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GUIDELINES

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EAACI Guidelines on Allergen Immunotherapy: House dust mite-driven allergic asthma

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Abbreviations: ACEI, Angiotensin-converting enzyme inhibitor; ACQ, asthma control questionnaire; ACT, asthma control test; AD, atopic dermatitis/eczema; AEs, adverse events; AHR, airway hyperreactivity; AID, autoimmune diseases; AIT, allergen immunotherapy; AQLQ, asthma quality of life questionnaire; AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; BAP, bronchial allergen provocation; BB, beta-blockers; DBPC, double-blind placebo controlled; EAACI, European Academy of Allergy and Clinical Immunology; FEF 25-75, forced expiratory flow at 25-75% of the pulmonary volume; FEV1, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; GRADE, The Grading of Recommendations Assessment, Development and Evaluation; HCP, healthcare professional; HDM, house dust mites; ICS, inhaled corticosteroids; MEF 25, maximal expiratory flow at 25% of forced vital capacity; MEF 50, maximal expiratory flow at 50% of forced vital capacity; MEF 75, maximal expiratory flow at 75% of forced vital capacity; PD20, provocative dose causing a 20% drop in FEV1; QoL, quality of life; RCTs, randomized control trials; ROB, risk of bias; SCIT, subcutaneous allergen immunotherapy; SLIT, sublingual allergen immunotherapy; SmPC, Summary of product characteristics; WAO, World Allergy Organization; WHO, World Health Organization.

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Abstract

Allergen immunotherapy (AIT) has been in use for the treatment of allergic disease for more than 100 years. Asthma treatment relies mainly on corticosteroids and other controllers recommended to achieve and maintain asthma control, prevent exacerbations, and improve quality of life. AIT is underused in asthma, both in children and in adults. Notably, patients with allergic asthma not adequately controlled on pharmacotherapy (including biologics) represent an unmet health need. The European Academy of Allergy and Clinical Immunology has developed a clinical practice guideline providing evidence-based recommendations for the use of house dust mites (HDM) AIT as add-on treatment for HDM-driven allergic asthma. This guideline was developed by a multi-disciplinary working group using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. HDM AIT was separately evaluated by route of administration and children and adults: subcutaneous (SCIT) and sublingual AIT (SLIT), drops, and tablets. Recommendations were formulated for each. The important prerequisites for successful treatment with HDM AIT are (a) selection of patients most likely to respond to AIT and (b) use of allergen extracts and desensitization protocols of proven efficacy. To date, only AIT with HDM SLIT-tablet has demonstrated a robust effect in adults for critical end points (exacerbations, asthma control, and safety). Thus, it is recommended as an add-on to regular asthma therapy for adults with controlled or partially controlled HDM-driven allergic asthma (conditional recommendation, moderate-quality evidence). HDM SCIT is recommended for adults and children, and SLIT drops are recommended for children with controlled HDM-driven allergic asthma as the add-on to regular asthma therapy to decrease symptoms and medication needs (conditional recommendation, low-quality evidence).

KEYWORDS
allergen immunotherapy, allergy, asthma, asthma control, asthma exacerbations, GRADE, house dust mites, lung function

1 | INTRODUCTION, BACKGROUND

Asthma represents a major health burden, currently affecting around 350 million people globally, with a projected increase to 400 million within the next 30 years.[1-5] It is responsible for considerable morbidity (hospitalization and unscheduled health care) as well as direct and indirect costs (72.2 billion Euro annually in the European Union), and mortality. The major economic impact is due to indirect costs, absenteeism, and decreased economic productivity.[6-9]

