no information was presented on the level of missing data and the validity of imputation approach used. The EAG highlights that the methodological literature on missing data is quite clear in that all analyses using LOCF are of questionable validity.

The EAG is also concerned with the lack of attempt by the company to capture the uncertainty linked to the distribution of patients across the AA+AR asthma control levels, and thus the uncertainty in the transition probabilities in the first cycle of the AA+AR model. The company presented three alternative scenarios considering data from three non-UK non-comparative observational studies. The EAG notes that it was not able to confirm the end of trial values presented for the CARIOCA/Demoly et al., 2022[27] in the publication cited by the company (see Table 13). Further detail and critique of these studies can be found in section 3.2.3. Although the EAG believes that these non-comparative observational studies may be more representative of clinical practice in this population than the MT-04 trial[1, 2] in terms of capturing asthma treatment as a stepwise approach according to disease control, the EAG acknowledges that the non-comparative observational design is of concern. In fact, the use of such studies to inform the asthma control levels in year 1 of the AA+AR model implied strong assumptions around the effectiveness of standard of care. The company assumes that the baseline distributions of patients across the asthma control levels of these studies are equivalent to standard of care and that, irrespective of the level of asthma control status at baseline, the same proportion of patients would be found at each level 1 year later. The EAG believes that this assumption is unrealistic as patients still do receive standard of care treatments, i.e., are not without treatment, which are also effective in asthma control, that would have been stepped up/down according to asthma control as per existing guidelines.

Issue: The short-term effectiveness parameterisation proposed by the company for AA+AR is not reflective of the progression in disease severity and the stepping up/down in treatments as observed in clinical practice.

Issue: The use of period 2 only (maintenance phase) or periods 2 and 3 (maintenance and ICS reduction phase) of the MT-04 trial to inform the AA+AR short-term effectiveness may not be reflective of clinical practice.

Issue: The use of an unadjusted post-hoc analysis to inform the AA+AR models' natural history and short-term treatment effectiveness parameterisation adds considerable uncertainty to this key model input parameter.

Issue: The use of ACQ scores mapped on to GINA to classify patients in terms of their asthma control is inconsistent with the approach taken by previous TAs.

Issue: The distributions of patients across asthma control levels at baseline and trial end are fixed, and thus, the uncertainty in the transition probabilities in the first cycle of the AA+AR model is not considered.

AR population

A post-hoc analysis of evidence from MT-06[4, 5] at baseline and trial end was used to inform the cycle 1/year 1 transitions between AR severity (mild, moderate and severe) health states in the AR model. To estimate treatment-specific transition probabilities the Allergic Rhinitis and its Impact on Asthma (ARIA) international guidelines (2016 revision)[51] were used. To define the severity of symptoms the ARIA guideline[51] considers a) sleep disturbance; b) impairment of daily activities, leisure and/or sport; c) impairment of school or work; and d) troublesome symptoms. When none of these symptoms (a to d) is present, the AR severity is classified as being mild. When at least one of these symptoms (a to d) is present, the AR severity is classified as being moderate-severe. As the ARIA[51] severity classification does not discriminate between moderate and severe AR, the company used the modified version of the ARIA[51] severity classification published by Valero et al., 2007.[52] The modified severity classification considered by the company was: mild AR - when none of these symptoms (a to d) is present; moderate AR – when 1 to 3 of these symptoms is present; and severe AR - when all 4 symptoms are present.

The proportion of people in each health state at baseline and at cycle 1 / year 1 was determined by the proportion of patients in each health state at the start (baseline) and end (during the last 2 weeks of the efficacy assessment period) of the MT-06 trial.[4, 5] To estimate these proportions, a post-hoc patient-level data analysis of the MT-06 trial[4, 5] was conducted using data on patients' rhinitis Daily Symptom Score (DSS) as a proxy for troublesome symptoms, and 3 HRQoL components (sleep disturbance, impairment of daily activities, leisure and/or sport and impairment of school or work) to match the

ARIA[51] severity classification. Two total rhinitis DSS score cut-offs were considered by the company to label the ARIA[51] item 'troublesome symptom' as being mild, moderate, or severe. A sub-sample of 576 patients (placebo (n=296); 12 SQ-HDM (n=280)) had sufficient information to implement this classification.

The proportions of patients at baseline and end of the MT-06 trial[4, 5] used by the company as base case and as scenario are presented in Tables 68 and 69 of the CS and are reproduced below in Table 17.

Table 17 Distribution of patients at MT-06 baseline and trial end – AR model base case and scenario.

Treatments	Standard of Care (n=296)		12 SQ-HDM (n=280)	
AR model base case*				
Timepoint	**Baseline (model start)**	**End of trial (cycle 1 / year 1)**	**Baseline (model start)**	**End of trial (cycle 1 / year 1)**
Mild	0 (0.0%)	127 (42.9%)	0 (0.0%)	153 (54.6%)
Moderate	176 (59.5%)	157 (53.0%)	162 (57.9%)	119 (42.5%)
Severe	120 (40.5%)	12 (4.1%)	118 (42.1%)	8 (2.9%)
AR model scenario**				
Timepoint	**Baseline (model start)**	**End of trial (cycle 1 / year 1)**	**Baseline (model start)**	**End of trial (cycle 1 / year 1)**
Mild	0 (0.0%)	182 (61.5%)	0 (0.0%)	186 (66.4%)
Moderate	185 (62.5%)	108 (36.5%)	171 (61.1%)	93 (33.2%)
Severe	111 (37.5%)	6 (2.0%)	109 (38.9%)	1 (0.4%)
Abbreviations: SQ, standardised quality; HDM, house dust mite; SOC, standard of care; AA, allergic asthma; AR, allergic rhinitis.				

Note: Table adapted from Tables 68-69 in the CS; * The AR model base case considers whether the cut-off for the 'troublesome symptoms' item was impaired by whether patients had an average rhinitis DSS score of 4; ** The AR model scenario considers whether the cut-off for the 'troublesome symptoms' item was impaired by whether patients had an average rhinitis DSS score of at least 6 or a score of at least 5 with one symptom being severe was used.

Points for critique

As for the AA+AR model, the EAG considers the effectiveness parameterisation proposed by the company to not be reflective of the progression in disease severity and the stepping up/down of treatment as observed in clinical practice. Real-world evidence from the REACT study (Fritzsching et al., 2022[31]) – where allergy immunotherapy subjects were propensity score matched adjusted 1:1 with control subjects – looked at AR prescriptions and provided evidence on how AR patients have been managed within each severity level, potentially reflecting the stepping up/down of treatment according to their AR severity requirements. The EAG is not clear why the company has not considered this aspect in their approach. The EAG acknowledges the methodological limitations of the REACT study, please see section 3.2.3.

The EAG has several concerns relating to how evidence from the MT-06 trial[4, 5] was used to inform the year 1 standard of care and intervention effectiveness as presented by the company. Firstly, an

unadjusted post-hoc analysis was performed using data collected within the MT-06[4, 5] baseline and trial end to inform the effectiveness in year 1 / cycle 1 of the AR model for both established clinical therapy and 12 SQ-HDM. As previously mentioned, limitations exist when post-hoc analyses are performed, one of the key limitations being the potential of identifying (spurious) statistical relationships that may erroneously suggest a cause and effect. Secondly, from Fig. 27 of the CS it is the EAG's understanding that complete evidence on the 3 HRQoL items and rhinitis DSS was only available for 576 patients, out of 656 in the placebo and 12 SQ-HDM arms of the trial. Thus, 80 (12.2%) patients were excluded from the implemented post-hoc analysis, in what the EAG believes to be a complete case analysis. The breakdown of what items were missing for each of these 80 patients were not provided to the EAG. During points for clarification, the company clarified that no methods were used to address the missing observations. The EAG believes the reason patients may not have complete HRQoL and DSS data could be linked to their outcomes, which could bias the patient distribution presented by the company.

The EAG is also concerned with the clinical validity of the use of the HRQoL items, in particular, the use of the modified classification by Valero et al. 2007,[52] to distinguish between ARIA[51] moderate and severe AR levels. Although the company stated at response to clarifications that the modified ARIA classification[52] has been validated, it was the opinion of the EAG's clinical expert that, although the ARIA guidance[51] is often used and is useful to distinguish mild cases from moderate/severe cases (to understand for whom there is a need to step up treatment), the modified classification[52] would not necessarily guide clinical management. However, the EAG believes that it is still reasonable to model moderate and severe health states separately given that HRQoL may differ by level of severity (even if treatment may not differ).

The use of rhinitis DSS score is seen as a good proxy to the HRQoL item relating to 'troublesome symptoms', often employed to monitor the evolution of symptoms. Nonetheless, the EAG has some concerns relating to the partial use of the DSS questionnaire considering 4 nasal related symptoms (runny nose, blocked nose, sneezing, and itchy nose) but excluding 2 ocular related symptoms (red and itchy eyes and watery eyes), when these symptoms often overlap. Furthermore, the EAG's clinical expert emphasised that no hard cut-off of the rhinitis DSS score exists to define what 'troublesome symptoms' are. Thus, the two rhinitis DSS score cut-offs implemented by the company to label the ARIA[51] item 'troublesome symptom' as being mild, moderate, or severe, may have no clinical support. At points for clarification, when questioned about the use of the HRQoL items and the DSS score, the company clarified that whilst the primary outcome, TCRS score, appropriately measures the impact of treatment on disease symptoms and use of medication to manage symptoms, the TCRS score does not correspond to any recognised categories of AR severity.

The EAG is also concerned with the lack of attempt to capture the uncertainty linked to the distribution of patients across the AR severity levels at baseline and trial end, and thus the uncertainty in the transition probabilities in the first cycle of the AR model. In response to points for clarification, the company replied that it considered the current model analyses sufficient in reflecting the uncertainty associated with the estimation of short-term effectiveness. The EAG fundamentally disagrees with this statement and the approach taken by the company. The EAG further notes that MT-06[4, 5] trial participants were asked about their rhinitis symptoms and HRQoL weekly during the treatment maintenance phase and daily during the efficacy assessment phase. Utilising only baseline and trial end collected data is seen by the EAG as a partial view of the symptoms experienced by patients, not capturing the possible fluctuations in rhinitis severity over time.

Issue: The short-term effectiveness parameterisation proposed by the company for AR is not reflective of the progression in disease severity and the stepping up/down in treatments as observed in clinical practice.

Issue: The use of an adjusted post-hoc analysis to inform the AR models' natural history and short-term treatment effectiveness parameterisation adds considerable uncertainty to this key model input parameter.

Issue: The distributions of patients across rhinitis severity levels at baseline and trial end are fixed, and thus, the uncertainty in the transition probabilities in the first cycle of the AR model is not considered.

4.2.6.2 Medium to Long-term treatment effectiveness (Year 2 / Cycle 2 onwards)

In the absence of medium to long-term RCT data on the effectiveness of 12 SQ-HDM for both AR and AA+AR populations, the company considered that possible transitions of patients across health states in each model were determined by an annual rate of change across 4 time periods. The 4 time periods considered by the company were years 2 to 5, years 5 to 10, years 10 to 20, and year 20 onwards. The annual rate of change determined the probability of transitioning from well-to-partly controlled / mild-to-moderate and from partly controlled-to-uncontrolled / moderate-to-severe for 12 SQ-HDM and standard of care, in the AA+AR / AR model, respectively. The company assumed that patients receiving standard of care remained stable during all years following Year 1 and thus observed an annual rate of change of 0% across the 4 periods. Tables 75 and 76 in the CS provided the annual rates of change assumed by the company for the medium to long-term treatment effectiveness. These are reproduced in Table 18 for completeness.

Table 18 Assumptions of the company over the medium to long-term effectiveness of 12 SQ-HDM and standard of care in the AA+AR and AR economic models, respectively.

Annual rate of change	12 SQ-HDM AA+AR / AR		SOC AA+AR / AR	
	Well-to-partly controlled / mild-to-moderate	Partly-to-uncontrolled / moderate-to-severe	Well-to-partly controlled / mild-to-moderate	Partly to uncontrolled / moderate-to-severe
Year 2 to year 5	-5.00%	-5.00%	0.00%	0.00%
Year 5 to year 10	-2.50%	-2.50%	0.00%	0.00%
Year 10 to year 20	2.50%	2.50%	0.00%	0.00%
Year 20 onwards	0.00%	0.00%	0.00%	0.00%

A negative probability indicates an improvement in health (backwards transition)
Note: Table adapted from Tables 75-76 in the CS;
Abbreviations: SQ, standardised quality; HDM, house dust mite; SOC, standard of care; AA, allergic asthma; AR, allergic rhinitis.

The company indicates that the assumptions over the annual rate of change for 12 SQ-HDM and standard of care over the medium to long-term for the two populations were validated in two separate advisory boards. Both panels agreed that after cessation of 12 SQ-HDM, treatment effectiveness is likely to have a sustained and clinically significant effect for at least 10 years with potential waning over the subsequent decade, with treatment effectiveness unlikely to completely disappear for HDM-sensitised AA patients.

The company also assumed that patients in the 12 SQ-HDM arm cannot decline to a state which is worse than patients receiving standard of care. That is, if there are less 'well controlled' or more 'uncontrolled' patients in the 12 SQ-HDM arm compared with the standard of care arm in the model, the numbers of patients in that health state are instead assumed equal. Furthermore, the company assumed that treatment waning was initiated in year 15 of the model and that by year 20, 80% of the patients in the 12 SQ-HDM treatment arm will be set to match the distribution of patients in the standard of care arm. The waning effect impacts patients' health state transitions, exacerbation rates (AA+AR model only), primary and secondary care costs, and QALYs.

To support the company's assumptions over the medium to long-term effectiveness in both AA+AR and AR populations, findings from the REACT study[31] were presented. Compared to the pre-index year, allergen immunotherapy was found to be consistently associated with greater reductions in AA prescriptions and AR prescriptions compared to control subjects, which was sustained for 9 years. The allergen immunotherapy group had a significantly greater likelihood of stepping down asthma treatment and demonstrated sustained, long-term reductions in the number of severe asthma exacerbations. Please see further discussion of the REACT study,[31]its limitations and findings in section 3.2.3.

Points for critique

The EAG acknowledges that limited evidence exists on the effectiveness of 12-SQ HDM and standard of care beyond 12 months. The EAG has numerous concerns relating to the medium to long-term effectiveness assumptions imposed by the company on the AA+AR and the AR economic models.

Firstly, the EAG is concerned with the lifetime time horizon utilized by the company and the fact that the only data on treatment effectiveness post-9 years is based on clinical expert opinion. As previously highlighted, Green et al., 2019[39] considered a 5-year time horizon and Hahn-Pedersen et al., 2016[38] and Green et al., 2017[40] considered a 9-year time horizon. Table 19 summarises the assumptions implemented in these three published cost-effectiveness analyses. It is worth noting also that Hahn-Pedersen et al., 2016,[38] Green et al., 2017[40] and Green et al., 2019,[39] applied medium to long-term effectiveness assumptions, not based on actual evidence, over utilities (e.g., 5% increase or decline in patients' quality of life per year), rather than on the probabilities of transitioning between health states – Table 19.

Table 19 Medium to long-term effectiveness assumptions for 12 SQ-HDM and standard of care presented in the cost-effectiveness literature for AR and AA+AR.

Study	Time horizon	Outcome subject to change	Treatment	Assumptions (base case)		
Time period				**Years 2-3**	**Years 4-5**	**Years 6-9**
Hahn-Pedersen et al,. 2016[38]	9 years	Utilities	**12 SQ-HDM+PhTx**	+5%	0%	-5%
			PhTx	0%	0%	-5%
Green et al,. 2017[40]	9 years	Utilities	**12 SQ-HDM+PhTx**	+5%	0%	-10%
			PhTx	0%	0%	-5%
Green et al,. 2019[39]	5 years	Utilities	**12 SQ-HDM+PhTx**	+5%	0%	N/A
			PhTx	0%	0%	N/A

A positive/negative proportion indicates an improvement/decrement in health utility.
Abbreviations: SQ, standardised quality; HDM, house dust mite; PhTx, pharmacotherapy

The EAG's clinical expert emphasised that the medium to long-term benefit of treatment with 12-SQ HDM and the likelihood of retreatment with 12-SQ HDM is predicated on the assumption of a 3-year treatment duration. Treatment durations lower than 3 years imply shorter or no medium to long-term benefit and may lead to the need for retreatment. This is supported by evidence from the Marogna et al., 2010 study.[32] This study found that in patients receiving 12-SQ HDM for 3 years, the clinical benefit persisted for 7 years, and in those receiving immunotherapy for 4 or 5 years, the clinical benefit persisted for 8 years. The EAG also notes the findings from Kiel et al., 2013,[53] which showed that, in the real world and when considering multiple allergens, time to treatment discontinuation is of

0.6 years for SLIT (substantially shorter than the recommended duration) and that this estimate could be even lower if restricting to HDM.

Another relevant study supporting the medium-to-long-term benefit of the intervention is the REACT study.[31] The REACT study[31] found that allergen immunotherapy was associated with greater reduction in prescriptions per subject over time compared to the control group. However, a much smaller reduction over the same period was found when looking at SLIT subgroup – figure S13 of the supplementary material of the paper. Please see a discussion of the REACT study in section 3.2.3. The opinion of the clinical experts in the two advisory boards[54, 55] performed by the company is, to some extent, aligned with this evidence; they agreed that treatment effectiveness was likely to be maintained for at least 10 years. As no clear evidence supports an increment in the effect of treatment, the EAG believes that the assumptions of improvements in health imposed by the company for 12 SQ-HDM from 2-5 and 5-10 years are neither appropriate nor supported by reliable evidence. The EAG could not validate the annual rate of change estimates used by the company in both economic models and is unaware where these values were sourced from. It is not entirely clear to the EAG if the estimates of annual rates of change were presented to and/or validated by the clinical experts taking part in the advisory boards.[54, 55] Thus, the EAG considers the annual rates of change used by the company to be arbitrary and not matching clinical expert statements. The EAG questioned the company about the annual rates of change estimates used at points for clarification, but no justification was provided for the values used.

Beyond 10 years, 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 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 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.

The EAG is also concerned with the assumption used in the company's model that patients in the 12 SQ-HDM arm cannot decline to a state which is worse than patients receiving standard of care. The EAG is concerned with its clinical validity and thus considers it to be uncertain.

Issue: The assumption of improvements in health imposed by the company for 12 SQ-HDM from 2-5 and 5-10 years are highly uncertain, speculative and are not supported by evidence.

Issue: Long-term effectiveness assumptions beyond 9 years are considered subjective and uncertain, being particularly uncertain beyond 20 years given the lack of evidence to support these.

Issue: The annual rates of change used by the company to reflect the medium to long-term effectiveness of 12 SQ-HDM and standard of care are arbitrary.

Issue: Assumptions on starting treatment waning at 15 years and of considering 80% of the treated patients moving to standard of care by year 20 are not supported by evidence and are considered highly uncertain.

Issue: The assumption that patients in the 12 SQ-HDM arm cannot decline to a state which is worse than patients receiving standard of care is uncertain.

4.2.6.3 Asthma exacerbations

The AA+AR model considers treatment specific asthma exacerbation probabilities (see Table 77, CS), with moderate and severe exacerbations modelled separately. In the company's submitted model, these probabilities were estimated based on the number of patients experiencing at least one exacerbation during period 3 (ICS reduction and efficacy assessment; 180 days) of the MT-04 trial,[1, 2] with the number of events per trial arm used to calculate annual probabilities (assuming a constant six-month rate).

The probabilities of moderate and severe exacerbations are applied in the model throughout the time horizon to the proportion of individuals in each alive health state and are not conditional on health state membership (for example, the probability of having a severe [or moderate] exacerbation is the same for individuals who are well controlled, partly controlled, or uncontrolled). The occurrence of exacerbation event also has no impact on subsequent health state membership. The assumptions on the relationship between asthma exacerbations and asthma control were not justified by the company. In the cohort initially treated with 12 SQ-HDM, the comparator-specific exacerbation probabilities are applied to individuals who no longer receive the treatment effect of 12 SQ-HDM, due to discontinuation or treatment effect waning. This is consistent with how treatment effectiveness on disease control was modelled.

Points for critique

The EAG does not consider that period 3 (ICS reduction and efficacy assessment) of MT-04[1, 2] is appropriate to inform treatment effectiveness estimates in the economic model. As mentioned in section 3.2.1, period 3 is not reflective of expected clinical practice in the UK as the protocol driven reduction of ICS (which was mandated for all patients in period 3) would not be recommended for individuals with uncontrolled asthma. Thus, the comparative effectiveness of 12 SQ-HDM vs standard of care in reducing asthma exacerbations is unlikely to be generalisable to clinical practice. At clarification stage, the EAG requested that the probabilities of exacerbation were updated using evidence from the treatment maintenance period 2b of MT-04[1, 2] or suitable external evidence to

overcome this issue. In reply, the company stated that the MT-04 trial[1, 2] did not collect the number of exacerbations in period 2b, but said that for *"period 2a and 2b, patients in the 12 SQ-HDM treatment arm have fewer adverse events that may be correlated with asthma exacerbations compared with patients in the placebo arm"*. They also caveated that limited inference could be made from these data, as the number of events were low and appeared to be equally distributed in both treatment groups. The EAG notes that data collected during period 2 (section 3.2.2, Table 10) suggests similar levels of change to disease control compared to baseline between trial arms in MT-04[1, 2], given the small and non-statistically significant mean differences in ACQ change from baseline at visit 6 and 8. A study by Meltzer et al. 2011[46] in patients with moderate to severe atopic asthma suggests ACQ scores are a good predictor of future risk of asthma exacerbations. The study estimated an increase of 50% in the risk of an asthma exacerbation for each 1-point increase in ACQ score, the risk of HR, 1.50; 95% CI, 1.03-2.2. Since the MT-04[1, 2] trial did not collect evidence on the occurrence of asthma exacerbations in period 2, the EAG considers that the ACQ evidence indicating similar levels of asthma control between 12 SQ-HDM and placebo over this period suggests that the 12 SQ-HDM treatment effect on exacerbations compared to placebo is negligible in period 2 of MT-04[1, 2]. Given the limitations of the evidence used to inform the asthma exacerbation probabilities in the AA+AR model and the concerns around the generalisability of this study to clinical practice, uncertainty on these parameters should be explored further.

The company did not comment on the use of evidence external to the MT-04 trial[1, 2] that could be used to explore the uncertainty of the12 SQ-HDM treatment effect on asthma exacerbations. The EAG did not identify external evidence which could be used to inform asthma exacerbation probabilities in the AA+AR model within the time constraints of this assessment but notes that the company did not report a systematic approach to identify such evidence.

The exacerbation probabilities were estimated based on the number of patients experiencing at least one exacerbation in period 3. This implies that the annual exacerbation probabilities applied in the model do not reflect the total number of events during the 180 days of period 3 for either treatment arm, but rather the probabilities of having a first exacerbation during that period. It is unclear how this would affect the robustness of the estimates of relative effectiveness of 12 SQ-HDM vs standard of care to reduce asthma exacerbations, particularly as individuals who experienced an exacerbation during period 3a could be discontinued from the trial (or have a dose adjustment).[1, 2] Those who experienced an asthma exacerbation during period 3b (ICS withdrawal period) were discontinued from the trial. Therefore, the exacerbation probabilities are based on an underestimation of the total number of events in period 3, as 83 individuals in the standard of care arm had 102 asthma exacerbations and 59 individuals in the 12 SQ-HDM arm had 74 events recorded in this period (MT-04 CSR,[2] panel 9-21). It is also worth noting that, by the start of period 3, 54 individuals had been

discontinued from the MT-04 trial[1, 2] (34 and 20 individuals from the 12 SQ-HDM and placebo arm, respectively).

The company's AA+AR model distinguishes between moderate and severe exacerbation events. Two previous NICE TAs in severe asthma [TA479,[47] TA751[49]] also modelled moderate and severe exacerbations, while other NICE TAs modelled only severe exacerbations [TA565,[48] TA880[12]] or distinguished exacerbations according to clinical significance (dependent on forced expiratory volume in 1 second [FEV1], TA278[16]). Although the definitions of moderate and severe exacerbations across appraisals approximately match the definitions in the MT-04 trial[1, 2] and, thus, what is used in the AA+AR model, these are modelled as health states in previous TAs and not as events. The EAG considers that it is appropriate to model exacerbations as events as per the CS. However, we note that this modelling choice introduces a risk of double counting utility impacts and some elements of resource use associated with health states; discussed in sections 4.2.7.2 and 4.2.8.7. Another difference between the CS and previous NICE TAs is the company's structural assumption that the probability of an exacerbation (moderate or severe) is the same regardless of level of asthma control. Clinical opinion to the EAG in TA880[12] noted that while exacerbations can happen in any health state, the risk of having an exacerbation will differ according to the level of asthma control, with higher risk of an exacerbation in uncontrolled than controlled asthma. The clinical adviser to the EAG also considered that it is more likely for patients to return to an uncontrolled asthma health state than to controlled asthma after an exacerbation. The impact of the company's assumptions on the relationship between the occurrence of exacerbations and the level of asthma control on the estimates of cost-effectiveness is unknown. It is possible that the company made this assumption as a simplification in the absence of data. However, the EAG notes that there is a disconnect between the exacerbation events and asthma disease control in the company's AA+AR model. The potential impact of this on the estimates of cost-effectiveness is unknown.

Issue: The use of period 3 (ICS reduction and efficacy assessment) of MT-04[1, 2] to inform the AA+AR effectiveness on asthma exacerbations is not reflective of clinical practice. Furthermore, the number of exacerbations reflected in the asthma exacerbation probabilities underestimates the total number of events in period 3.

Issue: Treatment effect of 12 SQ-HDM on exacerbations is informed by a single study and MT-04[1, 2] may not reflect exacerbation risks in the full AA+AR population for which this treatment is licensed. The company has not fully explored this area of uncertainty.

Issue: The impact of the company's assumption that the risk of an exacerbation is independent of the level of asthma control and that exacerbation events do not affect subsequent health state membership is unknown and has not been justified.

4.2.6.4 Mortality

The company models for AA+AR and AR assume that patients in the alive health states are at risk of age and sex adjusted all-cause mortality. The company states that all-cause mortality was informed by UK life tables, but it is not clear what time period was used to estimate the probability of death. The company did not consider disease-specific mortality in either model, as no deaths were reported in the MT-04[1, 2] or MT-06[4, 5] trials. This approach was considered by the company to be conservative for the AA+AR population, as a systematic literature review suggested an association between severe exacerbations and increased mortality risk.[16]

Points for Critique

The EAG was not able to replicate the age and sex adjusted all-cause mortality estimates in the models, although these seem close to Office for National Statistics (ONS) 2018-2020 estimates.[56] Given how similar these estimates are to ONS data, the EAG did not consider it a priority to correct the models as any impact on the estimates of cost-effectiveness would be negligible.

Previous NICE TAs in asthma have explicitly modelled asthma related mortality by establishing a link between severe exacerbations (and/or hospitalisations due to severe exacerbations) and asthma mortality. This results in an indirect treatment effect on mortality for the technologies under appraisal. Given the issues highlighted above regarding the estimation of the probabilities of asthma exacerbations, the EAG agrees with the exclusion of asthma related mortality from the AA+AR model.