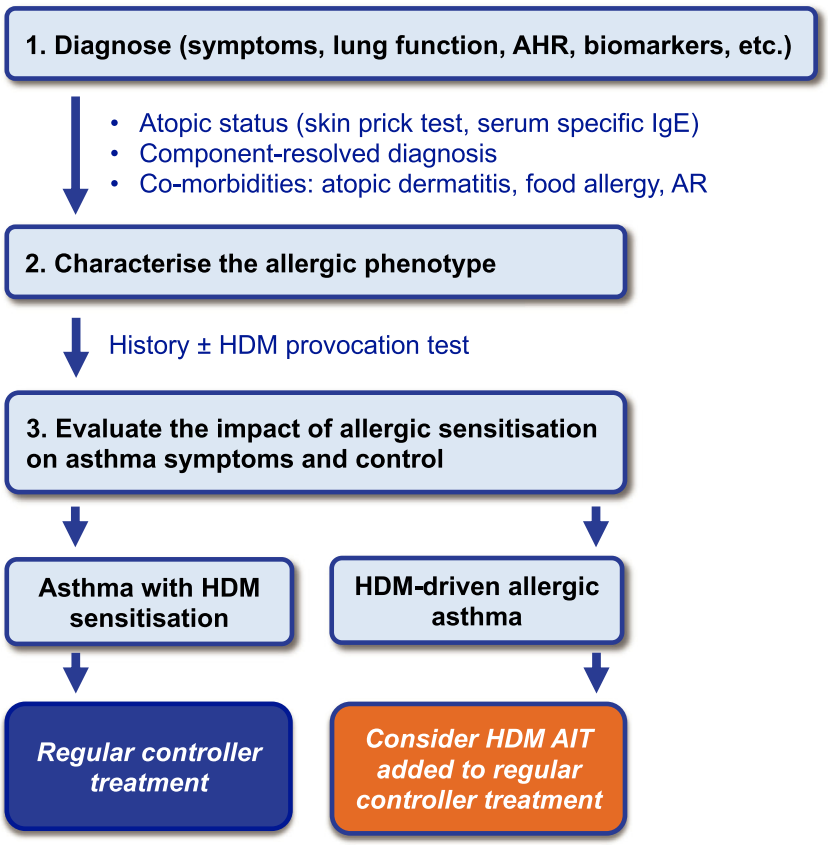

FIGURE 1 HDM-driven allergic asthma diagnosis

Assessing the role of allergic sensitization in asthma pathophysiology is an important step in disease workup because such patients might benefit from allergen immunotherapy (AIT) as add-on to pharmacological asthma therapy. The proportion of asthmatic patients with allergen sensitization varies between 30% and 79% in children[10-12] and from 30% to 60% in adults,[13-15] depending on the end points evaluated (sensitization or symptomatic allergic disease). Although type 2-driven inflammation is crucial in allergic asthma, the complexity of the underlying pathophysiological mechanisms means that there are a number of endotypes.[15-21] Assessment of endotypes is key for individualized management, including optimized AIT.

Remarkably, and probably due to the lack of robust evidence, no diagnostic tool or algorithm has been developed to discriminate between HDM-driven allergic asthma and asthma with HDM sensitization. At present, the diagnosis relies on the proof of HDM sensitization together with a detailed clinical history showing typical symptoms of asthma induced by HDM exposure (Figure 1 and Box 1). Sequential longitudinal assessments over a 1-year period to confirm the difficult diagnosis of HDM-induced asthma are an approach which might be advocated. In addition, the gold standard could be perfect asthma control in a HDM-free environment.[22]

An accurate diagnosis of HDM-driven allergic asthma includes (a) evidence of allergic sensitization to HDM and (b) confirmation of HDM exposure as the main driver of asthma symptoms and control by history. Potentially, allergen provocation (airway hyperreactivity [AHR]) testing may be required.

It is now recognized that house dust mites (HDM), such as *Dermatophagoides (D) pteronyssinus* or *D. farinae*, are the source of the most important indoor allergens associated with asthma worldwide and lead to the development of high-titer allergen-specific IgE. Substantial evidence associates allergic conditions such as asthma, allergic rhinitis (AR), atopic dermatitis (AD) with exposure to HDM, or other indoor allergens.[23-30] Data from longitudinal investigations suggest that the development of sensitization to HDM occurs before polysensitization.[31-33]

The rationale for AIT is the modification of the underlying allergic disease mechanisms triggering a sustained clinical effect based on allergen-specific tolerance, suppression of inflammation, and multicomponent clinical improvement.[34-36]

HDM AIT is currently administered in allergic asthma via either the subcutaneous (SCIT) or sublingual (SLIT) route, the latter with two alternatives: drops and tablets. Alternate routes, such as intralymphatic, are currently under investigation. Similar mechanisms of induction of allergen-specific IgG4, induction of IgE-blocking IgG antibodies, T-cell tolerance, and decrease in Th2 response are described both for SCIT and for SLIT.[34-36] Immunomodulation was shown for HDM AIT at a molecular level by favoring a broader blocking repertoire and inhibiting epitope spreading.[37]

BOX 1 Nomenclature and terms[21-24]

Anaphylaxis: severe, potentially life-threatening systemic hypersensitivity reaction characterized by rapid onset, life-threatening airway, breathing, or circulatory problems and usually, although not always, associated with skin and mucosal changes.

Allergen immunotherapy (AIT): procedure inducing tolerance to a specific allergen by repetitive administration of an allergen.

Adverse event (AE): reaction triggered by AIT administration; can be local or systemic; systemic AE has four degrees of severity.

Airway hyperreactivity (AHR): exaggerated response of the airways to specific (allergen) and nonspecific stimuli, which results in airway obstruction.

Allergic rhinitis (AR): inflammation of nasal mucosa induced upon exposure to an allergen together with the proof of immunological sensitization to that allergen.

Asthma control: evaluated over the past four weeks (GINA 2018):

- **controlled asthma** has daytime symptoms less than 2/week, no nighttime awakenings, reliever is needed for symptoms less than 2/week, and there is no activity limitation due to asthma;
- **partially controlled asthma**: failure to meet 1-2 of these criteria;
- **uncontrolled asthma**: failure to meet 3-4 of these criteria.

Asthma future risk: includes the risk of exacerbations, fixed airway obstruction, and adverse reactions to medications used to control asthma; lung function measurement is an important part of the assessment of future risk.

HDM-driven allergic asthma: typical symptoms of asthma (wheezing, cough, dyspnea, and chest tightness with evidence of reversibility) with exposure to HDM together with the proof of immunological sensitization to HDM.

Local reaction (LR): inflammatory response confined to the contact site.

Quality of life (QoL): the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals (WHO). In studies usually assessed by a standardized validated questionnaire estimating the impact of symptoms on daily activities.

Subcutaneous immunotherapy (SCIT): subcutaneous, injectable route of HDM administration.

Severe asthma: asthma that requires treatment with high-dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming "uncontrolled" or that remains "uncontrolled" despite this therapy (ATS/ERS consensus statement); severe asthma status is valid only after correct diagnosis of asthma and after all comorbidities and adherence to treatment are properly addressed.

Sublingual immunotherapy (SLIT): sublingual (drops or tablets) route of HDM administration.

A limited number of studies have been specifically designed to evaluate the efficacy and safety of HDM AIT in allergic asthma. Most data come from retrospective subgroup analyses from AIT trials in AR from which patients with concomitant asthma were analyzed. According to the European Medicine Agency guidance published in 2015, clinical trials of AIT in asthma should start as add-on therapy which has to be considered in the evaluation of the primary end point (eg, evaluation in the context of a stepwise reduction in controller medication). Lung function, composite scores, number of exacerbations, or reduced need for controller medication could be considered as primary end points.[38] The main issues with outcomes such as exacerbation are the rate of the events, which are infrequent in mild to moderate allergic asthma. The absence of daily symptoms and exacerbations define asthma control, but these criteria may respond differently to any specific intervention.[39] Thus, asthma outcomes recommended by health authorities might have different relevance compared to those reported in real life by patients with allergic asthma.[40-42]