4.2.6.5 Discontinuation

The company modelled per-cycle probabilities of discontinuing treatment with 12 SQ-HDM (due to i) AEs and ii) other reasons) using treatment discontinuation rates observed in the MT-04[1, 2] and MT-06[4, 5] trials for the AA+AR and AR models, respectively. Patients receiving standard of care within the AA+AR or AR models were not subject to a treatment discontinuation probability.

As for the most common AEs in the MT-04[1, 2] and MT-06[4, 5] trials, as the median onset time after treatment initiation and median resolution time were short in duration, the company assumed that all AEs and their associated costs occurred in the first model cycle only. Thus, the probability of discontinuation due to AEs is applied in the first model cycle. For both AA+AR and AR models, all patients who discontinued treatment due to AEs with 12 SQ-HDM incur a 1 month's cost of treatment with 12 SQ-HDM to account for any previous time on treatment prior to discontinuation. Post-discontinuation, 12 SQ-HDM patients are modelled as standard of care patients for the duration of the time horizon, experiencing the same transition probabilities, health care costs, and HRQoL as patients receiving standard of care (Table 20).

Table 20 Discontinuation due to AEs and other reasons for AA+AR and AR, respectively.

Discontinuation	Standard of Care	12 SQ-HDM	Overall, inc. 6 SQ-HDM
AA+AR – MT-04 trial (period 2 and period 3)	n=277	n=282	n=834
AEs leading to discontinuation – n (%)	8 (2.9%)	25 (8.9%)	45 (5.4%)
Due to other reasons* – total n (%)	22 (7.9%)	25 (8.9%)	78 (9.4%)
Lack of efficacy (a)	2 (0.7%)	1 (0.4)	4 (0.5%)
Lost to follow-up (b)	5 (1.8%)	3 (1.1%)	14 (1.7%)
Withdrawal of consent (c)	13 (4.7%)	15 (5.3%)	44 (5.3%)
Other, non-exacerbation related*** (d)	26-24= =2 (0.7%)	25-19= =6 (2.1%)	81-65= =16 (1.9%)
Proportion of patients to discontinue (company)		[(a)+(b)+(c)+(19.75%*25)]/ n= [1+3+15+(19.75%*25)]/n= =8.49%**	
Proportion of patients to discontinue (EAG)		[(a)+(b)+(c)+(d)]/n= [1+3+15+6]/n=8.87%**	
Proportion to receive 12 SQ-HDM benefit		50%**	
AR – MT-06 trial	n=338	n=318	n=992
AEs leading to discontinuation – n (%)	7 (2.1%)	13 (4.1%)	30 (3.0%)
Due to other reasons* – total n (%)	25 (7.4%)	16 (5.0%)	68 (6.9%)
Lack of efficacy (e)	2 (0.6%)	0 (0.0%)	4 (0.4%)
Lost to follow-up (f)	5 (1.5%)	1 (0.3%)	12 (1.2%)
Withdrawal of consent (g)	12 (3.6%)	9 (2.8%)	37 (3.7%)
Other (h)	6 (1.8%)	6 (1.9%)	15 (1.5%)
Proportion of patients to discontinue (company)		[(e)+(f)+(g)+(h)]/n= [0+1+6+9]/318=5.03%**	
Proportion to receive 12 SQ-HDM benefit		50%**	

Note: Table adapted from Tables 58-59 in the CS; * Other reasons as defined by the company; ** Assumed for years 1 to 3, i.e. the first 3 model cycles; *** An asthma exacerbation during Period 3A (ICS reduction) was not per se requiring trial discontinuation and patients had the possibility of continuing in the trial up to a maximum of 3 exacerbations. During Period 3B (ICS withdrawal) the protocol specified that patients should be discontinued following an exacerbation.

Probabilities of discontinuing treatment with 12 SQ-HDM due to other reasons were applied in the first 3 model cycles (i.e., 3 years) according to the 12 SQ-HDM treatment schedule. These probabilities were derived from the MT-04[1, 2] and MT-06[4, 5] trials and applied to the AA+AR and AR models, respectively. In both models, the probabilities of discontinuation due to other reasons are informed by the number of patients who discontinued treatment due to lack of efficacy, lost to follow-up, withdrawal of consent, and other reasons.

For the AA+AR model, the probability of discontinuation due to other reasons was estimated considering the entire sample of MT-04,[1, 2] rather than the 12 SQ-HDM arm, and estimated to be 19.75% (=1–65/81). Thus, the probability of 12 SQ-HDM discontinuation due to other reasons in the AA+AR population was estimated as 8.49% for the first model cycle and assumed the same for cycles 2 and 3 given the absence of additional data on the discontinuation of 12 SQ-HDM beyond 12

months. For the AR model, the probability of discontinuation due to other reasons was estimated as 5.03% for the first model cycle and assumed the same for cycles 2 and 3 given the absence of additional data on the discontinuation of 12 SQ-HDM beyond 12 months (Table 20).

Clinical experts from the company's advisory board[55] stated that patients who discontinue allergy immunotherapy treatment early may still receive treatment benefit. Two out of three clinicians said that half of patients who discontinue may still receive benefits, while one clinician said this would be a small number of patients. Thus, the company, in their base case and for both the AA+AR and AR populations, modelled the proportion of patients who discontinue treatment with 12 SQ-HDM but continue as 12 SQ-HDM patients is 50% for the first 3 model cycles. All patients who discontinue treatment with 12 SQ-HDM incur the cost of 6 months' treatment with 12 SQ-HDM to account for any previous time on treatment prior to discontinuation.

Points for critique

For the AA+AR population, the EAG believes that the evidence on discontinuation from the MT-04[1, 2] trial may not reflect the discontinuation rates observed in clinical practice. The discontinuation rates from MT-04[1, 2] considered by the company cover both period 2 and 3. Patients who discontinued in period 2, the maintenance period, have been kept on a limited number of standard of care therapies, irrespective of their asthma control. Thus, the EAG believes that the proportion of patients discontinuing in this period due to lack of efficacy has been underestimated. For period 3, the EAG believes that ICS withdrawal would not be mandated, and that patient discontinuation observed in the MT-04[1, 2] trial has limited external validity and relevance for clinical practice. Thus, and overall, the EAG considers that the discontinuation rates from the MT-04[1, 2] trial may not be reflective of the UK clinical practice.

The EAG notes that, for the AA+AR population, the company estimated the proportion of patients to discontinue (8.49%) considering the number of other non-exacerbation discontinuations for the entire MT-041, 2 sample, not just for the 12 SQ-HDM arm. Given that six non-exacerbation discontinuations were observed in the 12 SQ-HDM treatment arm, the EAG re-estimated the proportion of patients to discontinue to be 8.87% rather than 8.49% (Table 20).

In the absence of evidence, the EAG considers the assumption of using the discontinuation rates for years 2 and 3 (i.e., cycles 2 and 3 of the model) to be the same as the rate observed in year 1 (i.e., cycle 1) to be reasonable.

In Table 21, the EAG summarises existing evidence for AA+AR population on discontinuation rates studies previously discussed (TO-203-31,[57, 58] CARIOCA,[27] Reiber et al., 2021,[29] and Sidenius et al., 2021[30]). While for TO-203-31[57, 58] and Sidenius et al., 2021[30] studies the AEs and other rates of

discontinuation due to other reasons for 12 SQ-HDM are similar to what was observed in the MT-04[1, 2] trial, for both CARIOCA[27] and Reiber et al., 2021[29] studies, the discontinuation rates are higher. The EAG notes that the discontinuation rates related to AEs were similar across the different levels of asthma control in the CARIOCA[27] study.

The EAG considers the discontinuation rates used from the MT-06[4, 5] trial to inform the AR economic model to be reasonable and has no major concerns with this evidence. In Table 21, the EAG also provides evidence for the AR population on AE discontinuation rates. The EAG notes that AE discontinuation rates for 12 SQ-HDM in the P001[8, 9] study are higher than for MT-06,[4, 5] but that these are similar for the 12-18 and the 18+ age groups.

Table 21 Discontinuation due to AEs and other reasons for AA+AR and AR populations available from other studies, including non-interventional, on 12 SQ-HDM.

Discontinuation for AA+AR population	**Study arms**	
TO-203-31[57, 58]	**Placebo (n=274)**	**12 SQ-HDM (n=276)**
AEs leading to discontinuation – n (%)	7 (2.6%)	14 (5.1%)
Demoly et al., 2022 (CARIOCA) [27]	**N/A**	**12 SQ-HDM (n=494)**
AEs leading to discontinuation – n (%)	n/a	93 (18.8%)
Due to other reasons – total n (%)	n/a	253 (51.2%)
Lack of efficacy	n/a	8 (1.6%)
Lost to follow-up	n/a	92 (18.6%)
Withdrawal of consent	n/a	5 (1.0%)
Other (incl. low observance, economical reason, no return)	n/a	13+9+33= 55 (11.2%)
Reiber et al., 2021[29]	**N/A**	**12 SQ-HDM (n=424)**
AEs leading to discontinuation – n (%)	n/a	75 (17.7%)
Sidenius et al., 2021[30]*	**N/A**	**12 SQ-HDM (n=198)**
AEs leading to discontinuation – n (%)	n/a	15 (7.6%)
Due to other reasons – n (%)**	n/a	17 (8.6%)
Discontinuation for AR population	**Study arms**	
P001[8]	**Placebo (n=738)**	**12 SQ-HDM (n=743)**
AEs leading to discontinuation – n (%)	19 (2.6%)	73 (9.8%)
12 to 18 age group (n=189, 95/94)	1 (1.1%)	9 (9.6%)
18 to 50 age group (n=1054, 524/530)	16 (3.1%)	59 (11.1%)
50 + age group (n=238, 119/119)	2 (1.7%)	6 (5.0%)
TO-203-32[10, 11]	Placebo (n=319)	12 SQ-HDM (n=314)
AEs leading to discontinuation – n (%)	6 (1.9%)	4 (1.3%)

Note: Table adapted from Tables 60, 62 and 63 in the CS;

Finally, for both the AA+AR and the AR models, the EAG is concerned with the company's assumption that 50% of patients who discontinued still receive the benefits from 12 SQ-HDM over

the first 3 model cycles. The EAG notes that these estimates were elicited from clinical experts and that no consensus existed among all experts, with one clinical expert indicating that only a small number of patients who discontinued would receive treatment benefits. The EAG acknowledges that scenario analyses were performed on these parameters, reducing the proportion to 0% and increasing it to 100%. The EAG acknowledges also that this parameter was considered probabilistic in both AA+AR and AR models, however attached to an arbitrary 10% variation over the mean.

Issue: The discontinuation rates from the MT-04 trial[1, 2] may not be reflective of the UK clinical practice.

Issue: The assumption that 50% **of patients who discontinued still receive benefits from 12 SQ-HDM applied to the first 3 model cycles is considered uncertain.**

4.2.6.6 Adverse events

The adverse events considered by the company in the economic models are summarised in terms of incidence and duration in Tables 78 and 79 of the CS for the AA+AR and AR populations, respectively. The company claims that the adverse events included in the models are based on the common TEAEs in the clinical trials (MT-04[1, 2] and MT-06[4, 5] for the AA+AR and AR populations, respectively), and indicate that the adverse events listed correspond to events occurring in ≥2% of patients in either trial arm.

The probability of each individual adverse event in Tables 78 and 79 of the CS are considered in the model. The company states that cost and QALY losses associated with adverse events are applied in the first model cycle only and justifies this based on the early onset of most adverse events and the short median time until resolution for the most common TEAEs.

Points for critique

Although the company implies that adverse events in the models correspond to TEAEs occurring in ≥2% of patients (in either trial arm) for the MT-04[1, 2] and MT-06[4, 5] trials for the AA+AR and AR populations, respectively, this does not seem to be correct. Table 54 and Table 55 in the EAR Appendix list the adverse events that have not been included in the economic models, despite being described previously in the CS as to TEAEs occurring in ≥2% of patients (see Table 58 and Table 59 of the CS for trial MT-04[1, 2] and MT-06[4, 5], respectively). The company does not justify the decision to include in the models only some of the most common TEAEs in the trials.

In section 3.2.4, the EAG reports on the safety evidence considered by the company in the clinical sections, which included data from the 5 pivotal trials (MT-04[1, 2] and TO-203-31[57, 58] for the AA +AR population, and MT-06,[4, 5] TO-203-32[10, 11] and P001[8, 9] for the AR population). In contrast, the

economic models only considered evidence from the MT-04[1, 2] and MT-06[4, 5] trials for the AA+AR and AR populations, respectively. The TEAE rates were generally high across the 5 trials. The P001[8, 9] trial showed considerably higher TEAE rates for specific local AEs (e.g., throat irritation, oral pruritis, ear pruritis, oral discomfort, and oedema mouth). The company noted in their clinical sections (B.2.10, page 149 of the CS), the method by which safety evidence was collected differed between trials. In trial P001,[8, 9] structured questionnaires regarding 15 specific local AEs were used for the first (approximately) 28 days of treatment, while other trials did not solicit any particular AEs. The company highlights that unsolicited data collection may result in underreporting of adverse events, while solicited data collection inflate reporting rates. Given the issues with the two methods, the EAG considers that there is uncertainty on which data source better reflects the safety profile of 12-SQ-HDM in AR, the impact of which is not reflected in the company's cost-effectiveness analysis. Nevertheless, the data applied in the company models are better aligned with the treatment effectiveness data. Furthermore, the EAG considers that failure to reflect this uncertainty in the model is unlikely to affect the estimates of cost-effectiveness given that adverse events are not model drivers.

Although the company states in section B.3.3.5 of the CS (pages 192-193) that both cost and QALY losses associated with adverse events are considered in the AA+AR and AR models, QALY loss from adverse events is not parameterised in the models (section 4.2.7.2).

Issue: Not all TEAEs occurring in ≥2% of patients in the clinical trials (MT-04[1, 2] and MT-06[4, 5] for the AA+AR and AR populations, respectively) were included, which underestimated the probability of these adverse events in the AA+AR and AR models.

4.2.7 Health related quality of life

4.2.7.1 HRQoL evidence in the published literature

The CS contained a description of the search methods and search strategies to identify studies reporting utility values in HDM allergic rhinitis or HDM allergic asthma in Appendix A and Appendix B of a report by Initiate Consultancy Ltd.[59] Searches were carried out in February 2015 with a further updated search undertaken in March 2023.

The original SLR conducted identified 19 relevant studies, and the updated SLR identified an additional 18 studies of relevance. Following their review, the company identified 4 reports from 2 studies that were relevant for this appraisal: Hahn-Pederson et al., 2016,[38] Green et al., 2017,[40] Green et al., 2019,[39] and Briggs et al., 2021,[3] as these studies provided utilities related to data collected in the MT-04[1, 2] and MT-06[4, 5] trials. The company further noted the SLR did not identify any utility values for AEs associated with SLIT.

Points for critique

Although minor issues with the searches were identified, in general the EAG was satisfied that a comprehensive search was performed to identify studies reporting on health state utility values for this population. Details of the EAG appraisal can be found in Table 52 in the appendix**.**

4.2.7.2 HRQoL data from identified studies

Within their cost-effectiveness model, the company adopted two approaches to model HRQoL based on: i) treatment-specific and ii) health-state specific utilities. While treatment-specific utilities assign a specific utility value to treatments, health-state utilities provide quantitative measures of how strongly a patient values a certain health state. The company's base case analysis for both AA+AR and AR populations applies a treatment-specific approach. In Table 22 and the following sections a description of the sources of data and methods to support each approach is provided and critiqued by the EAG.

Table 22 HRQoL modelling approach

Utility approach	Treatment-specific utilities (company's base case)	Health state-specific utilities
AA+AR model	Source: MT-04[1, 2] trial data Type of analysis: post-hoc	Source: MT-04[1, 2] trial data Type of analysis: post-hoc analysis, as reported in Briggs et al., 2021[3]
AR model	Source: MT-06[4, 5] trial data Type of analysis: post-hoc, as reported in Green et al., 2017[40]	Source: MT-06[4, 5] trial data Type of analysis: post-hoc analysis

HRQoL in the AA+AR model

Treatment-specific utilities (company's base case): To derive the HRQoL for those receiving 12 SQ-HDM or standard of care, the following three step process took place. Using a post-hoc analysis of MT-04[1, 2] trial data, SF-36 scores were transformed into preference-based utilities using the SF-6D algorithm.[60] The mean difference in utility scores for patients in each group (treatment or placebo) was then calculated between visits 13 (end of trial) and 3 (baseline), i.e., the data was corrected for baseline to determine the between-group differences at the end of the relevant period. The mean change in utility was then added to the weighted average of the baseline utility (at visit 3) for all patients, irrespective of their treatment status, and used to derive the final utility scores used in the model: 0.785 for the 12 SQ-HDM group and 0.753 for the standard of care group (Table 80 in CS).

The company also derived similar treatment-specific utilities capturing the difference in mean utilities for each group between visit 9 (end of treatment maintenance phase) and visit 3 (baseline) and provided this as an alternative option in their economic model.

When using the treatment-specific utilities, the company imposed a restriction in the economic model that limited the sampling of utility values so that individuals on treatment with 12 SQ-HDM could not have lower utilities than those on standard of care. At the clarification stage, the company justified this assumption by stating that there is no clinical rationale suggesting that in the long-term, when initial TEAEs with impact on utility are no longer expected, HRQoL would be worse for those treated with 12 SQ-HDM compared to the standard of care.

In their original probabilistic analysis, the company applied an arbitrary 10% variation to the mean deterministic utility values. Following points for clarification, the company updated their parameters to reflect the SD estimates derived from the MT-04 trial.

Health state-specific utilities: Briggs et al., 2021[3] conducted a post-hoc analysis of MT-04[1, 2] trial data to derive health state-specific utilities. Using a mixed effects regression model, AQLQ data were mapped to EQ-5D-3L scores and used to predict estimates for five health states. The final model provided utilities for well controlled asthma (reference health state), and disutilities reflecting the move from a well controlled health state to partly controlled, uncontrolled, moderate exacerbation, and severe exacerbation. Briggs et al., 2021[3] also estimated the duration of each exacerbation by calculating the mean utilities for various outcomes (e.g., daytime asthma symptom control, predicted PEF, SABA intake, count of wakeups due to asthma) over several visits. Through this analysis, it was estimated that the mean duration of each exacerbation ranged from 14 days prior to 28 days post the peak exacerbation event. Table 83 of the CS provides the mean and standard error for EQ-5D-3L utility scores across each health state given a duration of exacerbation event from 7-28 days.

The model also considered disutilities associated with moderate and severe asthma exacerbations, which were sourced from Briggs et al., 2021[3] and applied to both HRQoL modelling approaches described above. The utility decrements were applied in the model assuming 28-day durations for the impact of an exacerbation.

In the company's base case, no AE-related utility decrements were applied. The company states that the SLR did not identify utility values for the AEs associated with SLIT and that the AEs were mild to moderate with short duration. Thus, the company did not consider that exclusion of disutilities associated with AEs would impact on the estimates of cost-effectiveness.

Utilities in the model were age and sex-adjusted to reflect HRQoL in the general population, as estimated by the Ara and Brazier, 2010[61] algorithm. The well controlled health state was then modelled as the reference state and applied as a multiplier to correct for age and sex-adjusted general population utilities. The model was constrained such that an individual's utility could not exceed that

of their equivalent general population estimated utility. The partly controlled and uncontrolled health states were then applied as a disutility relative to the well controlled health state.

The company additionally provided alternative health state utility estimates from the EUCOAST study[62] to support scenario analyses of the AA+AR model (see Table 84, CS). This study estimated HRQoL using EQ-5D-3L in adult patients with asthma (not specifically AA) in primary care settings in France and Spain according to the level of asthma control, as determined using the GINA guidelines.[6] These utilities where generally lower than the corresponding estimates in Briggs et al. 2021,[3] particularly estimates for the uncontrolled health state. The utility decrements associated with moving from the well-controlled to the partly controlled and uncontrolled health states were also of larger in EUCOAST[62] study compared to Briggs et al., 2021.[3]

In their original probabilistic analysis, the company applied an arbitrary 10% variation to the mean deterministic utility values. Following points for clarification, the company updated their parameters to reflect the variability estimates derived from Briggs et al., 2021[3] and EUCOAST.[62]

Points for critique

The EAG has several concerns with using the treatment-specific approach to HRQoL estimation as the base case for this submission. First, the treatment-specific approach to utility estimation does not align with the health state modelling structure for which the company has noted their preference compared to previous cost-effectiveness studies using MT-04[1, 2] trial data (Hahn-Pederson et al., 2016;[38] Green et al., 2019[39]). Second, the treatment-specific approach utilises HRQoL estimates derived from the SF-36 data collected in MT-04.[1, 2] In contrast, Briggs et al., 2021[3] mapped ACQ data to EQ-5D-3L. Where available, EQ-5D-3L data is preferred according to the NICE reference case.[63] The EAG's preferred approach is to use a health-state valuation of HRQoL and the health state utilities derived from Briggs et al., 2021.[3] Although not the preferred approach of the EAG, if a treatment-specific method were to be used, the EAG's preference would be to use the mean utilities for each group between visit 9 (end of treatment maintenance phase) and visit 3 (baseline), as it better aligns with the EAG's preferred assumptions for the short-term effectiveness (section 4.2.6.1).

The EAG considers that the company's restriction to the sampling of utilities when using treatment-specific utilities is insufficiently justified and does not allow a full consideration of parameter uncertainty in the probabilistic sensitivity analysis (PSA). Thus, this restriction should not be applied. The restriction impacts probabilistic results only. The EAG also considers there is a potential for double counting to some extent the utility impacts related to asthma exacerbations using the company's preferred treatment-specific approach, as it is unclear whether individuals with exacerbations were excluded from the post-hoc analysis dataset used to estimate these utilities.

The EAG considers that 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., 2021,[3] were negative and not accounted for in the probabilistic modelling. This issue is addressed in section 6.1. Briggs et al., 2021[3] has also noted that the MT-04[1, 2] trial data does not capture the HRQoL associated with repeat asthma exacerbations (i.e., the disutility of asthma exacerbations in the model represent the first exacerbation only rather than multiple exacerbations) and is therefore a limitation of this submission. Previous TAs (e.g., TA278[16] and TA751[49]) examined the impact of treatment on the rate of exacerbations and applied a utility decrement to each exacerbation event.

Within the MT-04[1, 2] trial data, it is presently not possible to differentiate how AA and AR symptoms could be interacting to affect patients' HRQoL. For example, if a patient has moderate AR symptoms and partly controlled asthma, their HRQoL will be the same as someone who has mild AR symptoms and partly controlled asthma, because HRQoL outcomes were measured in a post-hoc analysis for asthma control only. While this is a consideration for the EAG, given the current model structure does not provide mutually exclusive health states reflecting both AA and AR severity (section 4.2.2.1), the EAG considers that the evidence currently used from the MT-04[1, 2] trial data does not support a more complex model structure.

Finally, the company did not apply any AE-related utility decrements in their model. The EAG notes that the company did include the resource use and costs related to AEs. For consistency, the EAG's preferred approach would be to include AE-related utility decrements in the model. Nevertheless, the EAG recognises that this is unlikely to be a model driver given the mild severity and short duration of AEs in the pivotal trials.

HRQoL in the AR model

Treatment-specific utilities (company's base case): A post-hoc analysis was used to estimate the average treatment-related utility using EQ-5D data collected in the MT-06[4, 5] trial. Using a two-stage regression modelling approach to correct for skewed data for those in perfect health (with an EQ-5D score clustered close to 1), a binomial model with five regression variables (asthma status, age, rhinitis DSS, rhinitis daily medication score, and smoking status) was first used to estimate the proportion of observations in which patients were in perfect versus imperfect health. During the second stage, a generalised mixed linear model was used to estimate the average utility by treatment status for those in imperfect health (38.6%). Full details on this approach were reported in Green et al., 2017[40] and Poole et al., 2014.[64] The two-stage approach estimated the change in mean utility between visit 8 (end of trial) and visit 3 (baseline) and was reported as 0.919 for the 12 SQ-HDM group and 0.898 for the standard of care group. In their probabilistic analysis, the company applied an arbitrary 10% variation to the mean deterministic utility values.

No consideration of P001[8, 9] HRQoL data was given by the company in their original submission, which collected EQ-5D evidence in a population covering both adults and adolescents. In their updated model following points for clarification, the company provided multiple alternative utilities based on the P001[8, 9] trial EQ-5D-5L data, applying the UK tariff. Results include change in mean utility between visits 3 and 10, and visits 3 and 11, for the adult population only, adolescent population only, and both. As pointed out by the company (Appendix C of the company's reply to points for clarification), a decision was made during the trial to limit the number of subjects answering the EQ-5D-5L questions at Visit 10 and Visit 11. This restricted the analysis to 763 patients (12 SQ-HDM n=388; Placebo n=375), out of 1,482 patients recruited.

Health state-specific utilities: The CS does not sufficiently detail how health-state specific utilities were derived from MT-06[4, 5] trial HRQoL data. To support the health state-specific approach, the EAG believes a three-step approach was in place using a post-hoc analysis of MT-06[4, 5] trial data. First, using the ARIA[51] criteria, patients were identified in terms of their health state (experiencing mild, moderate, or severe AR symptoms). A similar two-stage approach as highlighted in the previous section was then used to estimate the average utility between visit 1 to 2 (baseline) and visit 7 to 8 (end of trial), first by treatment status, and then as a weighted average across the entire sample. Finally, the change in mean utility between visits was estimated using a weighted average of utilities for each health state. Mean utilities and number of patients within each group are provided in Table 82 of the CS. The company did not provide alternative utilities to support scenario analysis using a health state-specific approach in the AR model.

Utilities in the model were age and sex-adjusted similarly to the AA+AR model and no AE-related utility decrements were applied.

In their original probabilistic analysis, the company applied an arbitrary 10% variation to the mean deterministic utility values. Following points for clarification, the company updated their parameters to reflect the SD estimates for the P001[8, 9] trial only, as SD estimates were unavailable for the MT-06 trial.[4, 5]

Points for critique

The EAG considers that the treatment-specific approach to utility estimation does not align with the health state modelling structure for which the company has noted their preference compared to previous cost-effectiveness studies using MT-06 trial data.[40] The EAG's preferred approach is to use a health-state approach to HRQoL to be consistent with the proposed model structure.

At the clarification stage, the company provided average treatment-specific utilities using the EQ-5D-5L data collected during visits 3, 6, 10, and 11 in the P001[8, 9] trial (Table 7, response to clarification

questions). The EAG notes that, per an amendment to the P001 study protocol,[9] a reduced sample of was used to source EQ-5D-5L values during visits 10 and 11. Given the company did not provide further information on whether the reduced sample was or was not systematically different than the full sample in the trial, the EAG is currently unable to assess the representativeness of the reduced sample. The EAG further notes that the company provided treatment-specific utilities to reflect the change in HRQoL between visit 3 (randomisation) and visit 10 (efficacy assessment) or visit 11 (final/discontinuation). Given that patients were provided with open-label symptom-relieving medications two weeks prior to visit 10, and 43% of patients in the trial had an average rhinitis DMS above zero by visit 11, thus indicating potential use of open-label symptom-relieving medication, it is unclear what impact access to open-label medications have had on overall HRQoL. If a treatment-specific method were to be used, preference should be given to the mean utilities for each group between visit 10 (end of efficacy assessment period) and visit 3 (randomisation) before the introduction of other symptom-relieving medications. Finally, the use of EQ-5D-5L has been validated for adult populations only. There is literature suggesting the EQ-5D-5L questionnaire may not be appropriate for adolescent populations, given the design of the questionnaire may not reflect the development and cognitive abilities of this population.[65] Furthermore, there is a version of EQ-5D validated for use in children and adolescents aged 8-15 years, the EQ-5D-Y,[66] which could have been used to measure HRQoL in the adolescent subgroup. While the utility values obtained from the P001[8, 9] trial suggest greater HRQoL gains from 12 SQ-HDM versus placebo in adolescents than in adults, the EAG notes that it is unclear whether these findings are reliable given the methodological uncertainty of using the EQ-5D-5L for this subpopulation.