The Global Initiative for Asthma (GINA) 2018 report recommends the assessment of two domains: control, which includes current symptoms and future risk of exacerbations, progressive loss of lung function, and/or fixed airflow limitation and treatment issues, such as adherence and adverse effects. Achieving control of asthma is the major goal in current asthma management. Pharmacological and non-pharmacological strategies are adjusted in a continuous cycle that involves assessment, treatment, and review.[43] According to GINA, there is potentially a benefit associated with AIT in asthma if allergy plays a prominent role, for example, asthma with allergic rhinoconjunctivitis. In people with asthma and allergic sensitization, SCIT is associated with a reduction in symptom scores and medication requirements, and improved allergen-specific and nonspecific AHR. In patients sensitized to HDM, with AR and persistent asthma requiring ICS, with FEV1 >70% predicted, and with exacerbations despite taking Step 2 therapy, GINA suggests that SLIT can be considered as an add-on therapy (Evidence B).[43] In 2008, Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines[44] gave both SCIT and SLIT a conditional recommendation in allergic asthma due to moderate or low quality of evidence. However, ARIA 2008 guidelines were published before the publication of the trials specifically designed to evaluate the efficacy and safety of HDM AIT in allergic asthma. HDM AIT should be integrated into the general management of allergic asthma.

2 | SCOPE AND PURPOSE OF THE GUIDELINE

This Guideline has been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on AIT for Allergic Asthma and is part of the EAACI Guidelines on Allergen Immunotherapy.[45]

The aims of this Guideline are to provide evidence-based clinical recommendations for indications and contraindications to HDM AIT as add-on treatment for HDM-driven allergic asthma and to identify gaps in knowledge and/or implementation, unmet needs, and future perspectives.

This Guideline does not address the prevention of HDM-driven allergic asthma, which is covered in the EAACI Guidelines on Allergen Immunotherapy Chapter: Prevention of allergy.[46] It also does not address the potential long-term benefit of HDM AIT (after AIT cessation) due to lack of evidence. AIT with other allergens for allergic asthma (grass, trees, cat) will be addressed in a separate paper.

The primary audiences of these recommendations are clinical allergists, respiratory physicians, pediatricians, and other healthcare professionals (eg, doctors, nurses, and pharmacists) working across a range of primary, secondary, and tertiary care settings managing patients with allergic asthma. Industry representatives, healthcare managers, or policymakers may also find this Guideline useful.

3 | HOW TO USE THESE GUIDELINES

1. Disclaimer

The EAACI Guideline for HDM AIT for allergic asthma is not intended to impose a standard of care. It provides the framework for rational decisions in the management of allergic asthma using AIT by clinicians, patients, third-party payers, institutional review committees, and other stakeholders.

Statements regarding the underlying values and preferences as well as qualifying remarks accompanying each recommendation are an integral part of the Guideline and aim to facilitate more accurate interpretation. They should never be omitted or ignored when quoting Guideline recommendations.

2. Interpretation of strong and conditional recommendations (Table 1)

4 | METHODOLOGY

4.1 | Blended approach

1. GRADE assessment of the existing evidence of HDM AIT in asthma.[47-49]
2. Individual assessment of major randomized control trials (RCTs) and previous meta-analyses for HDM AIT in asthma.
3. Individual assessment of open studies, real-life studies, observational studies, surveys.

4.2 | Evaluation of the body of evidence

1. By delivery route of HDM AIT (SCIT, SLIT drops, SLIT-tablets)
2. Stratified for pediatric and adult populations

4.3 | Clinical questions and outcomes for HDM-driven allergic asthma

The following questions were identified for this guideline:

1. Should HDM SCIT vs no SCIT be used for treatment in pediatric patients with HDM-driven allergic asthma?
2. Should HDM SCIT vs no SCIT be used for treatment in adult patients with HDM-driven allergic asthma?
3. Should HDM SLIT drops vs no SLIT drops be used for treatment in pediatric patients with HDM-driven allergic asthma?
4. Should HDM SLIT drops vs no SLIT drops be used for treatment in adult patients with HDM-driven allergic asthma?