The points for critique pertaining to the AA+AR model for the AE disutilities and constrained sampling of treatment specific utilities apply equally to the AR model.

Finally, the EAG considers that parameter uncertainty was not appropriately reflected in the company's model, as the probabilistic analysis assumed an arbitrary 10% variation over the mean value.

Issue: The treatment-specific approach to HRQoL does not align with the model structures developed for AA+AR and AR, respectively.

Issue: The parameter uncertainty of treatment specific utilities in the AA+AR and AR models is artificially constrained.

Issue: The lack of inclusion of AE-related utility decrements, although expected to have minimal impact on cost-effectiveness results, creates inconsistencies in the model, as AE-related costs were included.

Issue: Utility estimates collected in P001[8, 9] suggest greater HRQoL gains from 12 SQ-HDM treatment in the adolescents compared to the adult subgroup, but were collected with an instrument that is not validated for adolescents.

4.2.8 Resources and costs

4.2.8.1 Confidential pricing arrangements

The EAG notes that there are a number of confidential commercial arrangements in place for drugs comprising established clinical practice/standard of care in the AR+AA population (but not the AR population). Table 23 presents details of which drugs have confidential prices that differ from the publicly available list prices used to generate the results in this report. These prices were made available to the EAG and were used to replicate all analyses presented in the EAR for consideration by the Appraisal Committee. Details of all confidential pricing arrangements and all results inclusive of these arrangements are provided in the confidential appendix to this report. These prices were correct as of 12th December 2023. The treatment acquisition costs used in the analyses presented in the company submission and the EAR (section 6) do not include confidential pricing agreements.

Table 23 Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of confidential arrangement
Omalizumab	Simple PAS price
Mepolizumab	Simple PAS price
Dupilumab	Simple PAS price
Tezepelumab	Simple PAS price

Abbreviations: PAS, patient access scheme

4.2.8.2 Resource use and cost evidence in the published literature

The CS contained a description of the search methods and search strategies to identify studies relating to healthcare costs and resource use in patients with HDM allergic rhinitis or HDM allergic asthma in Appendix A and Appendix B of a report by Initiate Consultancy Ltd.[67] Searches were carried out in February 2015 with a further update search undertaken in March 2023.

A total of ten studies[13, 36, 38, 40, 45, 68-73] were identified across the two literature searches, in which five studies[13, 38, 40, 45, 73] were considered as alternatives to inform the resource use for primary and secondary care (see Table 92, p214 of the CS). The company briefly describes the ten identified studies in section B.3.5 (p204-208 of the CS).

Points for critique

Although minor weaknesses with the searches were identified, in general the EAG was satisfied that a comprehensive search was performed to identify studies with cost and resource use for this population. Details of the EAG appraisal can be found in Table 53 in the Appendix.

4.2.8.3 Overview of resource use and costs in the models

The company's base case analysis includes resource use and costs relating to i) 12 SQ-HDM acquisition and administration; ii) standard of care treatment; iii) (disease) management (consisting of primary care and secondary care visits); iv) asthma exacerbations (only for AA+AR model); and v) AEs. In line with the NICE final scope, costs associated with diagnostic tests for HDM sensitisation have been also included in the company's economic model. Most costs for non-drug resource use were sourced from the National Schedule of Reference Costs 2021- 2022[74] and the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2022 Manual.[75] Costs were discounted at an annual rate of 3.5%.

A waning effect, similar to that applied to the medium-to-long-term treatment effectiveness (section 4.2.6), is implemented on the costs for primary and secondary care.

4.2.8.4 12 SQ-HDM acquisition and administration costs

The cost of treatment with 12 SQ-HDM includes the acquisition costs of the drug incurred over the assumed treatment duration and the one-off costs of i) face-to-face attendance with a respiratory specialist at treatment initiation, and ii) HDM sensitisation testing. As 12 SQ-HDM is an add-on therapy, the costs of standard of care are also incurred for individuals on treatment with immunotherapy; these are described separately in section 4.2.8.5. Table 24 summarises the resource use and costs associated with 12 SQ-HDM treatment in the company's base case analysis. These costs are the same in the AA+AR and AR models.

Table 24 Summary of resource use and costs of 12 SQ-HDM treatment in the company's base case

Item	Model input	Details and source
Drug acquisition costs per year		
12 SQ-HDM	£975.46	Calculated based on the dosing of 12 SQ-HDM for adults and adolescents: one oral lyophilisate daily. The list price of 12 SQ-HDM is £80.12 per pack of 30 tablets. The duration of treatment is three years (equivalent to three cycles).
Drug administration costs per year (applied in the 1st cycle only)		
12 SQ-HDM	£262.25	As the first dose of 12 SQ-HDM is administered under physician supervision, the model applies a one-off cost for Respiratory Medicine Service, Non-Admitted Face-to-Face Attendance, First (WF01B) - 2021-2022 NHS reference costs[74].
HDM sensitisation diagnostic cost (applied in the 1st cycle only)		

Item	Model input	Details and source
12 SQ-HDM	£2.96	One-off cost of diagnostic blood test, directly access pathology services, Haematology (DAPS05), 2021-2022 NHS reference costs[74].
Abbreviations: HDM, house dust mite; NHS, National Health Service; SQ, standardised quality		

Treatment duration was constrained at 3 years in accordance with international clinical guidance and consensus statements,[76, 77] which define a period of 3 years for AIT to achieve sustained disease modification. The recommendation for this specific treatment duration is supported by a prospective study of SLIT with HDM extract in AR, which suggested disease remission up to 7 years following 3 years of active treatment.[32] Those who discontinued 12 SQ-HDM due to adverse events incur a cost for one month of treatment, whereas those who discontinued due to other reasons incurred a cost of six months of treatment in the cycle they discontinued (sections 4.2.6.5 and 4.2.6.6).

Points for critique

Although the company's analyses limit 12 SQ-HDM treatment duration to 3 years, treatment duration is not restricted according to its market authorisation. It is, however, debatable what the optimal duration of treatment is.[76] Marogna et al. 2010[32] indicated that a 3-year course of SLIT may not yield a sustained long-term benefit and the optimal treatment duration would be 4 years. Clinical advice to the EAG also suggested that the 3-year treatment duration benchmark is historical. This benchmark is established so that long-term immunological and sustained benefits can be seen beyond symptomatic improvement. However, for patients who exhibit ongoing improvement nearing the end of the 3-year period who have not yet attained a stable state, treatment can be extended for an additional year. The company model does not present alternative treatment durations, so the EAG is concerned that the heterogeneity in this parameter has not been fully explored (section 4.2.6.2).

The company's model does not allow for treatment to be reinitiated. In the evidence base presented in the company's submission, the prospective study[32] permitted retreatment with 12 SQ-HDM if a reduction greater than 50% of the baseline symptom plus medications score was not maintained. Moreover, the retrospective cohort REACT study (section 3.2.3) using claims data from Germany indicated that the average total treatment duration with index-AIT in the main cohort of patients with AR with or without AA (549 days) substantially exceeded the duration to first discontinuation (216 days), suggesting that retreatment may have occurred.[31] The clinical adviser to the EAG considered retreatment possible (if infrequent) and to be generally associated with an initial shorter treatment duration than 3 years. Thus, the EAG is concerned that the company may have underestimated the cost of 12 SQ-HDM in UK clinical practice by not explicitly modelling retreatment.

Finally, the EAG believes that the cost of a generic diagnostic blood test may not represent the true cost of skin prick testing and/or IgE testing. However, the EAG is unable to address this uncertainty

given the time constraints of this appraisal. Furthermore, it is possible that patients on standard of care therapy alone have undergone testing for HDM sensitisation as part of a battery of tests for other allergens. If this is the case, then HDM sensitisation testing would not be an incremental cost for 12 SQ-HDM compared to standard care.

Issue: Although a recommendation exists for a 3-year treatment duration for allergy immunotherapy in AR, the optimal duration for AA+AR is uncertain.

Issue: Retreatment with 12 SQ-HDM is not considered by the company's model and, thus, the company's estimates for the cost of 12 SQ-HDM may be underestimated.

4.2.8.5 Standard of care treatment costs

The treatment costs associated with the standard of care pharmacotherapies are incurred by individuals in both the 12-SQ-HDM and standard of care treatment groups, but differences exist on the magnitude of these between groups.

AA+AR population

The standard of care costs for AA+AR include the costs associated with the clinical management of allergic i) asthma and ii) rhinitis. The AR management costs in the AA+AR model are informed directly by the AR model and are discussed below. Table 25 summarises the costs included in the company's base case analysis for the AA+AR population, including categories of cost which are discussed in subsequent sections (i.e., costs of primary care, secondary care, asthma exacerbations and AEs).

Table 25 Summary of resource use and costs used in the company's base case analysis for the AA+AR population

Item	Model input	Details and source
Standard of care treatment costs per year – AA+AR		
12 SQ-HDM	Health state: Well controlled: £310.23 Partly controlled: £326.34 Uncontrolled: £400.03	Includes costs for asthma management and costs for rhinitis management (linked to AR model). Costs of asthma management for the well-controlled health state for SoC is calculated based on the BTS/SIGN 2019 clinical guidelines[14] and assumptions on the distribution of patients across asthma management steps, informed by the CARIOCA[27] study. Unit costs of medication are from BNF[78] or eMIT[79]. To estimate the costs for partly controlled and uncontrolled health states for SoC, cost ratios relative to well controlled SoC are factored in (105.46% and 130.44%, respectively). These relative increases are obtained from the proportional rise in ICS daily use in the partly controlled vs well controlled and in uncontrolled vs well controlled health states across the two treatment arms in the maintenance phase of the MT-04 trial. Costs for the well-controlled health state for 12 SQ-HDM is calculated in the same way, with the only difference being the distribution across asthma management steps. An adjustment to the patient distribution across steps is
Standard of Care	Health state: Well controlled: £321.45 Partly controlled: £338.01 Uncontrolled: £413.71	

Item	Model input	Details and source
		made to incorporate the assumption that there is a 22.5% reduction in the proportion of patients in step 5 for 12 SQ-HDM compared to SoC (corresponding to an increase in the proportion of patients in step 4 for 12 SQ-HDM vs SoC).
Management costs per year – Primary care costs per year – AA+AR		
12 SQ-HDM	Health state: Well controlled: £78.27 Partly controlled: £82.54 Uncontrolled: £102.09	The calculation of annual cost for GP visits in the well controlled health state for SoC is as follows: • Number of annual GP visits by patients with mild-moderate-severe symptoms are taken from a modified Delphi panel[54] with seven physicians in the UK (see Table 93, p216 of the CS); • Annual costs of GP visits by GINA[6] treatment steps are then calculated using the unit cost for a GP visit sourced from PSSRU 2022[75] and the number of GP visits assuming the following correspondence between disease severity level and GINA treatment steps: mild <> steps 1 and 2, moderate <> steps 3 and 4, and severe <> step 5; • Annual costs for GP visits are then weighted by the distribution of treatment steps sourced from CARIOCA study[27] to derive an annual primary care cost for the well-controlled health state for SoC. The annual costs for partly controlled and uncontrolled health states for SoC are derived by multiplying the cost of well controlled SoC by the proportional increase in ICS daily use between partly controlled vs well controlled and uncontrolled vs well controlled across all patients in the treatment maintenance period of the MT-04 trial (the same ratios used in calculation of SoC treatment costs). The costs for GP visits with 12 SQ-HDM are derived by assuming a relative reduction in GP visits (-25.76%) observed during the MT-04 trial (visit 3–- randomisation–- to visit 13–- end of trial), which is assumed equivalent across health states.
Standard of Care	Health state: Well controlled: £105.42 Partly controlled: £111.18 Uncontrolled: £137.51	
Management costs per year–- Secondary care costs per year – AA+AR		
12 SQ-HDM	Health state: Well controlled: £265 Partly controlled: £265 Uncontrolled: £265	The secondary care costs are the same for all asthma control levels. The annual number of secondary care visits in SoC is sourced from an unpublished analysis of HES outpatient data (financial years from 2016 to 2021, see Appendix R2 of the CS). The unit cost for secondary care visits is sourced from 2021-2022 NHS reference costs[74]; Total Outpatient Attendance, Respiratory Medicine Service (340). The annual cost for secondary care visits for 12 SQ-HDM is derived by applying the relative reduction associated with 12 SQ-HDM (-54.58%) sourced from MT-04 trial (visit 3 – randomisation–- to visit 13 – end of trial) to the annual cost for standard of care.
Standard of Care	Health state: Well controlled: .£584 Partly controlled: £584 Uncontrolled: £584	
Asthma exacerbation costs – AA+AR		
	Moderate exacerbation: £111.95	Moderate exacerbation costs were calculated based on the assumption that 70% of moderate exacerbations are managed within primary care, which comprises of a GP visit, SABA and prednisolone use, based on GINA 2023 guidelines[44] (see Table 95, p218 of the CS), where 30% of cases require emergency visits. The unit cost of emergency visits is sourced from 2021-2022 NHS reference costs[74]: weighted average of emergency medicine investigations HRG up to category 4 treatment (VBO2Z-VB09Z).
	Severe exacerbation: £464.90	Severe exacerbation costs were calculated based on the assumption that 70% of severe exacerbations are managed within primary care (the same as for moderate exacerbations) and all patients are subsequently hospitalised, with 90% assumed to require an emergency department visit, 38% assumed to stay in the

Item	Model input	Details and source
		respiratory ward and 3% assumed to require ICU admission (Lane et al., 2006[80]).
Adverse event costs (applied in the 1st cycle only) — AA+AR		
12 SQ-HDM	£4.00	Calculated based on the probabilities of AEs (see Table 78, p192 of the CS) and the proportions of those with AEs requiring specific action consisting of temporary or definitive discontinuation from 12 SQ-HDM (14.96%) and SoC (9.25%) observed in the MT-04 trial. The unit cost of AE is the cost of GP visit, sourced from PSSRU 2022[75].
Standard of Care	£0.21	

Abbreviations: AA, allergic asthma; AEs, adverse events; AR, allergic rhinitis; BNF, British National Formulary; eMIT, electronic market information tool; GP, general practitioner; ICU, intensive care unit; GINA, Global Initiative for Asthma; HDM, house dust mite; HRGs, Healthcare Resource Groups; HES, Hospital Episode Statistics; ICS, inhaled corticosteroids; NHS, National Health Service; PSSRU, Unit cost of health and social care; SABA, short-acting beta-agonist; SQ, standardised quality; SoC, standard of care;

The company's base case derives the cost of managing asthma for the well-controlled health state in the standard of care treatment group from clinical guidance[14, 15, 44] (see Table 89, CS) according to asthma management step. The cost for a patient with well controlled asthma on treatment with standard of care is calculated by weighting the cost of each treatment step with the distribution across treatment steps, sourced from the CARIOCA study.[27] The treatment step distribution from Reiber et al., 2021[29] is also considered in a scenario.

The cost of the partly controlled and uncontrolled health states for standard of care is derived by uprating the well-controlled health state costs by the relative increase in ICS use observed between partly controlled/uncontrolled and well controlled asthma during the maintenance phase (period 2) of the MT-04 trial.

The company assumed that 12 SQ-HDM could delay severe asthma progression and reflected this in the model by applying a 22.5% reduction in the proportion of patients that progress to step 5 (and implementing a corresponding increase in the proportion of patients in step 4) for those treated with 12 SQ-HDM vs. standard of care. This reduction was informed by the company-led advisory board of eight respiratory physicians[55] (see Appendix M2 of the CS, p6).

The company's submission also presents a scenario where the treatment costs of asthma management for standard of care and 12 SQ-HDM arms are informed by the MT-04 trial (Table 87, CS). In this scenario, only the costs of ICS and SABA relievers by asthma control level were included in the treatment costs. The cost of ICS was estimated based on the average daily dose of budesonide across the treatment maintenance period (visits 4-8), while for SABA relievers it was based on the average intake of salbutamol estimated during the ICS reduction and efficacy assessment period (visits 9-12) (Table 87, CS). Health state treatment costs for this scenario are shown in Table 88 of the CS.

Points for critique

The EAG's main concern with the approach taken to estimate standard of care treatment costs is that it relies on numerous assumptions that are necessary due to i) the MT-04 trial not being reflective of UK clinical practice, and ii) the company's modelling approach not reflecting transitions between health states defined based on treatment steps. Thus, the company had to conflate all asthma management steps (1-5) in each of the three asthma control health states and assume a proportional difference in costs between levels of control based on MT-04 trial evidence on ICS dose differences in the treatment maintenance (that may not be suitable for this purpose). The EAG feels that a more appropriate approach would be to explicitly model step up/down of treatment as a function of asthma control. This would allow more closely capturing how improved disease control could lead to delays in progression and escalation of pharmacological treatment.

The assumptions made by the company in their costing approach also raise concerns. The company's costing approach (labelled 'micro-costing' in the CS; the EAG prefers not to use this term as the approach taken was not a 'micro-costing' procedure) may have overestimated costs of standard of care overall. The company's interpretation of clinical guidance when defining pharmacological treatment combinations at each asthma management step may not be reflective of average therapy use. Firstly, while the BTS/SIGN guidelines[14] recommend the use of SABA relievers across all asthma management steps as needed, the model assumes daily SABA use. Secondly, medication such as LTRA and theophylline are optional according to BTS/SIGN guidelines,14 whereas the company assumes that 25% and 100% of patients in steps 4 and 5 are treated with theophylline and LTRA, respectively. Thirdly, the model assumes that all patients eligible for biologics are currently using them, assumed to be 68% of patients at step 5 (17% of each 4 biologics). The EAG notes that the approach taken by the company may not reflect the biologic distribution and dosing variability observed in clinical practice, which may limit the validity of the cost estimates for standard of care. Given how similar standard of care costs are for patients on 12 SQ-HDM (as an add-on therapy), the impact of the potential overestimation of standard of care costs is not a cost-effectiveness driver.

The EAG notes that the biologics considered in the company's model include mepolizumab[81] (indicated for severe refractory eosinophilic asthma), and dupilumab (for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide.[49] The assumption that these two biologics are used in equal proportion to omalizumab (for severe allergic asthma)[16] and tezepelumab (for severe asthma)[12] may not be reflective of clinical practice given mepolizumab and dupilumab have more restricted indications than omalizumab and tezepelumab.

The treatment cost differences between the AA+AR alive health states are driven by the assumption that these cost differences are proportional to the difference in ICS use observed between levels of

asthma control (well controlled, partly controlled and uncontrolled asthma) in the MT-04 trial. This is a strong assumption, one that cannot be validated by the EAG. It implicitly assumes that the proportional increase in the ICS use between levels of asthma control in the MT-04 trial directly translates into a proportional increase in costs across all modelled medications. Given that there is no constant relationship between dose and cost that applies to all standard of care medications in the model, this assumption is likely not plausible.

The assumption regarding the treatment effect of 12 SQ-HDM on the reduction in biologic use compared to standard of care could not be validated with evidence from the MT-04 trial, as concomitant biologic treatments were not allowed in this study (section 3.2.1). The company elicited the 22.5% estimate but did not detail the elicitation method and the degree of heterogeneity in the clinicians' responses. This limits the EAG's assessment of the validity of the elicitation. The EAG is also concerned how the uncertainty around this parameter is modelled (i.e., through an arbitrary standard error of 10% of the mean value). While acknowledging the possibility for a treatment effect of SQ-HDM in reducing biologic usage versus standard of care, the magnitude and the associated uncertainty surrounding this effect remains uncertain. The EAG has identified an alternative source of evidence for the utilisation of biologics, which comes from the REACT study[31] (section 3.2.3 for study description). In the main cohort, which includes individuals with AR with and without asthma, the average prescriptions of biological drugs show small and non-significant statistical differences between those using AIT and those in the control group at year 3, 5, and 9 (see Table S17 in the appendix of the REACT study[31]). While the applicability of this evidence to the UK setting is uncertain due to the lack of information on dosing and the availability of biologics and potential dilution of effect due to the inclusion of individuals without asthma, it does not support the magnitude of effect on use of biologics for those being treated with 12 SQ-HDM.

As mentioned, the company also provides a scenario where treatment costs are informed directly by the MT-04 trial. The EAG does not consider this alternative evidence source to be preferable to the company's base case. First, the EAG considers that the pharmacotherapies allowed in the MT-04 trial are not reflective of the standard of care treatments available in UK clinical practice, as discussed in section 3.2.1. Second, the EAG believes that the SABA intake is unlikely to reflect usage of these drugs in clinical practice, as the ICS reduction was due to protocol and not driven by asthma control. The EAG considers it plausible that the use of SABA relievers in the ICS reduction and treatment efficacy period of the MT-04 trial may have been affected as a consequence of the reduction in ICS dosage.

The unit costs selected by the company are sourced from appropriate sources. The EAG identified a few discrepancies in unit costs of some drugs compared to the cited sources, but this may be due to price updates post-CS. The EAG corrects this issue (which also applies to the AR model) in section 6.

Issue: The company's modelling approach does not allow appropriately capturing the impact of 12 SQ-HDM on the utilisation of standard of care pharmacotherapy due to improved asthma control.

Issue: The company's interpretation of clinical guidance to inform standard of care treatment composition may have led to the overestimation of costs.

Issue: The distribution of biologic treatments included in the company's standard of care cost may not be reflective of clinical practice given the indication of these treatments. The assumption on the treatment effect of 12 SQ-HDM on the progression of patients to biologic treatment (step 5) relies on the validity of the company's elicitation and parameter uncertainty surrounding this effect may not be appropriately reflected in the model.

Issue: The differences in costs of standard of care between AA+AR model health states relies on a strong and implausible assumption that relative increases in ICS use between levels of control directly translate to a proportional increase in costs across all standard of care asthma medications.

AR population

The cost for established clinical management was informed by symptomatic medication use in the MT-06 trial by AR severity level and treatment arm. As mentioned above, this evidence was also used to inform the costs of standard of care AR pharmacotherapies in the AA+AR model. In the AA+AR model, the cost of standard of care AR pharmacotherapies is independent of asthma control levels (i.e., health state costs only differ according to treatment arm) and are estimated as a weighted average of AR treatment costs across AR severity levels (as informed by the distribution of disease severity of AR (without AA) elicited from the modified Delphi panel[54] [Appendix M2, CS]).

The company only includes the costs of oral antihistamine (desloratadine 5mg) and nasal corticosteroid (budesonide 64 μg/dose) medications in the estimation of standard of care treatment costs. Although the MT-06 trial also allowed the use of antihistamine medication for conjunctivitis symptoms, this cost was not included in the model. The EAG considers this may have been omitted by mistake but is not concerned the omission impacts on the cost-effectiveness outcomes.

Table 26 summarises the costs included in the company's base case analysis for the AR model, including categories of cost which are discussed in subsequent sections (i.e., costs of primary care, secondary care, and AEs).

Table 26 Summary of resource use and costs used in the company's base case analysis for the AR population

Item	Model input	Details and source
Standard of care treatment costs per year - AR		
12 SQ-HDM	Health state: Mild: £12.15 Moderate: £21.03 Severe: £19.86	Calculated based on resource use data (average daily doses) collected throughout MT-06 (visit 3 – post randomisation - to visit 8 – end of trial). Per-protocol medication included: desloratadine 5mg, budesonide nasal spray 64µg/dose, and azelastine 0.05% (the model does not include this cost component). The unit costs of budesonide and azelastine are from BNF[78], and desloratadine is from eMIT[79].
Standard of Care	Health state: Mild: £15.24 Moderate: £21.57 Severe: £30.86	
Management costs per year - Primary care cost per year - AR		
12 SQ-HDM	Health state: Mild: £24.05 Moderate: £24.97 Severe: £17.19	The numbers of annual GP visits by severity are sourced from a modified Delphi panel[54] involving seven physicians in the UK (see Table 93, p216 of the CS). Unit costs for GP visits is from PSSRU 2022[75]. The annual costs for GP visit in 12 SQ-HDM are based on the costs for GP visit in SoC and the observed relative reduction in GP/specialist visits (-4.92%) for 12 SQ-HDM compared to SoC during the MT-06 trial (visit 3 – post randomisation - to visit 8 – end of trial).
Standard of Care	Health state: Mild: £25.29 Moderate: £26.26 Severe: £18.08	
Management costs per year - Secondary care cost per year - AR		
12 SQ-HDM	£155	The secondary care cost is the same for all severity levels. The annual cost for secondary care visits in SoC is the same as for the AA+AR model. The annual cost for secondary care visits in 12 SQ-HDM is derived based on annual costs in SoC, factoring in the relative reduction associated with 12 SQ-HDM (-73.53%), as sourced from El-Qutob et al., 2016[13].
Standard of Care	£584	
Adverse event costs (applied in the 1st cycle only) - AR		
12 SQ-HDM	£4.54	Adverse event costs were calculated based on the probabilities of AEs (Table 79, p192 of the CS) and the proportions of those with AEs that required specific action in 12 SQ-HDM (12.63%) and SoC (15.29%), as observed in the MT-06 trial. The unit cost of AE is the cost of GP visit[75].
Standard of Care	£0.61	

Abbreviations: AA, allergic asthma; AEs, adverse events; AR, allergic rhinitis; BNF, British National Formulary; eMIT, electronic market information tool; GP, general practitioner; HDM, house dust mite; NHS, National Health Service; PSSRU, Unit cost of health and social care; SQ, standardised quality; SoC, standard of care;

Points for critique

The EAG considers the data source used to inform the standard of care resource use (i.e., MT-06), to be in line with the source of effectiveness data. However, the EAG is concerned about the generalisability of the standard of care medication costs to a UK clinical practice setting (section 3.2.2.3), given the MT-06 trial excluded the use of several pharmacotherapies available in the NHS (namely, intranasal anticholinergics, regular non-sedating oral H1-antihistamines, intranasal decongestants, and LTRA; see Table 3, CS). The EAG considers that if the positioning of 12 SQ-HDM is at the last line of treatment and for people whose disease could not be relieved by other pharmacotherapies available in the NHS, then symptomatic medications allowed in the MT-06 trial may be reflective of NHS clinical practice. However, the 12 SQ-HDM market authorisation does not

restrict the use of the immunotherapy when all other relevant treatments have been exhausted, and during the clarification stage, the company confirmed that 12 SQ-HDM be positioned in line with the marketing authorisation (section 2.2).

The unit costs selected by the company are sourced from appropriate sources. The EAG identified a few discrepancies in unit costs of some drugs compared to the cited sources, but this may be due to price updates post-CS. The EAG corrects this issue in section 6.

Issue: The generalisability of standard of care medication costs from the MT-06 trial to UK clinical practice is uncertain.

4.2.8.6 Management costs

The management costs include the costs associated with primary care and secondary care; these are described in detail and critiqued in turn for each population in the subsequent subsections.

Primary care costs

In both models, the costs of primary care include the costs of GP visits with the unit cost (£41 per visit) sourced from PSSRU 2022.[75] The EAG considers the unit costs selected by the company appropriate. Primary care costs differ across health states, but also across treatments under comparison (12 SQ-HDM is assumed to reduce the intensity of resource use across all health states compared to standard of care).

AA+AR population

The company's base case analysis based the standard of care annual number of GP visits (see Table 93, CS) on a modified Delphi panel[54] of seven UK practicing physicians (5 GPs and 2 consultants) commissioned by the company to characterise the UK treatment pathway in allergic respiratory disease (Appendix M1, CS). Since the Delphi panel elicited resource use by AA+AR severity level (mild, moderate and severe) rather than by asthma control levels, further assumptions were used to calculate health state primary care costs. The company took a three-stage approach to derive the primary care health state costs, which is not sufficiently detailed or justified in the CS. Examination of the model by the EAG suggests that this approach relies on the following assumptions and data sources:

i. The number of GP visits elicited from the modified Delphi panel[54] are translated into resource use by GINA asthma treatment guideline steps[44] assuming that mild disease corresponds to step 1 and 2, moderate to steps 3 and 4, and severe to step 5.

ii. The cost of GP visits by each GINA treatment step is calculated for the standard of care by applying the unit cost of a GP visit[75] to the derived resource use by GINA step and weighting the distribution across GINA steps from the CARIOCA study[27]. Corresponding costs by GINA step for 12 SQ-HDM are derived by applying a relative reduction in GP visits associated with 12 SQ-HDM vs standard of care from the MT-04 trial across all GINA steps. The company's base case analysis estimates a relative reduction of 25.76% from data collected in the period from randomisation to end of trial (visits 3 to 13). Following clarification, the company adjusted this reduction to 31.19% to include only visits post randomisation (visits 4 to 13) and stated that it was updated for the new model base case. The EAG notes this change was not implemented in the electronic version of the model (sections 5.1 and 6).

iii. For each treatment group (12 SQ-HDM and standard of care), the respective primary care costs for the well-controlled state were estimated as a weighted average of GP visit costs by GINA steps in the previous calculation stage (ii.). Costs for the partly controlled and uncontrolled health states were then derived by applying the relative increase of average ICS daily use between levels of asthma control to the treatment specific well controlled health state cost, as estimated in the treatment maintenance phase of the MT-04 trial (the same ratios used for the calculation of standard of care treatment costs, see section 4.2.8.5).

The AA+ AR model provides three other sources for the annual number of GP visits, namely the MT-04 trial,[1, 2] Demoly et al., 2016,[45] and Romano et al., 2023.[82] Demoly et al., 2016 was identified in the company's cost and resource use SLR. Romano et al., 2023 is a poster presentation reporting a cross-sectional study on the burden of allergic rhinitis in children (5-17 years old) in the UK and Canada. It is unclear whether the study has been published or peer-reviewed, and the CS does not state how it was identified. The EAG notes that although the same three-stage approach described above is used to derive primary care health state costs using the alternative sources, none of the reported resource use was stratified by AA+AR disease severity; the same value was assumed for all severity levels. Table 27 shows the underlying annual number GP visits by health state for the alternative evidence sources considered in the model.

Table 27 Number of annual GP visits from alternative evidence sources – AA+AR population

Annual GP visits*	Delphi panel54		MT-041, 2		Demoly et al., 201645		Romano et al., 202382	
	SoC	12 SQ-HDM	SoC	12 SQ-HDM	SoC	12 SQ-HDM	SoC	12 SQ-HDM
Well controlled	2.57	1.91	0.23	0.17	3.50	2.60	3.80	2.82
Partly controlled	2.71	2.01	0.25	0.18	3.69	2.74	4.01	2.98
Uncontrolled	3.35	2.49	0.31	0.23	4.57	3.39	4.96	3.68

* Extracted from the electronic version of the model; GP, general practitioner; SoC, standard of care

In the base case probabilistic analysis, the company assumed an arbitrary standard error of 10% of the mean value for the annual number of GP visits and for the relative reduction in GP visits associated with 12 SQ-HDM. Following points for clarification, observed standard errors were updated for the annual GP visits, as reported in Romano et al., 2023[82] (see 'Parameters' tab, column M, of the electronic updated company's model). Notably, the EAG could not validate the standard errors in this reference.

Points for critique

The EAG's main concern with the approach taken to estimate primary care costs is that it relies on numerous assumptions that are necessary due to the lack of alignment between the evidence used to inform these costs and the model structure. However, these assumptions were not justified by the company. First, the evidence elicited by the company to inform the annual number of GP visits was stratified by disease severity level, and the company's costing approach implicitly assumes that the elicited number of GP visits applies to individuals whose AA is well controlled. The EAG notes that, according to the information provided by the company, the clinical experts were asked *"On average, how many GP visits do patients have per year at each level of disease severity?*" (CS Appendix M1, p7). If the estimates elicited from the experts conflate GP visits across all asthma control levels, it may result in an overestimation of GP visit costs across all health states. Second, this costing approach required assuming a distribution of individuals across GINA treatment steps.[44] The company sourced this distribution from the CARIOCA study,[27] in contrast with what was done for the calculation of standard of care treatment (section 4.2.8.5), and did not explore other evidence sources. Third, the EAG is concerned about the validity of assuming that a link between the increase in the ICS use observed in the MT-04 trial and increase in GP visits across levels of AA control. This assumption implies that an increase in the dosage of ICS across levels directly translates into a proportionate increase in GP visits, but the company did not provide a clinical rationale for this. Finally, the company's approach to costing primary care heath states implies that cost savings from 12 SQ-HDM compared to standard of care result from i) increased time in the health states with lower levels of primary care resource use consumption, and ii) a treatment effect of 12 SQ-HDM independent of asthma control level. The EAG suspects there is uncertainty on whether the treatment

effect is independent of asthma control and is concerned that this assumption may have contributed to an overestimation of the cost savings in primary care.

The EAG further notes that all evidence sources used to inform the number of GP visits for the well-controlled health state in the company's analyses have limitations. The issues with the evidence elicited through the modified Delphi panel[54] have been highlighted above. The MT-04 trial suggests considerably lower primary care resource compared to other evidence sources, as illustrated in Table 27. Given this and concerns highlighted in section 3.2.1 about the generalisability of the MT-04 trial, the EAG does not consider MT-04 to be the most appropriate source of evidence for this parameter. The other two evidence sources[45, 82] that were provided for the number of GP visits in the standard of care arm also seem unlikely to reflect the AA+AR population in the model. It is not clear whether participants included in Demoly et al., 2016[4] had AA concomitant to AR, as the study did not collect this information directly. The study population in Romano et al., 2023[82] consisted of (UK and Canadian) children aged 5 to 17 years with moderate to severe AR, of which 40% also had AA. Since 12 SQ-HDM is not indicated in children with AA+AR, the study population does not match the AA+AR population in the CS. Thus, the EAG considers that the modified Delphi panel[54] provides the least flawed evidence to inform the number of GP visits for the well-controlled health state.

The EAG also considers it appropriate to source the relative reduction in primary care costs associated with 12 SQ-HDM from the MT-04 trial, but prefers to use the estimates from the treatment maintenance period (period 2) of the trial (7.35% reduction compared to standard of care, across visits 4 to 9) rather than the ICS reduction and treatment efficacy period (period 3) that was applied in the company's corrected base case (31.19% reduction compared to standard of care). The EAG notes, however, that the reduction in primary care contacts was estimated by the company based on the number of GP or specialist visits collected for each treatment arm, rather than only for the number of GP visits. While the EAG considers it reasonable to assume a similar reduction in GP visits as for GP and specialist visits (as the company did not have estimates disaggregated by type of visit), this provides additional uncertainty to the parameter.

Issue: Evidence used to inform primary care costs has limitations and is poorly aligned with the AA+AR model. Thus, the calculation of primary care costs requires strong assumptions, which have not been justified nor sufficiently tested, and may contribute to an overestimation of primary care cost savings associated with 12 SQ-HDM.

Issue: The relative reduction in GP visits associated with 12 SQ-HDM in the AA+AR population derived from the MT-04 trial is uncertain.

AR population

In the company's base case analysis, standard of care annual number of GP visits by level of disease severity was informed by evidence elicited in the same modified Delphi panel[54] used to inform these parameters in the AA+AR model (Appendix M1, CS). The Delphi panel elicited primary care resource use for the AR population by severity level (mild, moderate and severe). The annual cost of GP visits for the standard of care arm was calculated by severity level using the unit cost of a GP visit[75] multiplied by the resource use elicited in the Delphi panel.[54] The corresponding costs by disease severity level for 12 SQ-HDM were derived by applying a relative reduction in GP visits associated with 12 SQ-HDM vs standard of care (4.92%, as sourced from the MT-06 trial). The 12 SQ-HDM treatment effect on the annual number of GP visits is uniformly applied across all alive health states.

The AR model provides three other sources for the standard of care number of GP visits, namely the MT-06 trial,[4, 5] Demoly et al., 2016,[45] and Romano et al., 2023.[82] Table 28 summarises the annual number GP visits by health state for the alternative evidence sources considered in the model.

Table 28 Number of annual GP visits from alternative evidence sources – AR population

Annual GP visits*	Delphi panel[54]		MT-06[4, 5]		Demoly et al., 2016[45]		Romano et al., 2023[82]	
	SoC	12 SQ-HDM	SoC	12 SQ-HDM	SoC	12 SQ-HDM	SoC	12 SQ-HDM
Mild AR	0.96	0.91	0.10	0.10	3.50	3.33	3.90**	3.71
Moderate AR	2.42	2.30	0.10	0.10	3.50	3.33	3.90**	3.71
Severe AR	4.75	4.52	0.10	0.10	3.50	3.33	3.90**	3.71

* Extracted from the electronic version of the model; ** corrected following point for clarification; GP, general practitioner; SoC, standard of care

In the probabilistic base case analysis, the company assumed an arbitrary standard error of 10% of the mean value for the number of annual GP visits and for the relative reduction in GP visits associated with 12 SQ-HDM. Following the clarification stage, observed standard errors were updated for the number of annual GP visits, as reported in Romano et al., 2023.[82] Notably, the EAG could not validate the standard errors in this reference.

Points for critique

The EAG considers that the modified Delphi panel[54] is a reasonable source to inform the standard of care health state costs. The MT-06 trial[4, 5] may also be a reasonable alternative source of evidence, but the EAG notes that resource use appears to be considerably lower compared to alternative sources (Table 28). Romano et al., 2023,[82] as mentioned above, included children aged 5 to 17 years and thus does not match with the population of AR (adolescents and adults). Demoly et al., 2016,[45] an

observational survey in France, Italy, and Spain, may be less reflective of the UK practice. Thus, there is uncertainty on which is the most appropriate source of evidence to inform the primary care costs.

Similar to the AA+AR primary care health state costs, the company's base case approach implies that cost savings from 12 SQ-HDM compared to standard of care result from i) increased time in the health states with lower levels of severity and ii) a treatment effect of 12 SQ-HDM independent from AR severity. The EAG is concerned there is uncertainty on whether the treatment effect is independent of disease severity. Furthermore, the EAG notes that for the 12 SQ- HDM arm, the reduction in primary care visits was estimated by the company based on the number of GP or specialist visits collected for each treatment arm, rather than on the number of GP visits only. While the EAG considers that it is reasonable to assume a similar reduction in GP visits as for GP and specialist visits (as the company did not have estimates disaggregated by type of visit), this provides additional uncertainty in the parameter.

The EAG identified an error in the calculation of annual costs for GP visits based on severity levels in the model. The calculation error consisted of weighting the cost of GP visits for the distribution across severity levels. The EAG considers that the disease severity weighting is unnecessary, as the GP visits were elicited by severity level, and corrects this in section 6.1. It is possible the company introduced the disease severity weighting to build in differences in health state costs when using alternative evidence sources (that did not stratify resource use by disease severity level). This is not, however, detailed in the CS.

Issue: There is uncertainty on the most appropriate evidence source for annual GP visits by AR severity levels for the standard of care arm.

Issue: The relative reduction in GP visits associated with 12 SQ-HDM in the AR population derived from the MT-06 trial is uncertain.

Secondary care costs

In the base case analysis for both models, the secondary care costs consist of costs associated with outpatient visits. Secondary costs differ according to treatment arm (12 SQ-HDM or standard of care). For the standard of care arm, these costs are estimated by assuming an annual number of outpatient visits for those receiving standard of care therapy, multiplied by the relevant unit costs sourced from the 2021-2022 NHS reference costs.[74] The cost per visit (£219.50) was estimated as a weighted average across Non-Admitted Face-to-Face Attendance, including First (WF01B) and Follow-up (WF01A) visits for a Total Outpatient Attendance in the Respiratory Medicine Service.

Secondary care costs for the 12 SQ-HDM arm are calculated by applying an estimate of relative reduction in secondary care visits for 12 SQ-HDM compared to standard of care to the secondary care costs. In contrast to the primary care costs, secondary care costs are not conditional on disease severity or level of disease control, differing only by treatment group. The EAG considers that the unit cost estimated by the company for secondary care costs is reflective of the cost of outpatient appointments for AR and AR+AA in the NHS.

We detail and critique the sources of data used to inform the AA+AR and AR models in the subsequent subsections.

AA+AR population

The annual number of secondary care visits for the standard of care arm is sourced from Hospital Episode Statistics (HES) data in the company's base case analysis, as they considered this source to best reflect UK clinical practice. The HES analysis (see Appendices R1 and R2, CS) was commissioned by the company and estimated the average number of outpatient contacts in allergy patients in the HES database for the 2016-17 to 2020-21 financial years. Allergy patients were identified as those who had either a primary allergy diagnosis or activity in 1 of 3 allergy specialties (Paediatric Clinical Immunology and Allergy Service, Allergy Service and Clinical Immunology and Allergy Service), and who did not have diagnosis codes related to allergy and immunodeficiency (identified by either receiving immunoglobulins or continuous IV of therapeutic substances). The EAG notes that the estimate of the annual number of secondary care visits for the standard of care arm is thus not specific to patients with AA+AR with HDM-sensitisation, or AA+AR more generally. The company provided two alternative data sources in the model for the standard of care annual number of secondary care visits, namely the MT-04 trial[1, 2] and Demoly et al., 2016[45] (see Table 94, CS).

The relative reduction in secondary care visits of 12 SQ-HDM vs. standard of care was sourced from the MT-04 trial[1, 2] and was estimated as the proportional reduction in the average number of emergency room visits between treatment arms in the period between randomisation and the end of the trial (visits 3 to 13). Thus, the company assumes the 54.58% relative reduction in emergency care is reflective of the reduction of use of secondary care resources with 12 SQ-HDM.

The company further assumed in their probabilistic analysis an arbitrary standard error of 10% of the mean value for the number of secondary care visits and the relative reduction in secondary care visits associated with 12 SQ-HDM. Following points for clarification, observed standard errors were updated for the annual secondary visits, as derived from the HES analysis.

Points for critique

The EAG notes that use of a costing approach for secondary care resource use is not aligned with the model structure, as a direct treatment effect of 12-SQ HDM on this element of cost is applied. The differences in secondary care accrued by 12 SQ-HDM are not driven by health state membership and are thus disconnected from how treatment effectiveness was modelled.

The EAG considers that HES data may be the best source to inform the number of outpatient visits for standard of care in the company's base case analysis. In their response to clarification, the company stated that the HES analysis was not commissioned for this NICE submission and did not support quantifying outpatient contacts for rhinitis and asthma allergies. It is unclear whether the analysis could have been conducted to better reflect the population in the model (e.g., by further restricting diagnostic codes and type of activity).

Regarding the alternate sources of secondary care visits (MT-04[1, 2] and Demoly et al., 2016[45]) for those receiving standard of care therapy, the EAG is concerned that neither can appropriately represent the resource use for standard of care therapy in the UK. The EAG is not only concerned about the generalisability of the MT-04 trial to the UK population, as discussed in section 3.2.1, but also feels the number of emergency care visits reported in the MT-04 trial may not be reflective of secondary care resource use more generally.

The EAG is also concerned that the evidence used to inform the treatment effect of 12 SQ-HDM compared to standard of care may not be reflective of the impact of this treatment on secondary care resource use, as it relies on the assumption that the relative reduction in emergency care is equivalent to the relative reduction in outpatient care. The EAG also notes that in the MT-04 trial, the company collected resource use for specialist care (albeit aggregated with GP); they therefore could have explored this as a source of data to reflect the relative reduction in outpatient care visits.

Notably, the number of emergency visits in the MT-04 trial was generally low across treatment arms, which resulted in considerable parameter uncertainty on the relative reduction of outpatient care visits. This parameter uncertainty was not appropriately reflected in the company's model, as the probabilistic analysis assumed an arbitrary 10% variation over the mean value rather than use the observed trial evidence.

The company did not propose nor discuss alternative evidence sources to inform the impact of 12 SQ-HDM compared to standard of care on secondary care resource use. The EAG notes that the REACT study[31] (section 3.2.3) could have been used by the company as a source to externally validate this uncertain parameter. While the EAG acknowledges the methodological limitations of this study and the potential differences between the German and the UK health systems, the REACT study[31]

suggests a modest impact over time on hospital outpatient visits for AIT compared to control (see Table 29) in the full study population (AR with and without asthma). In the pre-existent asthma cohort, the odds ratios (ORs) comparing the proportion of patients who had outpatient visits with AIT vs. control suggested higher use with AIT in year 3 and 5 after AIT initiation (OR year 3 = 1.08 [95% CI 0.98-1.19], OR year 5 = 1.03 [95% CI 0.91-1.16]) and lower use at year 9 (OR year 9 = 0.85 [95% CI 0.49-1.57]), but were uncertain.

Table 29 Hospital outpatient visits in the REACT study[31]

Outpatient visits	AIT		Control		p-value
	N	mean (SD)	N	mean (SD)	AIT vs. control
Year 3	32112	0.14 (0.58)	32112	0.14 (0.58)	0.5274
Year 5	19783	0.15 (0.61)	19783	0.15 (0.61)	0.2644
Year 9	1846	0.13 (0.58)	1846	0.13 (0.56)	0.7280

Overall, the EAG is concerned that there is considerable uncertainty in the treatment effect of 12 SQ-HDM compared to standard of care on secondary care resource use, which has not been sufficiently explored by the company given this parameter drives the cost savings associated with 12 SQ-HDM in the model.

Issue: The secondary care evidence considered in the AA+AR model may not represent the resource use in the standard of care arm nor the treatment effect of 12 SQ-HDM in reducing secondary care visits.

AR population

The annual number of secondary care visits applied in the AR model for those receiving standard of care therapy is the same as for the AA+AR model described above, i.e., an analysis of outpatient HES data (see Appendices R1 and R2, CS) in a generic allergy population. The company also provided Demoly et al., 2016[45] (see Table 94, CS) as an alternative data source for this parameter.

The company did not use evidence from the MT-06 trial[4, 5] to inform either the number of secondary care visits or the effect of 12 SQ-HDM on secondary care visits relative to standard of care. Although the MT-06 trial collected the number of specialist visits (aggregated with GP visits), the company stated at the clarification stage that they had conservatively assumed that the number of GP/allergist visits recorded in the MT-06 trial were all GP appointments.

The relative reduction in secondary care visits of 12 SQ-HDM vs. standard of care applied in the model (73.53%) was sourced from an observational retrospective study in a population of HDM-induced AA and/or AR patients that was conducted in Spain[13]. The study compared patient outcomes before and after treatment with SCIT, including the reduction in unscheduled outpatient visits after treatments with SCIT.

In their probabilistic analysis, the company assumed an arbitrary standard error of 10% of the mean value for the relative reduction in secondary care visits associated with 12 SQ-HDM.

Points for critique

The concerns highlighted in the points of critique for the secondary care costs in the AA+AR model (described above) in terms of the (i.) disconnect between the costing approach and model structure, and (ii.) the generalisability of the HES analysis to the modelled population also apply to the AR population. Thus, we do not reiterate these concerns here.

The EAG is concerned that the company did not explore the use of the MT-06 trial data to inform the model parameters associated with secondary care costs. The EAG considers that the company could have assumed that the impact of 12 SQ-HDM vs. standard of care on secondary care visits would be equivalent to the impact on GP and specialist visits overall. The EAG is also concerned with the use of El-Qutob et al., study[13] to inform the relative reduction in secondary care visits for 12 SQ-HDM vs. standard of care in the company's base case analysis. First, this study relies on a before and after design to estimate the treatment effects, which may result in biased estimates. Further, the intervention in the study is SCIT, and it is unclear whether the treatment effects are generalisable to 12 SQ-HDM. Given there is some comparative evidence on outpatient visits for 12 SQ-HDM vs. standard of care from an RCT (MT-06), the EAG does not consider it is appropriate to utilise lower quality evidence from a different technology.

Overall, the EAG has established that there is considerable uncertainty on the treatment effect of 12 SQ-HDM compared to standard of care for secondary care resource use, which has not been sufficiently explored by the company, given this parameter drives the cost savings associated with 12 SQ-HDM in the company's analysis.

Issue: The secondary care evidence considered in the AR model may not represent the resource use in the standard of care arm nor the treatment effect of 12 SQ-HDM in reducing secondary care visits.

4.2.8.7 Asthma exacerbation costs

The cost of asthma exacerbations was only included for the AA+AR model. The composition of resource use attributed to asthma exacerbations differs according to severity level (see Table 95 and 96 of the CS for moderate and severe exacerbations, respectively) and includes both primary care and secondary care components. The company states that the figures in the CS were validated by an advisory board[55] of 8 UK respiratory clinicians (methodology and results detailed in Appendix M2, CS) and that while 12.5% of experts (n=1) did not consider these to reflect current management of exacerbations in the UK, they did not provide alternative estimates.

The primary care resource use associated with moderate asthma exacerbations applies to 70% of patients in the model and consists of one GP visit and one course of SABA and oral corticosteroids. The unit costs applied are consistent with those used to derive primary care costs and standard of care treatment costs (sections 4.2.8.6 and 4.2.8.5). The remaining 30% of patients are assumed to incur one visit the emergency department, which was costed as an emergency medicine investigation (£277.04 per visit).[74]

The cost of severe asthma exacerbations assumes the same level of primary care resource use as for moderate exacerbations. Secondary care resource use includes emergency department visits (incurred by 90% of patients), a respiratory ward admission (incurred by 38% of patients), and intensive care unit (ICU) stays (incurred by 3% of patients). NHS reference costs[74] were applied to these elements of resource use. The distribution of secondary care resource use was informed by Lane et al., 2006[80] a prospective observational study which reported the breakdown of costs of managing exacerbations in secondary care in 15 countries; the company based the secondary care distribution on the estimates obtained for Ireland. The company does not state how this study was identified.

Points for critique

The EAG's primary concern is that there may be some level of double counting of primary and secondary care costs associated with asthma exacerbations, given they may already be accounted for to some extent in the asthma management costs (section 4.2.8.6). The data sources used to inform the primary and secondary care resource use consumption for AA+AR management likely also capture health care contacts to manage asthma exacerbations, as exacerbation management was not explicitly excluded from those estimates.

Another issue pertains to whether the resources attributed to asthma exacerbations is reflective of UK clinical practice, particularly for the distribution of secondary care resource use associated with severe exacerbations. The study which informed this distribution of secondary care use[80] was not conducted in the UK, and suggested that the cost of exacerbations varies significantly by country. Although the company states that the figures were validated by an advisory board[55] of UK respiratory specialists, it

is not clear whether the distribution of secondary care resources was fully presented to the experts. The key results of the advisory board (Appendix M2, CS) do not include the breakdown of secondary care use for the management of severe exacerbations, stating only that all patients would be treated in secondary care. Furthermore, the experts are reported to have stated that they would manage severe exacerbations by increasing corticosteroid use and referral to the emergency department, and did not mention any other subsequent resource use such as hospitalisations and ICU stays. It is thus unclear whether the experts were shown the distribution of secondary care resource use for severe exacerbations as applied in the model, which implied hospital admission and ICU stays for 38% and 3% of patients, respectively.

In the CS (B.3.5.2), the company provided a comparison of the exacerbation costs applied in the model with those applied in a previous NICE appraisal of omalizumab[16], and noted that the costs of the latter may have been underestimated. The EAG extracted asthma exacerbation costs from the two most recent NICE TAs in asthma[12, 49] and contrasted these against those in the CS and TA278[16] in Table 30. The costs of severe exacerbations in TA880[12] is approximately half of the cost applied in this submission. In TA751,[49] the cost of a severe exacerbation was conditional on the setting in which the exacerbation was managed, varying from £141.02 to £2,045.56. The EAG notes that in trial MT-04[1, 2], less than 10% of the first severe exacerbation (in the ICS reduction/withdrawal period) required an emergency visit or hospitalisation, and the majority of these exacerbations were managed with systemic corticosteroids (Panel 9-19, MT-04 CSR[2]). The EAG considers that there is considerable uncertainty on the costs of managing severe exacerbations, and that these may have been overestimated in the CS, which would favour the cost-effectiveness of 12 SQ-HDM compared to the standard of care. Given the small incremental costs associated with asthma exacerbations (-£422 for 12 SQ-HDM vs. standard of care), this is, however, unlikely to be a key driver of cost-effectiveness.

Table 30 Comparison of asthma exacerbation costs in the CS and previous NICE TAs

	CS	**TA278[16]**	**TA751[49]**	**TA880[12]**
Moderate exacerbation	£111.95	£87.80	£95.49	-
Severe exacerbations	£464.90	£124.32*	Office visit: £141.02 A&E visit: £381.84 Hospitalisation: £2,045.56	£232.58**

Abbreviations: A&E, accident and emergency; CS, company submission; TA, technology appraisal

* non-severe exacerbations, **requiring hospitalisation

Issue: The cost of asthma exacerbations may not be reflective of exacerbation management in the NHS, and the cost of severe asthma exacerbations may have been overestimated, favouring the cost-effectiveness of 12 SQ-HDM relative to standard of care. Furthermore, the cost of exacerbations may already have been accounted for to some extent in other cost categories. The

potential overestimation of asthma exacerbation costs is, however, unlikely to be a key driver of cost-effectiveness.

4.2.8.8 Adverse event costs

The company's model included costs of the AEs considered for treatment effectiveness in the AA+AR and AR models (section 4.2.6.6). The approach taken to cost AEs is similar across models. The company assumes that not all AEs incur costs. A treatment-specific proportion of AEs is assumed to require management consisting of a single GP visit. These proportions were informed by the MT-04 (14.96% for 12 SQ-HDM and 9.25% for standard of care) and MT-06 (12.63% for 12 SQ-HDM and 15.29% for standard of care) trials for the AA+AR and AR models, respectively. The proportion of AEs requiring management was also assumed to correspond to the proportion of AEs in the trials that required action. The EAG notes action in this context consists of temporary or definitive treatment discontinuation.

The unit cost of AE management was estimated by multiplying the unit cost of a GP visit[75] by the proportion requiring management. Individual AEs were costed by multiplying the unit cost by the probability of the AE; these costs were then summed to estimate an overall cost of AEs for each treatment (see Table 25 and Table 26 for AE costs in the AA+AR and AR models, respectively). The AE cost is applied in the first cycle of the model to the full cohort.