TABLE 1 Interpretation of GRADE recommendations[44,45]

Implications	Strong recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals making decisions consistent with their values and preferences.
For policymakers	The recommendation can be adapted as policy or performance measure in most situations	Policymaking will require substantial debate and involvement of various stakeholders. Documentation of appropriate (eg, shared) decision-making processes can serve as performance measure.

TABLE 2 Classification of outcomes for HDM AIT for HDM-driven allergic asthma

Critical	Exacerbations	Number of exacerbations/number of patients
		Number of patients with at least 1 exacerbation
		Time to first asthma exacerbation upon ICS reduction/withdrawal
	Asthma control	ACQ score
		ACT
		"in-house" definitions
	Corticosteroid sparing effect	% decrease in ICS dose for asthma control
	Safety	Systemic reactions (WAO grading)
Important	Symptom score	"in-house" definitions
	Medication score	"in-house" definitions
	Quality of life	AQLQ
	Lung function	Small airways[a] (% or absolute improvement of MEF 25, MEF 50, MEF 75, FEF25-75)
		Allergen-specific AHR (increase in PD20 allergen)[b]
	Safety	Local reactions (WAO grading)
Low importance	Lung function	Improvement in FEV_1[a] (% or absolute)
		Nonspecific AHR (increase in PD20 methacholine, histamine)[b]

[a]As most of AIT trials in asthma enrolled subjects with normal lung function, the expected benefit on FEV_1 is of low importance; in contrast, the effect on small airways is important given the systemic effects of AIT.
[b]According to the biologic effect, the impact on allergen-specific AHR is expected to be significant (important outcome) compared to the effect on non-specific AHR (low importance outcome).

5. Should HDM SLIT-tablets vs no SLIT-tablets be used for treatment in pediatric patients with HDM-driven allergic asthma?
6. Should HDM SLIT-tablets vs no SLIT-tablets be used for treatment in adult patients with HDM-driven allergic asthma?

As per GRADE methodology, we classified outcomes into critical, important, and of low importance according to the classification of asthma outcomes in major RCT HDM AIT asthma trials as requested by the regulatory bodies (Table 2).

4.4 | Evidence review

Evidence summaries for each question were prepared by a methodologist using GRADE Pro GDT (www.gradepro.org). The GRADE approach was specifically used for this Guideline to bring it into line with other asthma guidelines.[41] The panel members reviewed the summaries of the evidence and provided feedback when appropriate. Evidence summaries are based on the systematic review conducted for this Guideline.[50] In addition, an updated search strategy was performed by delivery route (SCIT, SLIT drops, and SLIT-tablets) and for the pediatric and adult populations. The methods of the Cochrane Collaboration (www.handbook.cochrane.org) were adopted with the risk of bias at the outcome level assessed using the Cochrane Collaboration's risk of bias tool.[49] The certainty of the supporting evidence (also called confidence in the estimates of effects or quality of evidence) was assessed by applying the GRADE framework for interventions.[47-49] The certainty of the evidence was categorized as high, moderate, low, or very low based on consideration of risk of bias, directness of evidence, consistency and precision of the estimates, and other considerations. Low and very low certainty evidence indicates that the estimated effects of interventions are very uncertain, and any further research is very likely to influence current recommendations. The GRADE Pro GDT (www.gradepro.org) software was used to assess the certainty of evidence. Evidence on values and preferences and cost of AIT was also considered.

4.5 | Formulating the recommendations

As per GRADE methodology, the summary of judgments is provided for each recommendation. This includes evaluation of the importance of the problem, desirable and undesirable effects, certainty of evidence, values, balance of effects, resources required, certainty of evidence of required resources, cost-effectiveness, equity, acceptability, and feasibility.

4.6 | Document revision

Each member of the EAACI allergic asthma AIT guideline task force reviewed the final Guideline draft and approved the document. The document was revised to incorporate the pertinent comments suggested by the external reviewers.