Points for critique

The EAG noted in section 4.2.6.6 that AEs may not have been captured appropriately in the model. However, the costs associated with these are likely to be low as the level of care to manage these events is not very resource intensive. Thus, the EAG considers that a failure to appropriately capture AEs in the models will not have material impact on the estimates of cost-effectiveness.

5 COST EFFECTIVENESS RESULTS

The analyses presented in the CS and response to clarification questions do not include any confidential pricing arrangements. The ERG updated the company's deterministic base case results for the AA+AR model by incorporating the confidential PAS discounts for the treatments listed in section 4.2.8.1; results of this analysis are presented in a separate confidential appendix.

5.1 Company's cost effectiveness results

At the clarification stage, the company submitted an updated electronic version of the AA+AR and AR models. The updates consisted of the following minor revisions and corrections:

- Data on asthma control during period 2 visits were added to the 'Effectiveness' sheet.
- The model has been updated in the 'HRQoL' sheet to include utility estimates for the AR model from the P001[8, 9] trial for the adult subgroup, adolescent subgroup, and full population.
- MT-04 treatment-specific SD utilities were added to the 'HRQoL' sheet.
- Health state-specific SD utilities were added for Briggs et al., 2021,[3] EUCOAST (Spain),[62] and EUCOAST (France)[62] to the 'HRQoL' sheet.
- A switch was added to the 'Parameters' sheet to control whether treatment with 12 SQ-HDM can result in a lower utility score compared with standard of care using the treatment-specific approach to HRQoL.
- Updated estimates were added to the 'Management costs' sheet reflecting the average GP/specialist visits over the last 4 weeks of the treatment maintenance phase (period 2) in MT-04.
- An additional calculation was added to the 'Management costs' sheet to update the number of GP/specialist visits from MT-04 trial data, excluding data from Visit 3, which took place prior to randomisation. This amendment should have resulted in a change in the relative reduction in GP visits associated with 12 SQ-HDM (cell F23 of management cost tab) from 25.76% to 31.19%. However, while the company indicated they made this change to the base case parameters; the model itself was not updated to reflect the change. Therefore, the EAG notes there was no update in the base case cost-effectiveness results.
- Corrections were made to the Romano et al. 2023[82] annual number of GP visits per year in the 'Management costs' sheet.
- The company made corrections to some of the standard error values in the 'Parameters' sheet, so that where empirical evidence was available on the variance of parameters this was used to inform parameter uncertainty (as opposed to an arbitrary 10% variation over the mean parameter values in the original models). The EAG notes corrections were still required in the 'Parameters' sheet to update the uncertainty estimates such that they corresponded to the SD values provided through trial or alternative data sources (section 6).

The model updates highlighted above did not affect the base case model parameters. The company's deterministic base case model results, presented in Tables 99 and 100 of the company submission, are therefore unchanged.

The company's base case suggested that 12 SQ-HDM dominated standard of care (i.e., was less costly and generated more QALYs vs. standard of care) in both AA+AR and AR populations. The incremental costs associated with treatment and administration of 12 SQ-HDM compared to the standard of care (£2,683 and £2,868 for the AA+AR and AR models, respectively) were more than completely offset by cost savings in secondary care costs (-£3,725 and -£5,524 for the AA+AR and

AR models, respectively). The EAG notes that secondary care costs are a key cost-effectiveness driver in the company's base case analyses. Disaggregated company base case results are presented in Tables 101 and 102 of the CS.

5.2 Company's sensitivity analyses

5.2.1 Deterministic Sensitivity Analysis

In the original CS, the company performed a deterministic sensitivity analysis (DSA) to explore the effect of uncertainty across individual model parameters. The range within which the model parameters was varied was defined as one standard error above or below the mean parameter value in the CS. However, since the standard errors for the vast majority of parameters varied in the DSA was set to 10% of the mean parameter value in the original CS, this means that the DSA range was defined as a 10% arbitrary variation around the mean value for most parameters. The variation range of the utility parameters was further constrained so that treatment-specific utility for 12 SQ-HDM could not be lower than for standard of care.

Figures 31 and 32 of the CS provide results of the DSA presented as tornado diagrams of 12 SQ-HDM NMB at a cost-effectiveness threshold of £20,000 per additional QALY for all parameters, for which variation resulted in a minimum of £1,000 NMB change. The company concluded that the cost-effectiveness of 12 SQ-HDM in the AA+AR and AR populations was most sensitive to changes in the treatment-specific utilities. Variation of parameters within the DSA-defined ranges did not result in negative incremental NMB for 12 SQ-HDM, suggesting this treatment was always cost-effective at £20,000 per additional QALY in the company's DSA.

5.2.1.1 Points for critique

The EAG considers the company's DSA provides limited information, given it defined an arbitrary variation range for most parameters. The EAG would have preferred that DSA variation ranges had been defined on the basis of the plausible range for each parameter (based on empirical evidence and/or clinical opinion). The only parameters for which the company provided a clinical rationale for the variation range was for the treatment-specific utilities, which the company considered it implausible to have higher treatment utility with the standard of care than with 12 SQ-HDM (section 4.2.7.2).

5.2.2 Scenario Analyses

In the original CS, the company performed a range of scenario analyses to test the robustness of the model to alternative specifications. Results are provided in Table 105 of the CS. The company considered the cost-effectiveness base case results for the AA+AR and AR models to be robust to

scenario analysis, as all analyses resulted in positive incremental NMB for 12 SQ-HDM at £20,000 per QALY.

Following points for clarification, the company provided three additional scenario analyses, which we review here. First, a scenario was provided with the cost-effectiveness results for asthma control over period 2 (treatment maintenance phase) of the MT-04 trial (to visit 9). Results suggest a minimal material impact on cost-effectiveness, with no change in effectiveness parameters and a £9 increase in cost savings.

The company also provided a scenario where AA exacerbation costs were set to zero, to avoid any potential double counting of asthma exacerbation-related outpatient contacts. Results suggest a decrease in cost savings from -£2,094 in the base case to -£1,672, with no change in effectiveness parameters. 12 SQ-HDM is still considered dominant over the standard of care.

Finally, the company provided a scenario considering the option of estimating the relative reduction associated with 12 SQ-HDM based on the treatment maintenance phase (period 2) of the MT-04 trial. For this scenario, the relative reduction was changed from 25.76% to 18.73% and the relative reduction of secondary care visits was increased from 54.58% to 60.32%. Results of this analysis suggested no change in effectiveness parameters, and a marginal increase in cost-savings, from -£2,094 to -£2,392, with 12 SQ-HDM continuing to dominate over standard of care alone.

5.2.2.1 Points for critique

The EAG is concerned that uncertainty around model assumptions and evidence sources was insufficiently explored by the company, as highlighted throughout section 4 of the EAR. The EAG conducts further analyses in section 6 to test the robustness of the company's cost-effectiveness results.

5.2.3 Subgroup Analyses

The company conducted an analysis where the cohort starting age of the AR population was set to 12 years, which is described as an adolescent subgroup analysis. Results are reported in Table 106 of the CS and are similar to base case results for the full AR population.

5.2.3.1 Points for critique

The EAG considers that the analysis conducted by the company does not provide cost-effectiveness evidence for the adolescent AR population, as it only considers a different starting age for the model cohort without any change to the parameter estimates. While the EAG acknowledges the evidential challenges in characterising cost-effectiveness for this subgroup (section 4.2.3), it is not appropriate to describe this analysis as a subgroup analysis.

5.2.4 Probabilistic Sensitivity Analysis

The company conducted a PSA to account for joint parameter uncertainty and potential model non-linearity. The company estimated 2,000 iterations and provide results in Tables 103 and 104 for the AA+AR and AR models, respectively. Results are also depicted as scatter plots of the simulated incremental costs and QALYs for 12 SQ-HDM compared to standard of care in Figures 29 and 30 of the CS for the AA+AR and AR models, respectively.

As noted throughout sections 4.2.6, 4.2.7, and 4.2.8, the company applied an arbitrary 10% variation to the mean deterministic values for several model parameters, and did not provide a justification for this approach in the CS. Following points for clarification, the company updated standard error values where empirical evidence was available on the variance of parameters.

5.2.4.1 Points for critique

The EAG conducted updated model sensitivity analyses and found that 2,000 iterations of the PSA resulted in stable cost-effectiveness estimates. However, the EAG considers that parameter uncertainty was not appropriately reflected in the company's model, as the probabilistic analysis remained constrained to a 10% variation over the mean value for several parameters. Further, the EAG notes that the probabilistic incremental QALYs are approximately double that of corresponding deterministic values in both models; this may be an artefact of the treatment-specific utility constraint.

5.3 Model validation and face validity check

The company noted they undertook internal quality assurance measures to validate the model, including the use of extreme values and formula auditing to ensure consistency.

5.3.1 Points for critique

The EAG undertook further validation checks, including face validity checks between the model and CS and/or clarification response, as described in section 5.1, and did not identify major computational concerns with the model. As outlined in section 5.1 and section 6.1, the EAG has identified minor inaccuracies in the model; these are detailed in section 6.1.

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

As noted in section 4.2.8.1, there are several confidential commercial arrangements in place for drugs considered in the AA+AR model. These confidential commercial arrangements are not incorporated in the analyses presented in the EAR but in a confidential appendix, separate to the EAR.

6.1 Corrections to the company's updated base case analysis

The EAG identified a few minor errors and inconsistencies in the updated version of the company's model (submitted on the 5th December 2023) used to perform the analyses reported in section 5. The corrections and revisions applied to the company's updated model are summarised in Table 31, alongside the sections of the EAR where these have been discussed.

Table 31 Correction/revision to the company's updated base case model

Parameter	Correction / Revision	Section
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%)	4.2.6.5
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.	4.2.8.3
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.	4.2.8.5
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.	4.2.8.6
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., 2021[3], 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.	4.2.7.2

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 deterministic results of the corrected company's base case analysis (including the corrections described in Table 31) are reported in Table 32.

Table 32 Cost-effectiveness results for company's corrected base case analysis for AA+AR and AR populations respectively

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)	NMB (£20k/ QALY)	NMB (£30k/ QALY)
AA+AR									
Standard of care	£26,680	22.55	15.73						
12 SQ-HDM	£24,520	22.55	16.10	-£2,159	0	0.37	12 SQ-HDM dominant	£9,591	£13,307
AR									
Standard of care	£15,580	22.74	19.03						

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)	NMB (£20k/ QALY)	NMB (£30k/ QALY)
12 SQ-HDM	£12,681	22.74	19.29	-£2,899	0	0.26	12 SQ-HDM dominant	£8,176	£10,814

Abbreviations: AA: allergic asthma, AR: allergic rhinitis, HDM: house dust mite, LYG: life years gained, QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio, NMB: net monetary benefit, k: thousand.

The cost corrections and revisions (Table 31) had a small impact on the cost-effectiveness results and, on average, slightly increased incremental costs for both the AA+AR and AR models, compared to the company's updated base case results (section 5.1). Corrections did not impact total life years gained nor total QALY estimates.

6.2 Exploratory and sensitivity analyses undertaken by the EAG

A summary of the issues identified and critiqued in section 4, along with the scenario where the EAG addresses each issue in its additional analyses is shown in Table 33.

Table 33 Summary of the main issues identified by the EAG.

Critique item from section 4 and description The EAG considers:		Dealt with in scenario	In EAG's base case	Area of remaining uncertainty	Significant impact on ICER
Cost-effectiveness review					
Issue	The cost-effectiveness review was not fully comprehensive		No	Yes	No
Model structure					
Issue	The AA+AR model structure may not be suitable for decision making as it does not reflect options to step up treatment, being fit only for last line of treatment.		No	Yes	Unknown
Issue	A 1-year cycle length may not fully capture disease severity fluctuations		No	Yes	No
Population					
Issue	No adolescent subgroup related evidence was used to inform the AR model and evidence from adults is assumed generalisable to the adolescent subgroup.		No	Yes	Unknown
Treatment effectiveness - short-term					
Issue	The short-term effectiveness parameterisation proposed by the company for AA+AR and AR is not reflective of the progression in disease severity and the stepping up/down in treatments as observed in clinical practice		No	Yes	Unknown
Issue	The use of period 2 only (maintenance phase) or periods 2 and 3 (maintenance and ICS reduction phase) of the MT-04 trial to inform the AA+AR short-term effectiveness may not be reflective of clinical practice	1	Yes	Yes	No
Issue	The use of an unadjusted post-hoc analysis to inform the AA+AR and AR models' natural history and short-term treatment effectiveness parameterisation adds considerable uncertainty to this key model input parameter		No	Yes	Unknown
Issue	The use of ACQ scores mapped onto GINA to classify AA+AR patients in terms of their asthma control is inconsistent with the approach taken by previous TAs		No	Yes	Unknown
Issue	The distributions of patients across asthma control levels in the AA+AR model and across rhinitis severity levels in the AR model at baseline and trial end are fixed, and thus, the		Yes (probabilistic analysis)	No	No

Critique item from section 4 and description The EAG considers:		Dealt with in scenario	In EAG's base case	Area of remaining uncertainty	Significant impact on ICER
	parameter uncertainty in the transition probabilities in the first cycle of both models is not considered				
Treatment effectiveness - medium to long-term					
Issue	The assumptions of improvements in health imposed by the company for 12 SQ-HDM from 2-5 and 5-10 years are highly uncertain, speculative and are not supported by evidence	2	Yes	Yes	Yes
Issue	Long-term effectiveness assumptions beyond 9 years are considered subjective and uncertain, being particularly uncertain beyond 20 years given the lack of evidence to support these	2	Yes	Yes	Yes
Issue	The annual rates of change used by the company to reflect the medium to long-term effectiveness of 12 SQ-HDM and standard of care are arbitrary	2	Yes	Yes	Yes
Issue	Assumptions on starting treatment waning at 15 years and of considering 80% of the treated patients moving to standard of care by year 20 is not being supported by any evidence and are considered highly uncertain.		N/A (additional scenario to EAG BC)	Yes	No
Issue	The assumption that patients in the 12 SQ-HDM arm cannot decline to a state which is worse than patients receiving standard of care is uncertain.		N/A (additional scenario to EAG BC)	Yes	No
Treatment effectiveness - asthma exacerbations					
Issue	The use of period 3 (ICS reduction and efficacy assessment) of MT-04 to inform the AA+AR effectiveness on asthma exacerbations is not reflective of clinical practice. Furthermore, the number of exacerbations reflected in the asthma exacerbation probabilities is an underestimation of total number of events in period 3.	3	No	Yes	No
Issue	The impact of the company's assumption that the risk of an exacerbation is independent of level of asthma control and that exacerbation events do not affect subsequent health state membership is unknown and has not been justified		No	Yes	Unknown
Issue	Treatment effect of 12 SQ-HDM on exacerbations is informed by a single study and MT-04 may not reflect exacerbation risks in the full AA+AR population for which this treatment is licensed.		No	Yes	Unknown
Treatment effectiveness - discontinuation					
Issue	The discontinuation rates from the MT-04 trial may not be reflective of the UK clinical practice.		No	Yes	Unknown
Issue	The assumption of 50% of patients who discontinued to still receive the benefits from 12 SQ-HDM applied to the first 3 model cycles is considered uncertain		No (additional scenario to EAG BC)	Yes	No
Treatment effectiveness - adverse events					
Issue	Not all TEAEs occurring in ≥2% of patients in the clinical trials (MT-04 and MT-06 for the AA+AR and AR populations, respectively) were included, which underestimates the probability of these adverse events in the AA+AR and AR models		No	No	No
Health related quality of life					
Issue	The treatment-specific approach to HRQoL does not align with the model structures developed for AA+AR and AR, respectively	4	Yes	No	Yes
Issue	Parameter uncertainty of treatment-specific utilities in the AA+AR and AR models is artificially constrained.		Yes (probabilistic analysis)	No	No

Critique item from section 4 and description The EAG considers:		Dealt with in scenario	In EAG's base case	Area of remaining uncertainty	Significant impact on ICER
Issue	The lack of inclusion of AE-related utility decrements, although expected to have minimal impact on cost-effectiveness results, creates inconsistencies in the model as AE-related costs were included		No	No	No
Issue	Utility estimates collected in P001 suggest greater HRQoL gains from 12 SQ-HDM treatment in the adolescents compared to the adult subgroup, but were collected with an instrument that is not validated for adolescents.		No	Yes	No
Resources and costs - Treatment acquisition and administration					
Issue	Although a recommendation exists for a 3-year treatment duration for allergy immunotherapy in AR, the optimal duration for AA+AR is uncertain.		No	Yes	Unknown
Issue	Retreatment with 12 SQ-HDM is not considered by the company's model and, thus, the company's estimates for the cost of 12 SQ-HDM may be underestimated.		No	Yes	Unknown
Issue	The company's modelling approach does not allow appropriately capturing the impact of 12 SQ-HDM on the utilisation of standard of care pharmacotherapy due to improved asthma control.		No	Yes	Unknown
Issue	The company's interpretation of clinical guidance to inform standard of care treatment composition may have led to the overestimation of costs.		No	Yes	Unknown
Issue	The distribution of biologic treatments included in the company's standard of care cost may not be reflective of clinical practice given the indication of these treatments. The assumption on the treatment effect of 12 SQ-HDM on the progression of patients to biologic treatment (step 5) relies on the validity of the company's elicitation and parameter uncertainty surrounding this effect which may not be appropriately reflected in the model.	5	Yes	Yes	No
Issue	The differences in costs of standard of care between AA+AR model health states relies on a strong and implausible assumption that relative increases in ICS dose between levels of control directly translates to a proportional increase in costs across all standard of care asthma medications.		No (additional scenario to EAG BC)	Yes	No
Issue	The generalisability of standard of care medication costs from the MT-06 trial to UK clinical practice is uncertain.		No	Yes	Unknown
Resources and costs - management					
Issue	Evidence used to inform primary care costs has limitations and is poorly aligned with the AA+AR model. Thus, the calculation of primary care costs requires strong assumptions, which have not been justified or sufficiently tested, and may contribute to an overestimation of primary care cost savings associated with 12 SQ-HDM.		No	Yes	Unknown
Issue	The relative reduction in GP visits associated with 12 SQ-HDM in the AA+AR and AR populations derived from the MT-04 and MT-06 trials, respectively, are uncertain.	6 (for AA+AR only)	Yes	Yes	No
Issue	There is uncertainty in what the most appropriate evidence source is for annual GP visits by AR severity levels for the standard of care arm.		No	Yes	Unknown
Issue	The secondary care evidence considered in the AA+AR model and in the AR model may not represent the resource use in the standard of care arm nor the treatment effect of 12 SQ-HDM in reducing secondary care visits.	7	Yes	Yes	Yes
Issue	The costs of asthma exacerbations may not be reflective of exacerbation management in the NHS, and the cost of severe		No	Yes	Unknown

Critique item from section 4 and description The EAG considers:		Dealt with in scenario	In EAG's base case	Area of remaining uncertainty	Significant impact on ICER
	asthma exacerbations may have been overestimated, favouring the cost-effectiveness of 12 SQ-HDM compared to the standard of care. Furthermore, the costs of exacerbations may also already have been accounted for to some extent in other cost categories.				

As shown in Table 33, the EAG identified several limitations and areas of uncertainty in the company's cost-effectiveness analysis. Where the EAG considered that further exploration of the impact of these areas of uncertainty was warranted and possible, scenario analysis was performed (scenarios 1 to 7). Following that, and where the EAG considered that there was a more appropriate alternative approach, modifications were implemented in a cumulative manner and formed part of the EAG's preferred base case (section 6.4) Thorough descriptions of the scenarios that were considered for the definition of the EAG's base case are presented in section 6.2.1, and the impact on the estimates of cost-effectiveness is detailed in Table 44 (AA+AR) and Table 46 (AR). The cumulative impact on the ICERs of the EAG preferred assumptions are presented in section 6.3 and a subsequent analysis over the EAG base case assumptions is shown in section 6.5.

6.2.1 Developing the EAG base case

The scenario analyses which the EAG considered in defining our base case are described below and summarised in Table 34.

Table 34 Building the EAG base case - description of implemented scenarios.

Scenarios	Description
1. AA+AR: Using MT-04 maintenance phase to inform short-term effectiveness	The use of MT-04 trial evidence to inform decision making has been questioned. Evidence from period 2 and 3 of the MT-04 trial is not reflective of clinical practice in the UK. This scenario explores the use of evidence from the MT-04 maintenance phase (period 2 only) to inform short-term effectiveness.
2. AA+AR and AR: Considering evidence-based medium to long-term effectiveness assumptions	Medium to long-term effectiveness company assumptions of improvements in health imposed for 12 SQ-HDM are not supported by relevant evidence. The waning effect over 10-20 years elicited by clinical experts is uncertain. Waning assumptions implemented by the company are considered arbitrary. This scenario considers existing published evidence up to 10 years.
3. AA+AR: Considering a null probability of asthma exacerbations across levels of asthma control in each arm	The use of MT-04 trial evidence to inform AA+AR effectiveness on asthma exacerbations may not be reflective of clinical practice. The number of exacerbations reflected in the asthma exacerbation probabilities may be underestimated. The company's assumption that the risk of an exacerbation is independent of level of asthma control and that exacerbation events do not affect subsequent health state membership is uncertain. External evidence has not been explored. Given identified uncertainties, this scenario conservatively considers the probabilities of asthma exacerbations across the levels of asthma control in each treatment arm to be 0%.
4. AA+AR and AR: Considering health state-specific utilities and the most relevant utility sources	The use of the treatment-specific approach to utilities does not align with the model structures proposed by the company. This scenario considers a health-state approach for both AA+AR and AR models. Additionally, the treatment-specific approach in the AA+AR model uses utilities derived from SF-36 data collected in the MT-04 trial, which are lower in the NICE evidence ranking compared to EQ-5D mapped utilities. For the AA+AR model, health state utilities derived from Briggs et al., 2021[3], from mapping ACQ data to EQ-5D-3L, are considered. For the AR model, health state utilities derived directly from EQ-5D data collected in the MT-06 trial are considered.
5. AA+AR: Considering only relevant biologic treatments for the current decision problem	The company's model considered AA+AR patients to be eligible for the following biologics: omalizumab, mepolizumab, dupilumab, and tezepelumab. The EAG notes that from this list the only biologics relevant for the AA+AR population of the current decision problem are omalizumab and tezepelumab. This scenario considers only the relevant biologic treatments for the current decision problem.
6. AA+AR: Considering the MT-04 maintenance phase to estimate the treatment effect of 12 SQ-HDM in reducing primary care visits	For primary care resource use, the AA+AR model assumes a treatment effect for 12 SQ-HDM in terms of reducing the number of GP visits to 31.19% compared to standard of care. This was derived from the MT-04 trial (weeks 4-13 and excluding randomisation) and is considered very uncertain. Similar to what was done for scenario 1, this scenario considers the treatment effect for 12 SQ-HDM from the maintenance phase (weeks 4 to 9 excluding randomisation) of the MT-04 trial.
7. AA+AR and AR: Considering alternative estimates for the treatment effect of 12 SQ-HDM in reducing secondary care visits	For secondary care resource use, the AA+AR model assumes a treatment effect for 12 SQ-HDM in terms of reducing the number of outpatient visits to 54.58% compared to standard of care, which was derived from the MT-04 trial and is considered very uncertain. Similarly, the AR model assumes a 73.53% reduction compared to the standard of care, which was derived from El-Qutob et al., 2016 and is also considered very uncertain. This scenario explores the assumption of considering the relative reductions in primary care, given the effect of 12 SQ-HDM, to be exchangeable to secondary care (i.e., the relative reduction in visits are assumed to be 7.35% for the AA+AR model and 4.92% for the AR model, respectively, for both primary and secondary care).

6.2.1.1 Scenario 1: AA+AR: Using MT-04 maintenance phase to inform short-term effectiveness

In the company's AA+AR economic model under base case assumptions, evidence from MT-04[1, 2] at baseline and trial end, covering both maintenance (period 2) and ICS reduction and efficacy (period 3)

assessment phases, was used to inform the cycle 1/year 1 transitions between the well controlled, partly controlled, and uncontrolled AA health states in a post-hoc analysis. The EAG has fundamental concerns relating to the use of the MT-04 trial to inform the current decision problem and considers the non-adjusted post-hoc approach developed by the company to parameterise short-term effectiveness to be inappropriate. Nonetheless, in the absence of better evidence and acknowledging that the MT-04 trial may be the best evidence available, the EAG considers its use for the AA+AR model. The EAG believes that neither period 2 nor period 3 may be reflective of clinical practice in the UK, as patients, if uncontrolled, would neither be maintained in their current therapy(ies) nor would observe a reduction of ICS, respectively. Following previous economic analyses of 12 SQ-HDM for the AA+AR population,[38, 39] the EAG considers in this scenario the use of the maintenance period 2 to inform treatment effectiveness within the first year to be the most informative. The results of the post-hoc approach performed over MT-04 baseline and end of maintenance phase (period 2 only) are shown in Table 11. This scenario was considered for the EAG's base case.

6.2.1.2 Scenario 2: AA+AR and AR: Considering evidence based medium to long-term effectiveness assumptions

The company considered that possible transitions of patients across health states in each model were determined by annual rates of change across 4 time periods. The company assumed improvements in health for 12 SQ-HDM from 2-5 and 5-10 years. The EAG considers these assumptions not to be supported by available evidence. The company also assumed that treatment waning would be initiated in year 15 of the model and that by year 20, 80% of the patients in the 12 SQ-HDM treatment arm would match the distribution of patients in the standard of care arm. The EAG believes that any long-term effectiveness assumptions beyond 9 years are subjective and very uncertain, and that no evidence exists beyond 20 years. The company assumed that patients receiving standard of care remained stable during all years following Year 1 and, thus, observed an annual rate of change of 0%.

The EAG considers that evidence from the Marogna et al., 2010[32] and Fritzsching et al., 2022[31] studies (as discussed in section 4.2.6.2) support a sustained effect from 12 SQ-HDM from 2 to 10 years. The EAG considers the evidence beyond 10 years to be too uncertain to be considered in the economic modelling. Thus, the EAG considers in this scenario that patients in the 12 SQ-HDM treatment arm match the distribution of patients in the standard of care arm post-10 years. Table 35 shows the medium to long-term assumptions considered by the EAG in this scenario. This scenario was considered for the EAG's base case.

Table 35 Assumptions of the EAG over the medium to long-term effectiveness of 12 SQ-HDM and standard of care in the AA+AR and AR economic models, respectively.

Annual rate of change	12 SQ-HDM AA+AR / AR		SOC AA+AR / AR	
	Well-to-partly controlled / mild-to-moderate	Partly-to-uncontrolled / moderate-to-severe	Well-to-partly controlled / mild-to-moderate	Partly to uncontrolled / moderate-to-severe
Year 2 to year 10	0.00%	0.00%	0.00%	0.00%
Year 10 onwards	12 SQ-HDM patients to match Standard of Care			
A negative probability indicates an improvement in health (backwards transition) **Abbreviations:** SQ, standardised quality; HDM, house dust mite; SOC, standard of care; AA, allergic asthma; AR, allergic rhinitis.				

6.2.1.3 Scenario 3: AA+AR: Considering a null probability of asthma exacerbations across levels of asthma control in each arm

The company's AA+AR economic model under base case assumptions considers treatment-specific asthma exacerbation probabilities with moderate and severe exacerbations modelled separately. Exacerbation probabilities were estimated based on period 3 of the MT-04 trial. The EAG considers that the use of MT-04 to inform the AA+AR effectiveness on asthma exacerbations may not be reflective of clinical practice. Although information on asthma exacerbations was not collected in period 2 of the MT-04 trial, ACQ[20, 46] (an instrument to assess asthma control and a predictor of risk of future asthma exacerbations) data were available for this period and suggested negligible changes in asthma control from baseline for both treatment arms (section 3.2.2). Although the company's AA+AR model assumes independence between the risk of an exacerbation and the level of asthma control, as exacerbation events do not affect subsequent health state membership, this has not been justified. Given the link between asthma control and risk of exacerbations, this scenario conservatively assumes that similar levels of asthma control in period 2 of the MT-04 trial for both treatment groups result in no differences in the probability of asthma exacerbations between both groups. Due to how the company's model is set up (i.e., probabilities of asthma exacerbation are modelled independently for 12 SQ-HDM and standard of care), the scenario was implemented by setting the probabilities of asthma exacerbations to zero for both treatment groups. This scenario was not considered for the EAG's base case.

6.2.1.4 Scenario 4: AA+AR and AR: Considering health state-specific utilities and most relevant utility sources

Both AA+AR and AR company's models considered a treatment-specific approach to utilities in their base case. The EAG believes that a health state-specific approach to utilities is more aligned with the model structures proposed by the company. For the AA+AR model and using a post-hoc analysis of MT-04 trial data, SF-36 was used to derive treatment-specific utilities. The EAG considers the health state utilities derived by Briggs et al., 2021[3] from mapping ACQ data to EQ-5D-3L, to be aligned with the NICE reference case requirements.[63] For the AR model and using a post-hoc analysis of MT-

06 trial data, EQ-5D was directly used to derive utilities. The EAG considers the health state utilities derived from EQ-5D collected in MT-06 to be the most appropriate for the current decision problem. This scenario was considered for the EAG's base case.

6.2.1.5 Scenario 5: AA+AR: Considering only relevant biologic treatments

When selecting a 'microcosting approach' for the estimation of the standard of care costs in the AA+AR model, the company assumes that all patients eligible for biologics are currently using them, comprising 68% of patients, equally spread by each biologic (omalizumab, mepolizumab, dupilumab, and tezepelumab). The EAG notes that from the biologics considered by the company and given NICE recommendations[63] (section 2.2), the biologics relevant for the AA+AR population of the current decision problem are omalizumab and tezepelumab. This scenario was considered for the EAG's base case.

6.2.1.6 Scenario 6: AA+AR: Considering the MT-04 maintenance phase to estimate the treatment effect of 12 SQ-HDM in reducing primary care visits

In the AA+AR model, the company considered a treatment effect for 12 SQ-HDM in terms of reducing the number of GP visits to 31.19% compared to the standard of care (as stated by the company in response to clarification questions and corrected by the EAG in section 6.1). This was derived from the MT-04 trial (weeks 4-13 excluding randomisation) and is considered by the EAG to be very uncertain. Similar to what was done for scenario 1, the EAG considers the use of a treatment effect for 12 SQ-HDM derived from the maintenance phase (weeks 4 to 9 excluding randomisation) of the MT-04 trial to be more consistent. The use of weeks 4 to 9 (excluding randomisation) of the MT-04 trial to derive the effect of 12 SQ-HDM in reducing GP visits changes the value from 31.19% used by the company to 7.35%.

6.2.1.7 Scenario 7: AA+AR and AR: Considering alternative estimates for the treatment effect of 12 SQ-HDM in reducing secondary care visits

In the AA+AR model, the company considered a treatment effect for 12 SQ-HDM in terms of reducing the number of outpatient visits to 54.58% compared to the standard of care, which was derived from the MT-04 trial. In the AR model, the company considered a treatment effect for 12 SQ-HDM in terms of reducing the number of secondary care visits to 73.53% derived from El-Qutob et al., 2016[13]. Evidence from the REACT study[31] suggests that any treatment effect of 12 SQ-HDM on secondary care compared to standard of care may be negligible. The EAG considers the evidence considered by the company to inform the treatment effect of 12 SQ-HDM in reducing secondary care visits in both AA+AR and AR models to be very uncertain. In the absence of better-quality evidence, this scenario explores the assumption of considering the relative reductions in primary care, given the effect of 12 SQ-HDM, to be exchangeable to secondary care. That is, considering a relative reduction associated with 12 SQ-HDM of 7.35% for the AA+AR model and of 4.92% for the AR model,

respectively, for both primary and secondary care. Table 36 shows the secondary care estimates for the AA-AR and AR populations assumed by the company and considered by the EAG. This scenario was considered for the EAG's base case.

Table 36 Secondary care estimates for AA-AR and AR populations from alternative evidence sources

Secondary care - HES data analysis informing baseline secondary care estimates	AA+AR and AR models	AA+AR model	AR model
	Standard of care (baseline HES estimate)	12 SQ-HDM	
Company's model assumptions			
Relative reduction associated with 12 SQ-HDM (source)	N/A	54.58% (secondary care MT-04)	73.53% (El Qutob et al., 2016)
Impact on annual outpatient visits for all health states	2.66	1.21	0.70
EAG's model assumptions			
Relative reduction associated with 12 SQ-HDM (source)	N/A	7.35% (primary care MT-04)	4.92% (primary care MT-06)
Impact on annual outpatient visits for all health states	2.66	2.46	2.53

* Extracted from the electronic version of the model; SoC, standard of care, HES: hospital episode statistics

6.3 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

All results for the EAG's scenarios are based on a deterministic analysis because it was not feasible to run the model probabilistically across all scenarios within the time constraints of the STA. The scenario results presented in Table 37 to Table 43 refer to the total and incremental costs, total incremental QALYs, ICERs and NMB at £20,000 and £30,000 per QALY gained thresholds for the AA+AR and the AR populations. For completeness and to add to the interpretation of the results, each table presents, at the top, the company's corrected base case analysis results.

For both the AA+AR and AR models, the scenarios which are more impactful relative to the company's corrected base case on the estimates of cost-effectiveness are the following: using evidence-based medium to long-term effectiveness assumptions, using health state-specific utilities, and using alternative estimates for the treatment effect of 12 SQ-HDM in reducing secondary care visits. Only for the latter scenario is an ICER for 12 SQ-HDM vs. standard of care estimated in the Northeast quadrant of the cost-effectiveness plane (i.e., suggesting that 12 SQ-HDM is more costly and more effective), but is still below the £20,000/QALY gained cost-effectiveness threshold (£2,822/QALY gained and £8,550/QALY gained for the AA+AR and AR models, respectively). The remaining scenarios suggest 12 SQ-HDM is dominant over standard of care. The EAG notes the

substantial decrease in estimated incremental QALYs in the scenario where health state utilities were utilised (Table 40).

The results of the scenario using evidence-based medium to long-term effectiveness assumptions are mainly driven by an increase in secondary care costs for 12 SQ-HDM, costs which are identified as a key driver of cost-effectiveness. In this scenario, the distribution of patients across health states are matched between treatment from 10 years onwards, implying that primary and secondary costs are equivalent between treatment and comparator from that point onwards. Similarly, the results of the scenario using alternative estimates for the treatment effect of 12 SQ-HDM in reducing secondary care visits (that is, assuming that the relative reduction of secondary care visits to be the same as in primary care), show an increase in secondary care costs for 12 SQ-HDM, with estimated incremental costs of £1,049 and of £2,256 for AA+AR and AR models, respectively. This contrasts with the cost savings brought by 12 SQ-HDM and with 12 SQ-HDM considered as dominant over standard of care, as estimated by the updated results for both company models.

6.3.1 AA+AR: Using the MT-04 maintenance phase to inform short-term effectiveness

The results from scenario 1 of using the MT-04 baseline and end of maintenance phase (period 2 only) to inform short-term effectiveness are presented in Table 37.

Table 37 Summary cost-effectiveness results for scenario 1 for the AA+AR population - using MT-04 maintenance phase to inform short-term effectiveness

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)	NMB (£20k/ QALY)	NMB (£30k/ QALY)
Company's corrected base case results – using the MT-04 period between baseline and trial end (period 2 and 3)									
AA+AR									
Standard of care	£26,680	22.55	15.73						
12 SQ-HDM	£24,520	22.55	16.10	-£2,159	0	0.37	12 SQ-HDM dominant	£9,591	£13,307
Scenario 1 – using the MT-04 period 2 only									
AA+AR									
Standard of care	£26,841	22.55	15.73						
12 SQ-HDM	£24,669	22.55	16.10	-£2,171	0	0.37	12 SQ-HDM dominant	£9,599	£13,313

Abbreviations: AA: allergic asthma, AR: allergic rhinitis, HDM: house dust mite, LYG: life years gained, QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio, NMB: net monetary benefit, k: thousand.

6.3.2 AA+AR and AR: Considering evidence-based medium to long-term effectiveness assumptions

The results from scenario 2 of considering a sustained effect from 12 SQ-HDM from 2 to 10 years and where the distribution of patients in the 12 SQ-HDM treatment arm matches the distribution of patients in the standard of care arm post-10 years, are shown in Table 38.

Table 38 Summary cost-effectiveness results for scenario 2 for the AA+AR and AR populations - considering evidence-based medium to long-term effectiveness assumptions

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)	NMB (£20k/ QALY)	NMB (£30k/ QALY)
Company's corrected base case results – using medium to long-term assumptions as described in 4.2.6.2									
AA+AR									
Standard of care	£26,680	22.55	15.73						
12 SQ-HDM	£24,520	22.55	16.10	-£2,159	0	0.37	12 SQ-HDM dominant	£9,591	£13,307
AR									
Standard of care	£15,580	22.74	19.03	.					
12 SQ-HDM	£12,681	22.74	19.29	-£2,899	0	0.26	12 SQ-HDM dominant	£8,176	£10,814
Scenario 2 – evidence based medium to long-term effectiveness assumptions									
AA+AR									
Standard of care	£26,680	22.55	15.73						
12 SQ-HDM	£26,668	22.55	15.94	-£12	0	0.20	12 SQ-HDM dominant	£4,109	£6,158
AR									
Standard of care	£15,580	22.74	19.03						
12 SQ-HDM	£15,366	22.74	19.17	-£214	0	0.14	12 SQ-HDM dominant	£3,100	£4,543

Abbreviations: AA: allergic asthma, AR: allergic rhinitis, HDM: house dust mite, LYG: life years gained, QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio, NMB: net monetary benefit, k: thousand.

6.3.3 AA+AR: Considering a null probability of asthma exacerbations across levels of asthma control in each arm

The results from scenario 3 of using a null probability of asthma exacerbations across levels of asthma control in each treatment arm are presented in Table 39.

Table 39 Summary cost-effectiveness results for scenario 3 for the AA+AR population - using a null probability of asthma exacerbations across levels of asthma control in each arm

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)	NMB (£20k/ QALY)	NMB (£30k/ QALY)
Company's corrected base case results – using exacerbation probabilities sourced from period 3 of the MT-04 trial as described in section 4.2.6.3									
AA+AR									
Standard of care	£26,680	22.55	15.73						
12 SQ-HDM	£24,520	22.55	16.10	-£2,159	0	0.37	12 SQ-HDM dominant	£9,591	£13,307
Scenario 3 – using a null probability of asthma exacerbations across levels of asthma control in each arm									
AA+AR									
Standard of care	£24,114	22.55	15.82						
12 SQ-HDM	£22,376	22.55	16.18	-£1,739	0	0.36	12 SQ-HDM dominant	£8,926	£12,519

Abbreviations: AA: allergic asthma, AR: allergic rhinitis, HDM: house dust mite, LYG: life years gained, QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio, NMB: net monetary benefit, k: thousand.

6.3.4 AA+AR and AR: Considering health state specific utilities and most relevant utility sources

The results from scenario 4 of considering a health state utility approach for both AA+AR and AR models are shown in Table 40. The source of health utilities for the AA+AR model was the Briggs et al., 2021 study[3], which modelled EQ-5D-3L utilities mapped from ACQ data collected in the MT-04 trial using a mixed effects model. The source of health state utilities for the AR model was the EQ-5D data collected in the MT-06 trial.

Table 40 Summary cost-effectiveness results for scenario 4 for the AA+AR and AR populations – considering health state-specific utilities and most relevant utility sources

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)	NMB (£20k/ QALY)	NMB (£30k/ QALY)
Company's corrected base case results – treatment-specific utilities as described in 4.2.7.2									
AA+AR									
Standard of care	£26,680	22.55	15.73						
12 SQ-HDM	£24,520	22.55	16.10	-£2,159	0	0.37	12 SQ-HDM dominant	£9,591	£13,307
AR									
Standard of care	£15,580	22.74	19.03						
12 SQ-HDM	£12,681	22.74	19.29	-£2,899	0	0.26	12 SQ-HDM dominant	£8,176	£10,814
Scenario 4 – health state specific utilities and most relevant utility sources									
AA+AR									
Standard of care	£26,680	22.55	18.57						
12 SQ-HDM	£24,520	22.55	18.63	-£2,159	0	0.06	12 SQ-HDM dominant	£3,440	£4,080
AR									
Standard of care	£15,580	22.74	18.68						
12 SQ-HDM	£12,681	22.74	18.80	-£2,899	0	0.12	12 SQ-HDM dominant	£5,388	£6,633

Abbreviations: AA: allergic asthma, AR: allergic rhinitis, HDM: house dust mite, LYG: life years gained, QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio, NMB: net monetary benefit, k: thousand.

6.3.5 AA+AR: Considering only relevant biologic treatments

The results from scenario 5 of using only omalizumab and tezepelumab as relevant biologics for the current decision problem for the AA+AR population are presented in Table 41.

Table 41 Summary cost-effectiveness results for scenario 5 for the AA+AR population - using only relevant biologic treatments

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)	NMB (£20k/ QALY)	NMB (£30k/ QALY)
Company's corrected base case results – using the biologic treatments as described in section 4.2.8.5									
AA+AR									
Standard of care	£26,680	22.55	15.73						
12 SQ-HDM	£24,520	22.55	16.10	-£2,159	0	0.37	12 SQ-HDM dominant	£9,591	£13,307
Scenario 5 – using only relevant biologic treatments									
AA+AR									
Standard of care	£26,620	22.55	15.73						
12 SQ-HDM	£24,472	22.55	16.10	-£2,148	0	0.37	12 SQ-HDM dominant	£9,580	£13,296

Abbreviations: AA: allergic asthma, AR: allergic rhinitis, HDM: house dust mite, LYG: life years gained, QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio, NMB: net monetary benefit, k: thousand.

6.3.6 AA+AR: Considering the MT-04 maintenance phase to estimate the treatment effect of 12 SQ-HDM in reducing primary care visits

The results from scenario 6 of considering the treatment effect of 12 SQ-HDM in reducing primary care visits from the MT-04 trial maintenance phase are shown in Table 42.

Table 42 Summary cost-effectiveness results for scenario 6 for the AA+AR population - treatment effect of 12 SQ-HDM on primary care of 7.35%

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)	NMB (£20k/ QALY)	NMB (£30k/ QALY)
Company's corrected base case results – treatment effect of 12 SQ-HDM on primary care of 31.19%									
AA+AR									
Standard of care	£26,680	22.55	15.73						
12 SQ-HDM	£24,520	22.55	16.10	-£2,159	0	0.37	12 SQ-HDM dominant	£9,591	£13,307
Scenario 6 – treatment effect of 12 SQ-HDM on primary care of 7.35%									
AA+AR									
Standard of care	£26,680	22.55	15.73						
12 SQ-HDM	£24,837	22.55	16.10	-£1,843	0	0.37	12 SQ-HDM dominant	£9,275	£12,991

Abbreviations: AA: allergic asthma, AR: allergic rhinitis, HDM: house dust mite, LYG: life years gained, QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio, NMB: net monetary benefit, k: thousand.

6.3.7 AA+AR and AR: Considering alternative estimates for the treatment effect of 12 SQ-HDM in reducing secondary care visits

The results from scenario 7 of considering alternative estimates for the treatment effect of 12 SQ-HDM in reducing secondary care visits are shown in Table 43.

Table 43 Summary cost-effectiveness results for scenario 7 for the AA+AR and AR populations – considering alternative estimates for the treatment effect of 12 SQ-HDM in reducing secondary care visits

	Total Costs	Total LYG	Total QALYs	Incr. Costs	Incr. LYG	Incr. QALYs	ICER (£/ QALY gain)	NMB (£20k/ QALY)	NMB (£30k/ QALY)
Company's corrected base case results – treatment effect of 12 SQ-HDM on secondary care as described in 4.2.8.6									
AA+AR									
Standard of care	£26,680	22.55	15.73						
12 SQ-HDM	£24,520	22.55	16.10	-£2,159	0	0.37	12 SQ-HDM dominant	£9,591	£13,307
AR									
Standard of care	£15,580	22.74	19.03						
12 SQ-HDM	£12,681	22.74	19.29	-£2,899	0	0.26	12 SQ-HDM dominant	£8,176	£10,814
Scenario 7 – alternative estimates for the treatment effect of 12 SQ-HDM in reducing secondary care visits									
AA+AR									
Standard of care	£26,680	22.55	15.73						
12 SQ-HDM	£27,728	22.55	16.10	£1,049	0	0.37	£2,822	£6,383	£10,099
AR									
Standard of care	£15,580	22.74	19.03						
12 SQ-HDM	£17,836	22.74	19.29	£2,256	0	0.26	£8,550	£3,021	£5,659

Abbreviations: AA: allergic asthma, AR: allergic rhinitis, HDM: house dust mite, LYG: life years gained, QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio, NMB: net monetary benefit, k: thousand.

6.4 EAG's preferred assumptions

Overall, the scenario analyses in section 6.3 suggest that the estimates of cost-effectiveness for the AA+AR model to be robust to alternative assumptions relating to short-term effectiveness (scenario 1), of using a null probability of asthma exacerbations across levels of asthma control (scenario 3), of using only relevant biologic treatments (scenario 5) and of considering an alternative treatment effect of 12 SQ-HDM on primary care visits (scenario 6). Assumptions around the medium to long-term effectiveness (scenario 2), the use of a health-state approach to utilities (scenario 4) and relating to the treatment effect of 12 SQ-HDM in reducing secondary care visits (scenario 7) were the most impactful. Except for scenario 3, the assumptions of these scenarios are incorporated into the EAG

base case. The EAG considers the MT-04 evidence on asthma exacerbation to be uncertain, however, the assumption of a null probability of asthma exacerbations may be considered too conservative and not reflective of clinical practice, and thus should be seen as exploratory.

This section presents the results of the EAG's analyses, separately for the AA+AR and AR populations, that formed the EAG's base case assumptions. As in section 6.3, all presented results are based on a deterministic analysis, except for both EAG's base case analyses for which deterministic (Table 44 and Table 46) and probabilistic (Table 45 and Table 47) results are presented. The EAG notes that the probabilistic cost-effectiveness results consider the uncertainty on the short-term effectiveness of treatments in the first year of the model via a Dirichlet distribution. This parameter uncertainty was built in by the EAG under the following assumptions: patients do not get worse from baseline to year 1, and patients that transition to the well-controlled/mild health state in year 1 come from the partly controlled/moderate health states at baseline, respectively for the AA+AR and the AR model. The EAG notes also that the probabilistic results shown considered 2,000 Monte Carlo simulations and a 20% variation (instead of 10% as in the CS) over the mean parameter values as a measure of uncertainty for parameters in which the company claims information on parameter uncertainty was not available. Furthermore, the EAG switched off the company restriction of limiting the sampling of utilities so that the treatment with 12 SQ-HDM could not result in a lower utility score compared with standard of care.

Table 44 and Table 46 illustrate the results of the analyses that the EAG undertook as separate steps to form the EAG's base case for the AA+AR and AR populations, respectively. For the cumulative results within each population, incremental costs substantially increased, with 12 SQ-HDM now estimated to be more expensive than standard of care. Similarly, incremental QALYs substantially decreased in both populations, now estimated to be closer to 0, implying that cost-effectiveness results are very sensitive to the EAG's preferred set of assumptions. The EAG's base case-estimated incremental QALYs are aligned with the EAG's overall judgement of the clinical effectiveness evidence of 12 SQ-HDM vs standard of care for both the AA+AR and AR populations.

Table 44 Deterministic cost-effectiveness results for the EAG's preferred AA+AR model assumptions

Preferred assumption	Total Costs	Total QALYs	Incr. cost	Incr. QALYs	Cumulative ICER £/QALY	Section in EAG report
1. Company's updated base case						5.1
Standard of care	£26,217	15.73				
12 SQ-HDM	£24,124	16.10	-£2,094	0.37	12 SQ-HDM dominant	
2. Company's corrected base case						6.1
Standard of care	£26,680	15.73				
12 SQ-HDM	£24,520	16.10	-£2,159	0.37	12 SQ-HDM dominant	
3. Analysis 2 + MT-04 maintenance phase to inform short-term effectiveness						4.2.6.1
Standard of care	£24,669	16.10				
12 SQ-HDM	£26,841	15.73	-£2,171	0.37	12 SQ-HDM dominant	
4. Analysis 3 + evidence based medium to long-term assumptions						4.2.6.2
Standard of care	£26,841	15.73				
12 SQ-HDM	£26,824	15.94	-£16	0.20	12 SQ-HDM dominant	
5. Analysis 4 + health state specific utilities sourced from Briggs et al., 20213						4.2.7.2
Standard of care	£26,841	18.47				
12 SQ-HDM	£26,824	18.48	-£16	0.02	12 SQ-HDM dominant	
6. Analysis 5 + using only relevant biologic treatments						4.2.8.3
Standard of care	£26,780	18.47				
12 SQ-HDM	£26,775	18.48	-£5	0.02	12 SQ-HDM dominant	
7. Analysis 6 + estimate for the treatment effect of 12 SQ-HDM in reducing primary care visits derived from MT-04 maintenance phase (7.35% relative reduction)						4.2.8.3
Standard of care	£26,780	18.47				
12 SQ-HDM	£26,949	18.48	£169	0.02	£10,977	
8. EAG base case: Analysis 7 + estimate for the treatment effect of 12 SQ-HDM in reducing secondary care visits equivalent to the primary care relative reduction						4.2.8.3
Standard of care	£26,780	18.47				
12 SQ-HDM	£28,676	18.48	£1,895	0.02	£123,269	

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

When considering the probabilistic results of the EAG's base case analysis for the AA+AR population, the interpretation of the cost-effectiveness estimates remains the same as for the deterministic ones (Table 45). The probability of 12 SQ-HDM being cost-effective at a cost-effectiveness threshold of £20,000/QALY gained is estimated to be approximately 10%.

Table 45 Probabilistic cost-effectiveness results for the EAG's preferred AA+AR set of model assumptions

Preferred assumption	Total Costs	Total QALYs	Incr. cost	Incr. QALYs	Cumulative ICER £/QALY	Probability of 12 SQ-HDM being CE	
EAG base case						£20,000/ QALY	£30,000/ QALY
Standard of care	£26,852	18.37				10%	13%
12 SQ-HDM	£28,696	18.39	£1,844	0.02	£118,740		

Abbreviations: HDM: house dust mite, QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio, CE: cost-effective.

Table 46 Deterministic cost-effectiveness results for the EAG's preferred AR model assumptions

Preferred assumption	Total Costs	Total QALYs	Incr. cost	Incr. QALYs	Cumulative ICER £/QALY	Section in EAG report
1. Company's updated base case						5.1
Standard of care	£14,294	19.03				
12 SQ-HDM	£11,562	19.29	-£2,731	0.26	12 SQ-HDM dominant	
2. Company's corrected base case						6.1
Standard of care	£15,580	19.03				
12 SQ-HDM	£12,681	19.29	-£2,899	0.26	12 SQ-HDM dominant	
3. Analysis 2 + evidence based medium to long-term assumptions						4.2.6.2
Standard of care	£15,580	19.03				
12 SQ-HDM	£15,366	19.17	-£214	0.14	12 SQ-HDM dominant	
4. Analysis 3 + health state specific utilities from MT-06						4.2.7.2
Standard of care	£15,580	18.68				
12 SQ-HDM	£15,366	18.73	-£214	0.05	12 SQ-HDM dominant	
5. EAG base case: Analysis 4 + alternative estimate for the treatment effect of 12 SQ-HDM in reducing secondary care visits (4.92% relative reduction)						4.2.8.3
Standard of care	£15,580	18.68				
12 SQ-HDM	£18,116	18.73	£2,536	0.05	£50,479	

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

When considering the probabilistic results of the EAG's base case analysis for the AA+AR population, the interpretation of the cost-effectiveness estimates remains the same as for the deterministic ones (Table 47). The probability of 12 SQ-HDM being cost-effective at a cost-effectiveness threshold of £20,000/QALY gained is estimated to be approximately 10%.

Table 47 Probabilistic cost-effectiveness results for the EAG's preferred AR set of model assumptions

Preferred assumption	Total Costs	Total QALYs	Incr. cost	Incr. QALYs	Cumulative ICER £/QALY	Probability of 12 SQ-HDM being CE	
EAG base case						£20,000/ QALY	£30,000/ QALY
Standard of care	£15,537	18.68				10%	17%
12 SQ-HDM	£18,048	18.73	£2,511	0.05	£52,414		

Abbreviations: HDM: house dust mite, QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio, CE: cost-effective.

6.5 Further scenario analysis over the EAG's preferred base case analyses

The EAG also explored the impact of several assumptions over the EAG's base case analysis for each population. Table 48 and Table 49 provide the deterministic results of these additional scenarios for the AA+AR and AR populations, respectively.

For the AA+AR model, the following additional scenarios over the EAG base case were explored (Table 48):

- A long-term treatment waning assumption of 2.5%, starting at 10 years and ending at 20 years, applied to 50% of patients, and considering that the intervention arm is never worse than the comparator arm (scenario 4a) or that it can be worse than the comparator arm (scenario 4b) - no ongoing effect was assumed after 10 years, i.e., 100% waning of the effect of treatment;
- A long-term treatment waning assumption of 2.5%, starting at 15 years and ending at 20 years, applied to 80% of patients, and considering that the intervention arm is never worse than the comparator arm (scenario 5a) or that it can be worse than the comparator arm (scenario 5b) - no ongoing effect was assumed after 10 years, i.e., 100% waning of the effect of treatment;
- Proportion of patients who discontinue treatment with 12 SQ-HDM to be 0% (scenario 6) or 100% (scenario 7), instead of 50% as in the EAG's base case and the company's corrected base case;
- Using a treatment-specific utility approach and the MT-04 trial maintenance phase as utility source (scenario 8), instead of the health state utility approached sourced from Briggs et al., 2021[3] as in the EAG's base case;
- Using MT-04 trial data as the treatment cost source (scenario 9), instead of the 'microcosting approach' as in the EAG's base case;
- Using data from Reiber et al., 2021[29] as the asthma treatment step source (scenario 10), instead of Demoly et al., 2022 (CARIOCA)[27] as in the EAG's base case;

- Considering no treatment effect of 12 SQ-HDM in reducing escalation to step 5 and, thus, no reduction in the use of biologic treatments (scenario 11), instead of a 22.5% reduction assumed in the EAG's base case and the company's corrected base case;
- Using MT-04 trial data to inform the number of annual GP visits by asthma control level (scenario 12), instead of using data elicited in a Delphi panel[54] as in the EAG's base case and the company's corrected base case;
- Considering the same cost weight by asthma control level (scenario 13), instead of the cost weight based on ICS reduction observed in the MT-04 trial as in the EAG's base case and the company's corrected base case;
- A treatment effect of 12 SQ-HDM, in terms of reducing the number of GP visits, from the MT-04 trial weeks 4 to 13, excluding randomisation, of 31.19% (scenario 14), instead of weeks 4 to 9 as in the EAG's base case; and
- A treatment effect of 12 SQ-HDM, in terms of reducing the number of secondary care visits, from the MT-04 trial to 54.58%, as in the company's corrected base case (scenario 15), instead of assuming this reduction to be equivalent to the one observed for primary care visits, as in the EAG's base case.