4.7 | Stakeholders involvement

The EAACI task force on AIT for allergic asthma included members from a wide range of countries, professional backgrounds (allergy, pediatrics, internal medicine, pulmonology, basic and clinical immunology, primary care), and patient representatives. The whole allergy community, connected specialities, and representatives of AIT

vaccine manufactures were given the opportunity to review and comment on the draft guideline, where appropriate revisions were made.

4.8 | Conflict of interest

In accordance with EAACI policy, everyone who is intellectually involved in the project (ie, considered for guideline authorship) disclosed all potential conflict of interest in writing at the beginning, middle, and end of the project.

4.9 | Other considerations

Appropriate representation of all stakeholders, peer review by invited experts from a full range of organizations, countries, and professional backgrounds, and editorial independence were ensured. Identifying gaps, barriers, and facilitators was an important part of the process. All stakeholders had an opportunity to comment on the draft guideline publicized on the EAACI Website for a 3-week period (November 2018) to allow any omissions or errors in the evidence base to be highlighted. The development of AIT for allergic asthma was funded and supported by EAACI. The funder did not have any influence on the guideline production process, on its contents, nor on the decision to publish.

The review of this guideline is planned for 2022 but will be brought forward if there are any prior major developments in the evidence.

5 | EVALUATION OF THE BODY OF EVIDENCE

5.1 | GRADE assessment of the existing evidence

The summary of findings (SOF) and evidence profiles are presented in Annexe A (Appendix S1).

5.2 | Individual assessment of major RCTs and previous meta-analyses

5.2.1 | HDM SCIT

Wang et al[51] investigated children and adults with HDM allergic asthma in a randomized double-blind, placebo-controlled (DBPC) trial funded by ALK-Abelló. They reported exacerbations defined by the number of courses of oral corticosteroids required to restore asthma control. No significant difference was found between the SCIT and placebo groups. A difference in favor of SCIT for decreased exacerbation frequency and severity as well as overall symptoms measured with a self-evaluation questionnaire was observed.

In an open randomized clinical trial in children with asthma funded by Allergopharma, SCIT with a mite allergoid added to pharmacotherapy permitted a reduction in the dose of ICS needed to maintain disease control compared with pharmacotherapy alone.[52]

In a randomized DBPC trial funded by Allergopharma, the minimal ICS dose for asthma control was evaluated as the secondary outcome for four doses of HDM SCIT vs placebo in 146 adult patients with asthma. The interventions were given for approximately 7 months. A statistically significant decrease in ICS dose was only observed in the highest dose SCIT group. While average Asthma Control Test (ACT) scores improved in all dose groups, the only statistically significant change was recorded for the medium SCIT dose.[53]

Three small prospective DBPC trials funded by Laboratorios LETI assessed HDM efficacy and safety of HDM AIT in adults with allergic asthma.[54-57] In two studies, allergen-specific AHR evaluated with bronchial allergen provocation (BAP) was the main outcome, with symptom and medication scores as secondary outcomes. In the study of Basomba, clinical scores were the primary outcomes.[56] All trials reported a significant increase in BAP PD_{20} FEV_1 and improvement in symptom and medication scores. BAP was not influenced by a placebo effect. One trial also reported a significant improvement in quality of life (AQLQ).[55]

In an open study evaluating 42 children with HDM allergic asthma SCIT, there was a significant improvement in BAP PD_{20} FEV_1. Interestingly, BAP differentiated between responders (60.7%) and nonresponders. Although all SCIT-treated children reported subjective improvement in their symptoms, only the responders required less medication after SCIT.[57]