Most of the additional scenarios considered showed the robustness of the AA+AR model EAG's base case results, with ICERs above £50,000/QALY gained. The exceptions were: the scenario where a treatment-specific approach to utilities is used, which increases incremental QALYs to 0.16 (compared to 0.02 in the EAG's base case) and, thus, reduces the ICER to £11,506/QALY gained; and the scenario where the effect of 12 SQ-HDM in reducing secondary care visits is based on the MT-04 trial data, which decreases incremental costs to £169 (compared to £1,895 in the EAG's base case).

Table 48 Deterministic cost-effectiveness results for the additional scenarios over the EAG's AA+AR model base case

Preferred assumption	Total Costs	Total QALYs	Incr. cost	Incr. QALYs	ICER £/QALY	Section in EAG report
1. Company's updated base case						5.1
Standard of care	£26,217	15.73				
12 SQ-HDM	£24,124	16.10	-£2,094	0.37	12 SQ-HDM dominant	
2. Company's corrected base case						6.1
Standard of care	£26,680	15.73				
12 SQ-HDM	£24,520	16.10	-£2,159	0.37	12 SQ-HDM dominant	
3. EAG base case						6.4
Standard of care	£26,780	18.47				
12 SQ-HDM	£28,676	18.48	£1,895	0.02	£123,269	
4a. EAG base case + altered long-term assumptions: 2.5%, waning start 10 years; waning end 20 years; applied to 50% of patients - intervention arm never worse than comparator arm						4.2.6.2
Standard of care	£26,780	18.47				
12 SQ-HDM	£28,041	18.49	£1,261	0.02	£51,943	

Preferred assumption	Total Costs	Total QALYs	Incr. cost	Incr. QALYs	ICER £/QALY	Section in EAG report
4b. EAG base case + altered long-term assumptions: 2.5%, waning start 10 years; waning end 20 years; applied to 50% of patients - intervention arm can be worse than comparator arm						4.2.6.2
Standard of care	£26,780	18.47				
12 SQ-HDM	£28,098	18.47	£1,317	0.00	£2,014,636	
5a. EAG base case + altered long-term assumptions: 2.5%, waning start 15 years; waning end 20 years; applied to 80% of patients - intervention arm never worse than comparator arm						4.2.6.2
Standard of care	£26,780	18.47				
12 SQ-HDM	£28,204	18.49	£1,423	0.02	£64,313	
5b. EAG base case + altered long-term assumptions: 2.5%, waning start 15 years; waning end 20 years; applied to 80% of patients - intervention arm can be worse than comparator arm						4.2.6.2
Standard of care	£26,780	18.47				
12 SQ-HDM	£28,236	18.48	£1,456	0.01	£164,814	
6. EAG base case + Proportion of patients who discontinue treatment with 12 SQ-HDM and modelled as 12 SQ-HDM patients for the first 3 model cycles is 0% (rather than 50%)						4.2.6.5
Standard of care	£26,780	18.47				
12 SQ-HDM	£28,765	18.48	£1,984	0.01	£139,302	
7. EAG base case + Proportion of patients who discontinue treatment with 12 SQ-HDM and modelled as 12 SQ-HDM patients for the first 3 model cycles is 100% (rather than 50%)						4.2.6.5
Standard of care	£26,780	18.47				
12 SQ-HDM	£28,587	18.49	£1,807	0.02	£109,435	
8. EAG base case + altered utility approach to treatment-specific and using the MT-04 trial maintenance phase as source						4.2.7.2
Standard of care	£26,780	15.50				
12 SQ-HDM	£28,676	15.66	£1,895	0.16	£11,506	
9. EAG base case + altered treatment cost source to MT-04 trial						4.2.8.5
Standard of care	£21,404	18.47				
12 SQ-HDM	£23,436	18.48	£2,033	0.02	£132,188	
10. EAG base case + altered asthma treatment step source to Reiber et al., 2021[29]						4.2.8.3
Standard of care	£24,132	18.47				
12 SQ-HDM	£26,116	18.48	£1,985	0.02	£129,088	
11. EAG base case + Excluded reduction in biologics (relative reduction of 0%)						4.2.8.5
Standard of care	£26,780	18.47				
12 SQ-HDM	£28,828	18.48	£2,048	0.02	£133,173	
12. EAG base case + altered GP visit source to MT-04						4.2.8.6
Standard of care	£24,374	18.47				
12 SQ-HDM	£26,322	18.48	£1,949	0.02	£126,742	
13. EAG base case + disregarded the cost weighting based on ICS reduction as observed in MT-04						4.2.8.6
Standard of care	£25,727	18.47				
12 SQ-HDM	£27,662	18.48	£1,935	0.02	£125,860	
14. EAG base case + assuming a treatment effect of 12 SQ-HDM, in terms of reducing the number of GP visits, from MT-04 (31.19%) as in company's base case						4.2.8.6
Standard of care	£26,780	18.47				
12 SQ-HDM	£28,502	18.48	£1,722	0.02	£111,959	
15. EAG base case + assuming a treatment effect of 12 SQ-HDM, in terms of reducing the number of outpatient visits, from MT-04 (54.58%) as in company's base case						4.2.8.6
Standard of care	£26,780	18.47				
12 SQ-HDM	£26,949	18.48	£169	0.02	£10,977	

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

For the AR model, the following additional scenarios over the EAG base case were explored (Table 49):

- A different cut-off for 'troublesome symptoms' (rhinitis DSS score of at least 6 or a score of at least 5 with one symptom being severe), providing a different distribution of patients across rhinitis severity levels. That is, assuming different short-term effectiveness for 12 SQ-HDM and standard of care for the first year/model cycle (scenario 4), instead of the cut-off for 'troublesome symptoms' based on an average rhinitis DSS score of 4, as assumed in the EAG's base case and the company's corrected base case;
- A long-term treatment waning assumption of 2.5%, starting at 10 years and ending at 20 years, applied to 50% of patients, and considering that the intervention arm is never worse than the comparator arm (scenario 5a) or that it can be worse than the comparator arm (scenario 5b) - no ongoing effect was assumed after 10 years, i.e., 100% waning of the effect of treatment;
- A long-term treatment waning assumption of 2.5%, starting at 15 years and ending at 20 years, applied to 80% of patients, and considering that the intervention arm is never worse than the comparator arm (scenario 6a) or that it can be worse than the comparator arm (scenario 6b) - no ongoing effect was assumed after 10 years, i.e., 100% waning of the effect of treatment;
- Proportion of patients who discontinue treatment with 12 SQ-HDM to be 0% (scenario 7) or 100% (scenario 8), instead of 50% as in the EAG's base case and the company's corrected base case;
- Using a treatment-specific utility approach and the MT-06 trial as utility source (scenario 9), instead of a health state utility approached as in the EAG's base case;
- Using MT-06 trial data to inform the annual GP visits by rhinitis severity level (scenario 10), instead of using data elicited in a Delphi panel[54] as in the EAG's base case and the company's corrected base case; and
- A treatment effect of 12 SQ-HDM, in terms of reducing the number of secondary care visits, to 73.53%, from the before and after study by El Qutob et al., 2016[13], as in the company's corrected base case (scenario 15), instead of assuming this reduction to be equivalent to the one observed for primary care visits, as in the EAG's base case.

Most of the additional scenarios considered showed the robustness of the AR model to the EAG's base case results, with ICERs above £30,000/QALY gained. As seen in the AA+AR model, in the AR model the exceptions were: the scenario where a treatment-specific approach to utilities is used, which increases incremental QALYs to 0.14 (compared to 0.05 in the EAG's base case) and, thus, reduces the ICER to £17,576/QALY gained; and the scenario where the effect of 12 SQ-HDM in reducing secondary care visits is based on the El Qutob et al., 2016[13] data, which indicates 12 SQ-HDM is cost saving, and, thus, dominant over the standard of care.

Table 49 Deterministic cost-effectiveness results for the additional scenarios over the EAG's AR model base case

Preferred assumption	Total Costs	Total QALYs	Incr. cost	Incr. QALYs	ICER £/QALY	Section in EAG report
1. Company's updated base case						5.1
Standard of care	£14,294	19.03				
12 SQ-HDM	£11,562	19.29	-£2,731	0.26	12 SQ-HDM dominant	
2. Company's corrected base case						6.1
Standard of care	£15,580	19.03				
12 SQ-HDM	£12,681	19.29	-£2,899	0.26	12 SQ-HDM dominant	
3. EAG base case						6.4
Standard of care	£15,580	18.68				
12 SQ-HDM	£18,116	18.73	£2,536	0.05	£50,479	
4. EAG base case + altered short-term assumptions to consider a different cut-off for 'troublesome symptoms' (as additional scenario – A – presented by the company)						4.2.6.1
Standard of care	£15,255	18.93				
12 SQ-HDM	£17,820	18.96	£2,565	0.02	£117,305	
5a. EAG base case + altered long-term assumptions: 2.5%, waning start 10 years; waning end 20 years; applied to 50% of patients - intervention arm never worse than comparator arm						4.2.6.2
Standard of care	£15,580	18.68				
12 SQ-HDM	£17,833	18.75	£2,253	0.07	£33,595	
5b. EAG base case + altered long-term assumptions: 2.5%, waning start 10 years; waning end 20 years; applied to 50% of patients - intervention arm can be worse than comparator arm						4.2.6.2
Standard of care	£15,580	18.68				
12 SQ-HDM	£17,884	18.74	£2,303	0.06	£37,687	
6a. EAG base case + altered long-term assumptions: 2.5%, waning start 15 years; waning end 20 years; applied to 80% of patients - intervention arm never worse than comparator arm						4.2.6.2
Standard of care	£15,580	18.68				
12 SQ-HDM	£17,901	18.75	£2,320	0.07	£34,073	
6b. EAG base case + altered long-term assumptions: 2.5%, waning start 15 years; waning end 20 years; applied to 80% of patients - intervention arm can be worse than comparator arm						4.2.6.2
Standard of care	£15,580	18.68				
12 SQ-HDM	£17,930	18.74	£2,350	0.06	£36,209	
7. EAG base case + Proportion of patients who discontinue treatment with 12 SQ-HDM and modelled as 12 SQ-HDM patients for the first 3 model cycles is 0% (rather than 50%)						4.2.6.5
Standard of care	£15,580	18.68				
12 SQ-HDM	£18,135	18.73	£2,555	0.05	£52,200	
8. EAG base case + Proportion of patients who discontinue treatment with 12 SQ-HDM and modelled as 12 SQ-HDM patients for the first 3 model cycles is 100% (rather than 50%)						4.2.6.5
Standard of care	£15,580	18.68				
12 SQ-HDM	£18,098	18.73	£2,517	0.05	£48,844	
9. EAG base case + altered utility approach to treatment-specific and using the MT-06 trial as source						4.2.7.2
Standard of care	£15,580	19.03				
12 SQ-HDM	£18,116	19.17	£2,536	0.14	£17,576	
10. EAG base case + altered GP visit source to MT-06						4.2.8.6
Standard of care	£13,887	18.68				
12 SQ-HDM	£16,504	18.73	£2,617	0.05	£52,081	
11. EAG base case + assuming a treatment effect of 12 SQ-HDM, in terms of reducing the number of outpatient visits, from El Qutob et al., 2016[13] (73.53%) as in company's base case						4.2.8.6
Standard of care	£15,580	18.68				
12 SQ-HDM	£15,366	18.73	-£214	0.05	12 SQ-HDM dominant	

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

6.6 Conclusions of the cost effectiveness section

The company developed two *de novo* Markov models to assess the cost-effectiveness of 12 SQ-HDM compared with standard of care for treating HDM-induced AA+AR and AR populations, respectively.

The company systematic review of cost-effectiveness studies identified 5 cost-utility studies which the EAG deemed relevant for the decision problem. It is not clear how the cost-effectiveness systematic review results informed the company's cost-effectiveness analyses, although the EAG notes that data from the pivotal trials to this appraisal, MT-04[1, 2] for AA+AR and MT-06[4, 5] for AR, have been utilised in some of the identified studies but under a different (less complex) modelling approach. The cost-effectiveness review was deemed not fully comprehensive by the EAG. The EAG identified two health technology assessments of SLIT for HDM sensitised patients, one relating to each population, with cost-effectiveness evidence relevant to the decision problem of the current appraisal, none recommending SLIT due to insufficient evidence to support clinical and/or cost-effectiveness.

The EAG deems that the submitted evidence for the AR model partially reflects the decision problem defined in the final scope. The AR model was populated with MT-06 trial evidence in adults, which was generalised to adolescents, implicitly assuming that no difference in cost-effectiveness exists between the two subpopulations, an assumption which the EAG finds uncertain. Furthermore, the EAG considers the restricted pharmacotherapy used in the MT-06 trial not to be representative of UK standard of care. If the positioning of 12 SQ-HDM is at the last line of treatment (and for people whose disease could not be relieved by other pharmacotherapies available in the NHS), then pharmacotherapies allowed in the MT-06 trial may be reflective of NHS clinical practice. Therefore, the EAG considers that the AR model can be mostly informative if no other treatments are available, i.e., at the last line of treatment.

The EAG considers that the submitted evidence for the AA+AR model does not appropriately reflect the decision problem defined in the final scope. This mainly stems from the use of the MT-04 trial, which was not designed to assess comparative efficacy of 12 SQ-HDM and is considered by the EAG of limited use to inform decision making. Thus, it is important to emphasise that all cost-effectiveness results for the AA+AR population presented in the company's submissions and the EAR are affected by the uncertainty in the underpinning clinical effectiveness evidence and how this evidence was parameterised within the AA+AR model via a post-hoc analysis. The EAG considers that the AA+AR model does not accurately reflect the clinical management of asthma which would, in clinical practice, involve a stepwise approach to assessing, treating, and monitoring patients' asthma control. Thus, the findings of the AA+AR cost-effectiveness analysis need to be interpreted in the context of

these limitations, which the EAG believes will substantially impair their usefulness to inform decision making. Nevertheless, the EAG, within the limits of the existing evidence and the available time frame for this appraisal, attempted to alleviate these limitations by changing a number of the company's model assumptions in the EAG base case. Further, the EAG performed extensive additional analysis to reflect existing parameter uncertainty and aid decision making so that the committee can consider the clinical plausibility of alternative assumptions and, in turn, examine their impact on cost-effectiveness. A similar approach was taken for the AR model.

In the absence of better evidence, the EAG considered use of the MT-04 trial data to populate the AA+AR model, although restricting its use to the maintenance phase (period 2 of the trial), as in previously published economic analyses. The medium to long-term effectiveness estimates informing both AA+AR and AR company's models are based on assumptions. The EAG considered the assumptions of improvements in health imposed by the company for 12 SQ-HDM from 2 to 10 years not to be supported by evidence. Furthermore, the company's long-term effectiveness assumptions beyond 9 years are considered by the EAG as subjective and uncertain. The EAG's preference is for an evidence-based approach to effectiveness, suggesting stable effects from 2 to 10 years for both arms, and with patients in the 12 SQ-HDM treatment arm matching the distribution of patients in the standard of care arm post-10 years. Furthermore, the company's choice over a treatment-specific approach for utilities does not align with the model structures being proposed, with the EAG giving preference to a heath state utility approach. Finally, substantial limitations were identified in the evidence informing how 12 SQ-HDM affects the number of outpatient visits. As it was not possible to appropriately inform this parameter with quality evidence, the EAG considered a reduction in outpatient visits to be equivalent to the one observed for primary care visits.

For both the AA+AR and AR models, the company's base case analysis results were not robust to scenarios relating to using evidence-based medium to long-term effectiveness assumptions, using health state-specific utilities and of using alternative estimates for the treatment effect of 12 SQ-HDM in reducing secondary care visits. The EAG base case for the AA+AR population suggests that 12 SQ-HDM is slightly more effective and more costly than standard of care. Similarly, the EAG base case for AR suggests that 12 SQ-HDM is slightly more effective and more costly than standard of care. These findings were observed in both deterministic and probabilistic modelling of each model.

Apart from the issue highlighted above relating to the AA+AR model not adequately reflecting asthma management and the stepping up/down in treatment according to patients' asthma control, the EAG considers the assumptions around the treatment effect of 12 SQ-HDM in reducing secondary care visits to remain a key area of uncertainty in both the AA+AR and AR models, and a key driver of cost-effectiveness. Both evidence from the MT-04 trial used in the AA+AR model and from the before and after study by El-Qutob et al., 2016[13] are considered very uncertain. Evidence from the

REACT study[31] suggests that any treatment effect of 12 SQ-HDM on secondary care compared to standard of care may be negligible. Supported on this and in the absence of evidence of better quality, the EAG explored the assumption of considering the relative reductions in primary care, given the effect of 12 SQ-HDM to be exchangeable to secondary care. Nonetheless, further high-quality evidence should be sought to complement existing evidence so that uncertainty in this specific model input parameter is substantially reduced.

Overall, the cost-effectiveness analyses performed by the EAG suggests that ICER's may exceed the conventional thresholds used by NICE in the comparison of 12 SQ-HDM and standard of care in the AA+AR and AR populations. These findings are, in general, robust to the assumptions being varied in the EAG's additional analysis, except when a treatment-specific approach to utilities and a treatment effect of 12 SQ-HDM in reducing the number of outpatient visits, as in the company's base case, are taken. Nevertheless, the EAG notes that several uncertainties remain unaddressed.

7 SEVERITY MODIFIER

The company claims that the technology is not expected to meet the criteria for a severity weight.

Following NICE's methods guidance,[63] the EAG calculated the absolute and proportional QALY shortfall using a published calculator by Schneider et al., 2021.[83] The EAG confirms that 12 SQ-HDM does not meet the criteria for a severity weight.

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APPENDICES

APPENDIX 1. SYSTEMATIC LITERATURE REVIEWS

Table 50 Relevant cost-effectiveness studies

Study	Objective and setting	Summary of model	Patient population	QALYs (and evidence source)	Costs (and evidence source)	Incremental Costs, Incremental Effects, ICER (£/QALY gained) and overall conclusions
Bruggenjurgen et al., 2008[37]	Cost effectiveness of SCIT in addition to symptomatic treatment (ST) compared with ST alone for treating patients with HDM induced allergic rhinitis and allergic asthma in a German health care setting.	Markov model, 15-year time horizon, 1-year cycles, 3% discounting, societal perspective. Health states included: mild allergic rhinitis, moderate to severe allergic rhinitis, moderate to severe allergic rhinitis and mild allergic asthma, moderate to severe allergic rhinitis and moderate to severe allergic asthma, no symptoms, dead.	Children 6–12 years, Adolescents 13–18 years, and Adults 19–65 years with allergic rhinitis and allergic asthma	Utilities of a large German pilot project on acupuncture, which also examined patients with different allergic diseases, were incorporated: mild allergic rhinitis, 0.7579; moderate to severe allergic rhinitis, 0.7378; severe allergic rhinitis and mild allergic asthma, 0.7317; severe allergic rhinitis and moderate to severe allergic asthma, 0.6985; no symptoms, 0.7841; and death, 0.0.	The calculation of the average annual cost per patient in each of the illness states was based on a German study by Schramm et al. This study provided direct and indirect costs (attributable to disability, early retirement, and loss of work by patients and caregivers) stratified by severity, which were derived from retrospective interviews on physician-recruited patients.	SCIT ICER of €19,787 per additional QALY. SCIT and ST were both more effective and less costly compared with ST only. The ICER was higher in adult patients (€22,196 per QALY) than in children (€12,750 per QALY) or adolescents (€14,747 per QALY). This finding was mainly driven by the reduction in indirect costs. At WTP €50,000 per QALY, SCIT was considered a cost-effective treatment.

Hahn-Pedersen et al., 2016[38]	Cost-effectiveness of ACARIZAX plus pharmacotherapy versus placebo plus pharmacotherapy in patients with house dust mite allergic asthma that is uncontrolled by inhaled corticosteroids, in a German setting.	Pharmacoeconomic model using a simplified decision tree structure, 9-year time horizon, 3% discounting. Societal perspective. Modelled based on MT-04 trial maintenance period, as it was better aligned with clinical practice. QALY scores and health care resource use data recorded in the MT-04 trial were applied to each treatment group and extrapolated over a 9-year time horizon. For this extrapolation, costs that occurred during year one were applied equally across all years. To examine the effect of treatment on patient health, QALY scores were altered using an annual rate of change in utility. Deterministic sensitivity analysis was also performed.	HDM allergic asthma patients already taking pharmacotherapy whose symptoms are not well controlled.	Utility values used in the model were taken from the end of the maintenance period in MT-04 trial (i.e., before ICS reduction and removal). Within the trial the SF-36 health survey was used to measure patient utility. A 5 % increase in utility for ACARIZAX patients during years 2 and 3 of treatment was assumed, based on the assumption that patients continue to receive a clinical benefit from treatment. For pharmacotherapy it was assumed that patients' health remains stable, assuming that the improvement observed for pharmacotherapy patients will remain throughout this period. It was assumed that both patient groups remain stable for years 4 and 5 (i.e., 2 years post- treatment discontinuation), followed by a 5 % decline in health during years 6–9.	Within MT-04, patients recorded medication use using electronic diaries during the last 4 weeks of the maintenance period. Physician and emergency room visits were recorded at each visit. All resources recorded within MT-04 were combined with relevant unit costs from a German perspective, to estimate mean patient costs over a one-year time horizon. The cost of ACARIZAX was also included. ACARIZAX first tablet should be taken under the surveillance of a physician. This additional visit was incorporated into the model. The analysis considered sick days to capture the impact of indirect costs.	ACARIZAX produced an extra 0.66 QALYs at an incremental cost of €2673, which equates to an ICER of €4,041. Total annual indirect costs were included the total per patient costs rose to €6,760 for ACARIZAX and €5,188 for pharmacotherapy respectively, with overall incremental costs reducing from €2,673 to €1,572. At a WTP of €40,000 per additional QALY, treatment was considered cost-effective.

Green et al., 2017[40]	Cost-effectiveness of SQ HDM SLIT tablet in addition to pharmacotherapy *vs* pharmacotherapy alone for the treatment of house dust mite allergic rhinitis in Germany.	Pharmacoeconomic model using a simplified decision tree structure, 9-year time horizon, 3% discounting. Societal perspective. Patients in the SQ HDM SLIT-tablet group remain on treatment for three years before switching to allergy pharmacotherapy only. Patients in the comparator group remain on pharmacotherapy for the full time horizon. QALY scores and health care resource use data from the MT-06 trial were applied to each treatment group and extrapolated over a 9-year time horizon. Deterministic and probabilistic sensitivity analyses were also performed.	Patients suffering from persistent moderate to severe HDM allergic rhinitis, with or without allergic asthma, despite the use of allergy pharmacotherapy.	MT-06 trial collected patient utilities using the EQ-5D health survey. Regression analysis (two stage) used to correct for skewed data and estimate average utility for those in less than perfect health, by treatment group. To account for the impact of AIT during the treatment period, the analysis assumed that patients taking SQ HDM SLIT tablet will have a 5% increase in utility during each year of treatment (i.e., a 5% improvement in HRQoL), while patients on pharmacotherapy were assumed to have a stable HRQoL during this period. In years 6-9, the treatment group was assumed to have a 10% decline in utility and the pharmacotherapy group a 5% decline in utility.	Costs were estimated by taking health care resource use values from the MT-06 trial and multiplying by the unit price of that resource for the German market. MT-06 trial data on resource use (e.g., doctors' visits) was considered. The cost of SQ HDM SLIT tablet was also included within the treatment group. The annual costs generated were applied equally across all years in the model. One extra doctor's visit for all patients on SQ HDM SLIT tablet was included. To capture the indirect costs of allergic rhinitis on society, sick days were also incorporated into the analysis (sourced from literature).	In the base case analysis, compared with allergy pharmacotherapy, SQ HDM SLIT tablet led to a QALY gain of 0.31 at an incremental cost of €2,276 over the 9-year time horizon. This equated to an ICER of €7,519/QALY gained. The treatment was cost-effective for all scenarios analysed (WTP €40,000 per QALY gained). Model results were highly sensitive to all parameters except unit price of SQ HDM SLIT tablet. The results of the PSA indicate that SQ HDM SLIT tablet has a probability of cost-effectiveness of 61.4%.

Green et al., 2019[39]	Cost-effectiveness of the 12 SQ HDM SLIT tablet plus pharmacotherapy versus pharmacotherapy alone in the treatment of AA from the perspective of three Eastern European countries: Czech Republic, Poland and Slovakia.	Pharmacoeconomic model using a simplified decision tree structure, 5-year time horizon, 3% discount rate for costs in Czech Republic, 5% in Poland and Slovakia. 3% discount rate for QALYs in Czech Republic, 3.5% in Poland and 5% in Slovakia. Health care payer perspective. Utility scores and health care resource use data recorded in the MT-04 trial were applied to each treatment group and extrapolated over a 5-year time horizon. Two scenarios were used to investigate the impact of changes on long-term patient health for both groups, which was measured by annual changes in QALY scores. Deterministic sensitivity analysis was also performed.	Patients with HDM allergic asthma (AA)	Utility values used in the model were taken from the end of the maintenance period in MT-04 (i.e. before ICS reduction and removal). Utility data was corrected for average baseline utility. The utility values from MT-04 were used for the first year of the analysis. For the remaining 4 years of the time horizon the utilities were extrapolated based on the following assumptions: - in year 2-3 an increased treatment effect and, therefore, further increase in utilities of 5% in the treatment arm. - during year 4-5, the effect is sustained due to the disease modifying effect.	The following cost inputs were included in the models: the cost of the SQ HDM SLIT tablet (treatment arm only), specialist/ general physician visits, emergency room visits, ICS use and SABA use. The total usage of these resources was based on data recorded in the MT-04 trial per treatment arm and extrapolated over the full time horizon. The total annual costs were estimated by combining the resource use with country specific cost data and prices. To reflect the local health care setting and treatment practice, some adjustments had to be made to the different models.	SQ HDM SLIT was associated with higher overall costs of approximately € 2,500 to € 3,000, but also improves patient outcomes via QALY gains of approximately 0.35. These results indicate that the SQ HDM SLIT tablet is a cost-effective treatment for HDM allergic asthma in Czech Republic, Poland and Slovakia, as shown by the ICERs of less than € 10,000 per additional QALY in all three countries.