Several studies assessed the immunological and functional effects of HDM SCIT in adults with mild allergic asthma, and these provide indirect evidence for the efficacy of SCIT. In a randomized DBPC study (Alvarez et al), 26 asthmatic subjects were randomized to receive liposome-entrapped *D. pteronyssinus* via SCIT (n = 12) or placebo (n = 11). An allergen bronchial challenge was performed at the beginning (T0) and after 1 year of treatment (T12). The day before and 24 hours after the allergen provocation, patients were challenged with methacholine (Mch), and blood and sputum samples were obtained. Dose-response curves to Mch were evaluated in terms of Mch-PD_{20}, slope (Mch-DRS), and level of plateau. Blood and sputum eosinophils and serum levels of eosinophil cationic protein (ECP) and intercellular adhesion molecule-1 (ICAM-1) were measured. At T12, previous to the allergen challenge, the active group showed higher values of both FEV_1 and Mch-PD20 and lower values of Mch-DRS. At T12, before the allergen challenge, serum ECP levels increased in the placebo group and blood eosinophils showed a trend toward lower numbers in the active group. The immediate response and the changes in Mch-DRS values, sputum eosinophils, and serum ECP levels, following the allergen challenge, were attenuated in the active group.[58]

5.2.2 | HDM SLIT drops

In the Cochrane SR and meta-analysis by Normansell et al,[59] a wide but varied reporting of largely unvalidated asthma symptom and

medication scores precluded a meaningful meta-analysis. A general trend suggested a benefit for SLIT over placebo, but variation in scales made the results difficult to interpret. In addition, this SR evaluated SLIT for all allergens and did not differentiate between drops and tablets. The meta-analysis by Compalati et al. identified 12 randomized, DBPC studies that assessed HDM SLIT in patients with AR or asthma (382 patients with AR and 476 with allergic asthma). They reported a large overall benefit for SLIT for symptom scores and decrease in rescue drug use. However, authors found considerable inter-study heterogeneity.[60] Kim et al[61] evaluated seven studies for symptom score and six with reported medication score. The strength of evidence was high for improving asthma symptoms and moderate for reducing asthma medication. However, most of the studies included small numbers of patients, for example, Yukselen 11 SLIT vs 10 placebo, Lue 10 children on SLIT and 10 on placebo, Pajno 24 children with 12 on SLIT, Hirsch 30 children, Tari 58 children with both rhinitis and asthma, and Bahçeciler 15 children with rhinitis and asthma. The larger studies included were by Niu et al which included 97 children and 49 on SLIT and by Ippoliti et al including 86 children and 47 on SLIT. The meta-analysis of Liao et al[62] included 11 open or double-blind studies with a total of 454 children with asthma/rhinitis who were sensitized to HDM, ranging from 15 to 109 patients. A large overall reduction in asthma symptom scores but not in medication scores was found; significant inter-study heterogeneity was reported.

The RCT study of Wang funded by Stallergenes Greer, which included 484 asthmatic adults (SLIT n = 308 and placebo n = 157), evaluated as the primary efficacy outcome asthma control and a well-defined ICS dose step-down. Although asthma control was achieved by a slightly greater proportion of patients in the active treatment group than in the placebo group, the primary efficacy criterion was not met because of a higher than expected asthma control rate in the whole study population. In view of the wide range of ICS daily doses used by the patients, a post hoc analysis by asthma severity was performed. This revealed significant clinical benefits in actively treated subjects with moderate, persistent asthma at baseline (401-800 μg budesonide) with better achievement of well-controlled asthma and totally controlled asthma, a higher percentage of patients with an ACQ score <0.75 and a greater mean reduction in ICS use.[63]

In another DBPC trial funded by Stallergenes Greer, adults with asthma were randomized to receive active treatment (n = 322) or placebo (n = 162) during 52 weeks. The incidence of exacerbations was similar between the active and placebo groups; there was no effect on lung function or on the quality of life (QoL).[64]

5.2.3 | HDM SLIT-tablets

Clinical efficacy of the SQ-HDM SLIT-tablet in asthma has been evaluated in adults in three DBPC randomized trials funded by ALK.[65–67] Each trial had a different asthma-related end points: ICS dose decrease, average asthma symptom score, and time to first asthma exacerbation upon ICS dose decrease.