Parra-Padilla et al., 2021[7]	Cost-effectiveness of SCIT plus ICS vs ICS for AA, in paediatric and adult patients with or without AR, from the perspective of the Colombian healthcare system	Markov model, 10-year time horizon, 3-month cycles. 5% discounting. Health system perspective. Health states: GINA Step 2, GINA Step 3, Asthma in remission, Overall death. The amount of medication required for disease control used as a proxy of asthma severity levels and defined the different health states: - GINA Step-3 (medium dose of ICS + Salbutamol), - Step-2 (low dose of ICS + Salbutamol), - asthma in remission (complete withdrawal of medications), - any-cause death Deterministic sensitivity analysis, probabilistic sensitivity analysis, and scenario analyses used to test robustness of results.	Paediatric and adult patients with AA with or without AR. Moderate persistent HDM induced AA.	EQ-5D utility values reported by Szende et al., 2009[84] for intermittent, mild, and moderate severity levels in Hungary were used. Utilities were assigned to asthma without medication in remission, GINA Step 2, and GINA Step 3 states in the model, respectively. Disutilities associated with exacerbations were obtained from a previous study by Lloyd et al., 2007[85] that reported changes in baseline EQ-5D utility values in patients from the UK.	Included costs of medications, medical services (outpatient visits and specialized care), and ambulatory services (i.e., laboratory/image procedures). Costs per year were calculated by multiplying individual cost inputs with age-specific medication doses and medical services frequency considered to be appropriate to achieve disease control - based on local and international clinical guidelines.	AA only: SCIT+ICS would avert a total of 847 exacerbations per 1,000 patients treated compared to the ICS strategy. This, together with savings in medications, would generate 0.37 additional QALYs and additional costs of US$828 per patient. ICER: US$19,282 per additional QALY, making the SCIT+ICS cost-effective. AA+AR: yielded an ICER 27.3% lower compared to the base case scenario suggesting increased cost-effectiveness of the intervention in paediatric patients with AA+AR. In all evaluated analyses, the SCIT+ICS remained cost-effective. Probabilistic sensitivity analysis indicated that SCIT+ICS was cost-effective in 95.2% of iterations, and in 88.7% of iterations was associated with a gain in QALYs.

Table 51 ERG appraisal of evidence identification for the SLR on cost-effectiveness studies.

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	YES	
Were appropriate sources searched?	PARTLY	The INAHTA database, a key source for identifying health technology assessments from national and international HTA agencies, was not searched. The NICE website was searched however searching of other HTA agency websites was not undertaken. Some conference abstracts would have been retrieved through searches of Embase, however no further searching of individual conference proceedings were carried out.
Was the timespan of the searches appropriate?	YES	Database inception to February/March/April 2023. All Ovid databases were search on 3rd March 2023. CEA Registry was searched on 12th April 2023. NICE website searched on 15th February 2023.
Were appropriate parts of the PICOS included in the search strategies?	PARTLY	Population (HDM allergic rhinitis OR HDM allergic asthma) AND Study design (economic evaluations). It was inappropriate to limit the searches of NHS EED, by study design. Population terms only should have been used to search this database.
Were appropriate search terms used?	PARTLY	Search terms for economic evaluations in MEDLINE and Embase were very narrowly focused, relevant subject headings in MEDLINE were missing (e.g. cost-benefit analysis/) incorrect subject headings in MEDINE were used (e.g. cost utility analysis/ does not exist in MEDLINE), and searches in the title field for economic evaluation terms were missing in both MEDLINE and Embase. Search terms for the population were appropriate.
Were any search restrictions applied appropriate?	NOT APPLICABLE	
Were any search filters used validated and referenced?	NO	Searches were restricted to economic evaluations in MEDLINE and Embase. However validated study design search filters were not used for this, nor were any validated search filters referenced. Therefore, it is possible that relevant economic evaluations could have been missed. Validated search filters for the identification of economic evaluations with clearly reported performance data for both MEDLINE and Embase are available and would have been more appropriate to use for this SLR to identify all relevant economic evaluations.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Table 52 EAG appraisal of evidence identification – HRQoL SLR

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	PARTLY	Some minor details were missing in the original submission but were provided in the company response to the PfC. A PRISMA flow diagram was missing for the original search results from February 2015, however a written overview of results was given.

		The design and length of the search strategies made them difficult to untangle and follow. However, the main sections of the strategies relevant for this SLR – terms for the population and terms for health state utility values - were included within the much broader strategies presented.
Were appropriate sources searched?	YES	
Was the timespan of the searches appropriate?	YES	Database inception to March 2023.
Were appropriate parts of the PICOS included in the search strategies?	YES	Population (HDM allergic rhinitis OR HDM allergic asthma) AND Outcomes (Utilities OR HRQoL).
Were appropriate search terms used?	YES	
Were any search restrictions applied appropriate?	PARTLY	A publication date limit of 2015 onwards was used in the 2023 update searches. This would not have identified studies with a publication year prior to 2015 but only available in the databases after the original 2015 searches were carried out. Conference abstracts and proceedings were removed from the 2015 Embase search results.
Were any search filters used validated and referenced?	YES	In the company response to the PfC, details were given of any validated search filters that were used within the strategies and references provided. Where validated filters were not available, a more pragmatic approach was taken with a detailed description given of the methods used to create the filters used. This was a valid and appropriate way of dealing with this issue.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Table 53 EAG appraisal of evidence identification – resource use and costs SLR

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	PARTLY	Some minor details were missing in the original submission but were provided in the company response to the PfC. A PRISMA flow diagram was missing for the original February 2015 searches, however a written overview of results was given. The design and length of the search strategies made them difficult to untangle and follow. However, the main sections of the strategies relevant for this SLR – terms for the population and terms for costs or resource use - were included within the much broader strategies presented.
Were appropriate sources searched?	YES	
Was the timespan of the searches appropriate?	YES	January 2000 to March 2023.
Were appropriate parts of the PICOS included in the search strategies?	YES	Population (HDM allergic rhinitis OR HDM allergic asthma) AND Outcomes (costs OR resource use).
Were appropriate search terms used?	YES	

Were any search restrictions applied appropriate?	PARTLY	A publication date limit of 2015 onwards was used in the 2023 update searches. This would not have identified studies with a publication year prior to 2015 but only available in the databases after the original 2015 searches were carried out. An appropriate limit was applied to exclude studies indexed with non-European country subject headings, which matched the inclusion criteria. Conference abstracts and proceedings were removed from the 2015 Embase search results.
Were any search filters used validated and referenced?	YES	In the company response to the PfC, details were given of any validated search filters that were used within the strategies and references provided. Where validated filters were not available, a more pragmatic approach was taken with a detailed description given of the methods used to create the filters used. This was a valid and appropriate way of dealing with this issue.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

APPENDIX 2. ADVERSE EVENTS AND UTILISATION OF BIOLOGICS

Table 54 Adverse events not included in the AA+AR model

AA+AR model	Placebo (N=277)		12 SQ-HDM (N=282)	
Adverse events	**Events**	**Probability**	**Events**	**Probability**
Nausea	0	0 %	8	2.84%
Lip oedema	0	0 %	10	3.55%
Pharyngeal oedema	0	0 %	6	2.13%
Swollen tongue	0	0 %	6	2.13%
Lip pruritis	0	0 %	8	2.84%
Accidental overdose	12	4.33%	16	5.67%

Table 55 Adverse events not included in the AR model

AR model	Placebo (N=338)		12 SQ-HDM (N=318)	
Adverse events	**Events**	**Probability**	**Events**	**Probability**
Lip oedema	2	0.59%	9	2.83%
Pharyngeal oedema	0	0.00%	8	2.52%
Oral discomfort	0	0.00%	10	3.14%
Tongue oedema	0	0.00%	9	2.83%
Eye pruritus	3	0.89%	7	2.20%

Table 56 Biological drug prescriptions reported for the main cohorts in the REACT study[31]

	AIT		Control	
	N	**Mean (SD)**	**N**	**Mean (SD)**
Year 3	32,112	0.002 (0.11)	32,112	0.003 (0.17)
Year 5	19,783	0.002 (0.10)	19,783	0.002 (0.11)
Year 9	1,846	0.00 (0.00)	1,846	0.003 (0.12)

AIT, allergen immunotherapy; SD: standard deviation

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 23 January 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Prohibition of established clinical management treatments which are routinely used in the NHS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3 The EAG state that glucocorticoids and antihistamines were prohibited in the MT-04 and MT-06 trials. Antihistamines, and oral and short-acting parenteral glucocorticoids were not prohibited in the MT-04 trial. Desloratadine (oral antihistamine) and azelastine (antihistamine eye drops) were provided as symptomatic medications in the MT-06 trial. Antihistamines other than these were prohibited in the MT-06.	Amend statement in EAG report to split list of prohibited medication by trial, and correct statement on prohibited medication in the MT-04 and MT-06 trials.	Incorrect listing of prohibited medication in the MT-04 and MT-06 trials.	For antihistamines: Please note that the EAG reported the prohibition of antihistamines in MT-04 based on the details provided by the company in Table 37 of the CS. The EAR text has been amended to reflect that some antihistamines were prohibited in MT-06 and that antihistamines were not prohibited in MT-04. For glucocorticoids: The EAG does not see a factual inaccuracy, given that panel 5-4 of the MT-04 CSR reports that oral and short-acting parenteral glucocorticoids were prohibited.

Section 2.3 The EAG state that that the populations recruited to the allergic asthma trials were restricted by ACQ score which would not happen in the NHS. This is incorrect.	Remove comment that ACQ would not be collected in the NHS.	The GINA guideline references the asthma control questionnaire (ACQ) and asthma control test (ACT) as examples of numerical asthma control tools for assessing symptom control. Both the ACQ and ACT are recommended in NICE's quality standard on asthma (QS25). ACT scores are done in practice as part of QOF in primary care in which the scores are used to assess asthma status and the potential need to step up or down on asthma treatments.	Not a factual inaccuracy. The EAG did not comment that ACQ would not be collected in the NHS. The statement referred to in Section 2.3 is clearly linked to Section 3.2.1 which notes that the exclusion of patients with an ACQ>1.5 would not be reflective of NHS practice as they would be eligible to receive SQ-HDM SLIT.
Section 3.2.1 The EAG state that in the AA+AR trials concomitant treatment given in both the intervention and control arms was not adjusted by stepping treatment up or down	Remove comment from report.	ICS and SABA use in the trial could be adjusted as needed to control for asthma symptoms throughout the trial. As stated in the MT-04 trial protocol and CSR, symptomatic medications were allowed to be used as	We have clarified this statement by adding "….to the extent expected to be seen in an NHS setting." to the end of the sentence.

according to required level of asthma control. This is incorrect.		needed in addition to the IMP to which the subjects had been randomised. ICS was provided as budesonide powder for inhalation in strengths of 100 or 200 µg/dose and was to be used as daily controller treatment of asthma until period 3B (ICS withdrawal) (or throughout the trial for subjects having an asthma exacerbation in period 3A (ICS reduction) and continuing the trial). SABA was provided as salbutamol for inhalation in a strength of 200 µg/dose for use as needed to control of asthma symptoms throughout the trial.	
Section 3.2.1 The EAG state that the reduction of ICS in the MT-04 trial does not reflect NHS practice.	Amend statement to correctly reference the BTS guidelines on treatment stepdown.	In clarification, the company provided references to the current BTS/SIGN 2019 asthma management	Not a factual inaccuracy – the EAG's adviser was clear in noting that, in the NHS, blanket mandatory ICS reductions and withdrawal for all

This is an oversimplification and is not factually accurate in all cases.		guidelines which state (Section 7.6): "Patients should be maintained at the lowest possible dose of inhaled corticosteroid. Reduction in inhaled corticosteroid dose should be slow as patients deteriorate at different rates. Reductions should be considered every three months, decreasing the dose by approximately 25–50% each time." As such, in relation to current clinical guidelines, the mandated ICS reduction during Period 3a can be considered reflective of current clinical practice.	patients would not be seen.
Section 3.2.1 The EAG highlight that the clinicaltrials.gov website had an alternative definition of the primary trial outcome compared with the trial	Remove this section of commentary from the EAG report.	The trial protocol and ICTR correctly define the primary outcome of the MT-04 trial. These are the only sources that should be considered by the EAG with respect to the	Not a factual inaccuracy.

protocol and ICTR documentation. The EAG go on to state that the significance and implications of these definition differences is unclear and of concern. This is an inappropriate and misleading comment from the EAG and has no impact on the clinical trial data or this appraisal.		definition of trial design and outcomes. If there is an error on the clinicaltrials.gov website, this has no impact on the MT-04 clinical trial, its findings, or interpretation of those findings.	

Issue 2 Clinical relevance of the magnitude of the efficacy estimates of 12 SQ-HDM

N/A

Issue 3 Numerous important methodological limitations seen across the 12 SQ-HDM trials

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6 The EAG state that the MT-04 trial was designed for regulatory approval of 12	The statement should be removed from the EAG report.	This is an unsupported opinion of the EAG and not a factually correct statement.	The EAG has removed the sentence. The EAG highlights that the bulk of the argument of that

SQ-HDM and not to evaluate its comparative effectiveness. This statement is factually inaccurate.			paragraph remains, i.e., the EAG's concerns relating to the pivotal trial (MT-04) informing the AA+AR economic model, and its adequacy to inform the current decision problem.

Issue 4 The AA+AR model structure does not appropriately reflect the clinical management of asthma which, in clinical practice, involves a stepwise approach to assessing, treating, and monitoring patients' asthma control.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6. In reference to a model structure presented in Schmitt et al., 2020, the EAG state that it is unclear why the company has not explored or discussed this alternative modelling approach. The EAG have failed to consider commentary by	The EAG should consider the response to question B.8 from the company at clarification and adjust their response accordingly.	The company believe that the EAG have provided contradictory preferences in regard to alternative model structures. With specific reference to this issue, the source referenced by the EAG was not identified by the company, and hence could not have been examined at the point of model conceptualisation and development. At clarification the company highlighted that estimates of efficacy informing patient	Not a factual inaccuracy. The EAG reiterates that the AA+AR model presented by the company imperfectly reflects asthma management, which, in clinical practice, involves a stepwise approach to assessing, treating, and monitoring patients' asthma control.

the company in response to question B.8 at clarification referring to alternative model structures. Furthermore, this was not a reference identified by the company, and hence, it is impossible that the company could have explored this alternative.		transitions between treatment subgroups would be limited, as patients can be on multiple combinations of symptomatic therapies. Furthermore, as the 12 SQ-HDM randomised trials had limitations on the use of symptomatic treatments to minimize the interference with the efficacy assessment, patients in the trial could not be grouped by GINA treatment steps. The company would also highlight that, according to both the GINA and BTS/SIGN guidance, the primary function of pharmacological management in asthma is to achieve long-term asthma disease control. The stepping up/down of treatment comes secondary to the successful control of asthma. Additionally, whilst modelling specific treatment steps may add accuracy in estimating treatment costs, this would likely have no impact on patients' quality of life, which is driven by symptom control and risk of adverse outcomes (the two key domains of asthma control). Moreover, as background SOC costs are generally inexpensive generic treatments, these are unlikely to affect the estimates of cost-effectiveness given that SOC costs are not model drivers.	In the EAR the EAG provided a summary of Schmitt et al., 2020 approach to modelling as an example of what the EAG understands to be appropriate modelling of how progression of disease severity can be modelled. The EAG has clarified the text on page 72/73 to reflect this: "The EAG believes that the approach taken by Schmitt et al., 2020 to estimate treatment effectiveness and asthma disease progression would have been more appropriate than the company's approach. The EAG is unclear why the company has not explored or discussed alternative approaches to modelling disease progression similar to the one presented in Schmitt et al., 2020. " The EAG has considered the company's response to question B.8 at clarification stage. The company's response highlights the

		The EAG fail to reflect on the company's responses at clarification and provide not valid economic or clinical justification for suggesting an alternative model structure.	limitations of the 12 SQ-HDM randomised trials (MT-04 in particular) in being vehicles to appropriately model disease progression as advocated by the EAG. This evidence limitation does not mean that the modelling approach proposed by the EAG is not appropriate. No further changes were made.
Section 4.2.2 The EAG incorrectly quote Green et al., 2017 and provide a misleading conclusion.	Amend the quote in the EAG report to correctly reflect the statement in Green et al., 2017.	The EAG state the following: "The EAG would like to acknowledge and highlight what has already been noted by Green et al., 2017. While patients suffering from AR [and AA+AR] may commonly experience subtle and varying changes in their overall health, which would indeed be better captured using a more complex modelling approach that allows patients to transition across multiple health states over time, the data captured in MT-04, and MT-06, are insufficient to support accurate estimation of these changes in the overall burden of disease (section 4.2.6)."	We have clarified the paragraph as follows: "The EAG would like to acknowledge and highlight what has already been noted by Green et al., 2017. While patients suffering from AR [and AA+AR] may commonly experience subtle and varying changes in their overall health, which would indeed be better captured using a more complex modelling approach that allows patients to transition across multiple health states over time, the data captured in MT-06 may be insufficient to support

		The correct statement in Green et al., 2017 is: "Allergic rhinitis is a progressive condition where the patients will commonly experience regular changes in their overall health, and variations are often subtle. These will be driven by changes in a patient's condition and symptom exacerbations. These variations would be better captured using a more complex modelling approach, such as a Markov model, which facilitates the use of health states to predict changes in patient outcomes. However, given the data that are currently available, developing a Markov model that accurately estimates changes in patient health (eg, disease severity) is a challenging proposition." It is key to note that the authors do not state that the MT-04 and MT-06 data are insufficient for modelling changes in the burden of disease as implied by the EAG.	accurate estimation of these changes in the overall burden of disease (section 4.2.6). The EAG believes that the same issue applies when using MT-04 evidence to inform the AA+AR model."

Issue 5 AR adolescent subgroup: The EAG considers that the generalisation of cost-effectiveness findings over 12 SQ-HDM from AR adults to AR adolescents to be uncertain.

N/A

Issue 6 Evidence used to inform short-term effectiveness evidence and its parameterisation in the AA+AR and AR models are uncertain.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6 The company believe that the EAG have misinterpreted the MT-04 trial data. The EAG state it is concerned that neither period 2 or period 3 are reflective of clinical practice in the UK as patients, if uncontrolled, would not be maintained in their current treatment(s) (as per period 2).	EAG to adjust critique in line with correction.	As noted in Issue 1, ICS and SABA use in the trial could be adjusted as needed to control for asthma symptoms throughout the trial. Therefore, in Period 2, ICS and SABA doses could be adjusted to manage patients who did not have controlled asthma. In Period 3, SABA doses could be adjusted freely.	Please see reply to issue 1, third comment. For clarity, on page 74 of the EAR we have cross referenced section 3.2.1 on the critical appraisal of 12 SQ-HDM trials.
Section 4.2.6.6 The EAG state that the TEAE rates were generally high across the 5 trials.	Remove statement.	This is an inappropriate hanging comparison. The EAG fail to provide sufficient commentary that would suggest the TEAE rates are high either in comparison with other treatments for AR or AA, or more generally.	Not a factual inaccuracy. We have added a cross reference to Section 3.2.6.1, where the EAG notes that more than half of AEs reported in the 12 SQ-HDM group were treatment related adverse events (TRAEs).

Issue 7 For both AA+AR and AR models, medium to long-term effectiveness estimates are based only on assumptions.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6.2. The EAG have incorrectly interpreted the assumption in the company's model that patients in the 12 SQ-HDM arm cannot decline to a state which is worse than patients receiving standard of care. Whilst the EAG clinical expert states that polysensitised patients will be affected by external factors that would influence disease severity, this does not influence the relative effectiveness of 12 SQ-HDM as an add-on therapy to SOC. The cost-effectiveness analysis presents an intervention arm, in which patients receive 12 SQ-HDM, and a comparator arm, in which patients do not receive 12	The company propose that the EAG remove this as an issue.	Whilst it may be true that patients who are poly-sensitised experience worse health compared with mono-sensitised patients, as this will be equal in both the intervention and comparator arm, this factor does not impact the incremental cost-effectiveness of 12 SQ-HDM. Additionally, even if this interaction was considered relevant, the EAG present no rationale to explain why 12 SQ-HDM would result in worse health outcomes compared to standard of care. As 12 SQ-HDM is added to standard of care, even if patients do not respond to 12 SQ-HDM, no changes will be made to their existing pharmacotherapy. Hence, there is no rationale to assume that patients in the 12 SQ-HDM	For clarity the EAG has made changes to pages 82, 83 and 126 of the EAR to: "The EAG is also concerned with the assumption used in the company's model that patients in the 12 SQ-HDM arm cannot decline to a state which is worse than patients receiving standard of care. The EAG is concerned with its clinical validity and thus considers it to be uncertain." The EAG highlights that this assumption is not part of the EAG base case, although its impact is explored in scenario analyses over the EAG base case.

SQ-HDM. Across both arms, it is considered that patients are homogeneous. Therefore, the proportion of patients who are poly- or mono-sensitised will be the same across both treatment arms. As such, any difference in the interaction of external factors affecting poly-sensitised patients will be equal across both treatment arms.		treatment arm would decline to a state worse than those in the comparator arm.	

Issue 8 Evidence used to inform the AA+AR population effectiveness on asthma exacerbations is not reflective of clinical practice.

N/A

Issue 9 A treatment-specific approach to HRQoL was used in the company's base case, which does not align with the model structures developed for AA+AR and AR, respectively.

N/A

Issue 10 Treatment costs in both the AA+AR and the AR models are uncertain.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.8.5 The EAG state that the differences in costs of standard of care between AA+AR model health states relies on a strong and implausible assumption that relative increases in ICS use between levels of control directly translate to a proportional increase in costs across all standards of care asthma medications. The EAG cannot determine that this assumption is implausible. The EAG provide no evidence to support this position, which directly contradicts expert clinical opinion included in the submission.	The EAG amend and remove the unsupported opinion that this assumption is implausible.	The company made an assumption of a proportional increase in health state SOC treatment costs based on relative ICS use in the MT-04 trial during the treatment maintenance phase. This assumption reflects the average bundled treatment costs for patients who have either uncontrolled, partially controlled, or controlled AA. As there are 5 possible treatment steps, it is not implausible that on average, changes in ICS doses may also correlate to changes in other AA treatment doses. In the company's advisory board (Appendix M2), 100% of clinicians agreed that patients who have controlled asthma have a decreased use of reliever and maintenance therapy compared to	Not a factual inaccuracy. On pages 103/104 the EAR states that: " The treatment cost differences between the AA+AR alive health states are driven by the assumption that these cost differences are proportional to the difference in ICS use observed between levels of asthma control (well controlled, partly controlled and uncontrolled asthma) in the MT-04 trial. This is a strong assumption, one that cannot be validated by the EAG. It implicitly assumes that the proportional increase in the ICS use between levels of asthma control in the MT-04 trial directly translates into a proportional increase in costs across all modelled medications. Given that there

		patients who have partially controlled or uncontrolled asthma.	is no constant relationship between dose and cost that applies to all standard of care medications in the model, this assumption is likely not plausible." The EAG is not contradicting expert clinical opinion. Clinicians agreed that patients who have controlled asthma have a decreased use of reliever and maintenance therapy compared to patients who have partially controlled or uncontrolled asthma, not that a direct relationship between increase in ICS use and increase in costs across all modelled medications existed. It is the understanding of the EAG that the company's assumption is not supported by the company's advisory board and reiterates that this assumption is strong and implausible.

Issue 11 Management costs in both the AA+AR and the AR models are uncertain.

N/A

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 14	Trial data	No CIC marking required	CIC marking removed
Page 23/24	Cost-effectiveness results	No CIC marking required	
Page 39	Trial data	No CIC marking required	CIC marking removed
Page 40	Trial data	No CIC marking required	CIC marking removed
Page 41	Trial data	No CIC marking required	CIC marking removed
Page 42	Trial data	No CIC marking required	CIC marking removed
Page 43	Trial data	No CIC marking required	CIC marking removed
Page 44	Trial data	No CIC marking required	CIC marking removed
Page 45	Trial data	No CIC marking required	CIC marking removed
Page 46	Trial data	No CIC marking required	CIC marking removed

Page 47	Trial data	No CIC marking required	CIC marking removed
Page 48	Trial data	No CIC marking required	CIC marking removed
Page 54	Trial data	No CIC marking required	CIC marking removed
Page 55	Trial data	No CIC marking required	CIC marking removed
Page 56	Trial data	No CIC marking required	CIC marking removed
Page 57	Trial data	No CIC marking required	CIC marking removed
Page 58	Trial data	No CIC marking required	CIC marking removed
Page 59	Trial data	No CIC marking required	CIC marking removed
Page 83	Trial data	No CIC marking required	CIC marking removed
Page 84	Trial data	No CIC marking required	CIC marking removed
Page 86	Economic model calculations and trial data	No CIC marking required	CIC marking removed
Page 87	Economic model estimations and trial data	No CIC marking required	CIC marking removed
Page 101	Economic model calculations	No CIC marking required	CIC marking removed
Page 102	Economic model calculations	No CIC marking required	CIC marking removed

Page 103	Economic model assumptions	No CIC marking required	CIC marking removed
Page 106	Economic model calculations	No CIC marking required	CIC marking removed
Page 109	Annual GP visits from alternative evidence sources used to populate the economic model	No CIC marking required	CIC marking removed
Page 110	Estimate using trial data	No CIC marking required	CIC marking removed
Page 111	Annual number of GP visits used to populate the economic model	No CIC marking required	CIC marking removed
Page 112	Economic model calculation and description of how this figure was estimated	No CIC marking required	CIC marking removed
Page 124	The corrected proportion of AA and AR patients to discontinue treatment and cost-effectiveness results	No CIC marking required	CIC marking removed
Page 125	Cost-effectiveness results	No CIC marking required	CIC marking removed
Page 129	Secondary care visit reduction economic model input	No CIC marking required	CIC marking removed
Page 132	No. of patients assumed to be eligible for biologics	No CIC marking required	CIC marking removed

Page 132	The number of reduced primary and secondary care visits with 12 SQ-HDM	No CIC marking required	CIC marking removed
Page 133	Secondary care estimates used in economic model	No CIC marking required	CIC marking removed
Page 133	Cost-effectiveness results	No CIC marking required	CIC marking removed
Page 134	Cost-effectiveness results	No CIC marking required	CIC marking removed
Page 135	Cost-effectiveness results	No CIC marking required	CIC marking removed
Page 136	Cost-effectiveness results	No CIC marking required	CIC marking removed
Page 137	Cost-effectiveness results	No CIC marking required	CIC marking removed
Page 138	Cost-effectiveness results	No CIC marking required	CIC marking removed
Page 139	Cost-effectiveness results	No CIC marking required	CIC marking removed
Page 140	Cost-effectiveness result description	No CIC marking required	CIC marking removed
Page 141	Cost-effectiveness results for EAG's preferred AA + AR model assumptions and cost-effectiveness probability	No CIC marking required	CIC marking removed
Page 142	Cost-effectiveness results for EAG's preferred AA + AR and AR model assumptions and cost-effectiveness probability	No CIC marking required	CIC marking removed

Page 143	Cost-effectiveness results for EAG's preferred AR model assumptions	No CIC marking required	CIC marking removed
Page 144	EAG's cost-effectiveness results	No CIC marking required	CIC marking removed
Page 145	EAG's cost-effectiveness results	No CIC marking required	CIC marking removed
Page 146	EAG's cost-effectiveness results	No CIC marking required	CIC marking removed
Page 147	EAG's cost-effectiveness results	No CIC marking required	CIC marking removed
Page 149	EAG's cost-effectiveness results descriptions	No CIC marking required	CIC marking removed