In a large randomized DBPC study, Mosbech et al[65] included 604 subjects with controlled (ACQ <1) and partially controlled (ACQ 1-1.5) mild to moderate asthma and a history of HDM AR. Participants were randomized to receive three active doses of a HDM SLIT-tablet or placebo. The primary end point was the lowest ICS dose needed to maintain asthma control. The difference in the decrease in ICS dose between active and placebo at the end of trial assessment period was 81 μg. The benefit was observed only for the highest dose (six SQ-HDM). A post hoc analysis showed that subjects with a daily ICS dose of 400-800 μg and partly controlled asthma at randomization experienced a significantly higher treatment benefit for the highest dose in terms of ICS dose decrease (327 μg), AQLQ and ACQ compared to the rest of the trial population.[68]

A randomized DBPC study of Nolte et al[66] evaluated HDM asthma as secondary end point in allergen exposure chamber. Eighty-three subjects received two different active doses and 41 received placebo. Both doses of 12 and six SQ-HDM for 24 weeks resulted in a statistically significant improvement vs placebo in reported average asthma symptom score during allergen challenge, with greater efficacy of the 12 SQ-HDM dose.

In the randomized DBPC study of Virchow et al,[67] the primary end point was time to first moderate or severe asthma exacerbation during a 6-month ICS reduction period. The trial included 834 adults with HDM-driven allergic asthma. After 7-12 months of treatment with the HDM SLIT-tablet (6 SQ-HDM [n = 275] and 12 SQ-HDM [n = 282]) or placebo (n = 277), daily ICS use was reduced to 50% for 3 months, followed by complete ICS withdrawal for 3 months for the remaining subjects who had not experienced an asthma exacerbation during the previous study phases. The trial included 834 adults with HDM not well-controlled allergic asthma (ACQ score of 1-1.5) and HDM AR, with a need for daily ICS treatment equivalent to budesonide 400-1200 μg. There was a significant risk reduction in the time to first asthma exacerbation vs placebo, as observed by hazard ratios of 0.69 and 0.66 for 6 SQ-HDM and 12 SQ-HDM, respectively. Treatment with 12 SQ-HDM resulted in a 34% risk reduction compared to placebo. This study showed that the addition of HDM SLIT improved time to first moderate or severe asthma exacerbation during ICS reduction, with an estimated absolute reduction at six months of nine to 10 percentage points. The reduction was primarily due to an effect on moderate exacerbations.

Combined clinical safety data from the SQ-HDM tablet trials indicate that it is well tolerated, and the observed safety and tolerability profile correspond with the observed profile for other SLIT products.

As a result of these trials the HDM SLIT-tablet is recommended for HDM-induced allergic asthma not well controlled by ICS and associated with mild to severe HDM-induced AR, when the patients' asthma status is carefully evaluated before the initiation of treatment. GINA 2018 recommends SLIT with HDM as an add-on therapy (Evidence B) in patients with exacerbations despite taking Step 2 therapy to decrease mild and moderate asthma exacerbations.

In the pediatric population, the randomized DBPC trial of Pham-Thi et al,[69] funded by Stallergenes Greer, included 111 children, 55 on AIT. It showed no additional benefit of SLIT-tablets 300 IR to improve lung function or decrease symptoms or medication use after 18 months of treatment.

5.3 | Individual assessment of open studies, real-life studies, observational studies, surveys

A recent prospective, multicentre, noninterventional study evaluated 220 patients (117 adults, 103 children) with HDM allergy receiving SCIT with allergoid preparation. Organ-specific key symptoms and the use of concomitant anti-allergic medication were assessed at baseline and after 12 and 24 months. 63% of adults and 64% of children had bronchial symptoms, and they decreased significantly at 12 and 24 months in parallel with the use of symptomatic medication. During the 24-month study period, AEs were observed in 3.4% adults and in 6.8% children. All local AEs related to the study drug (erythema, swelling, and pain at the injection site). Serious AEs were reported in three adults and one child: a grade-II anaphylactic reaction (one adult) controlled by oral antihistamines (no hospitalization) classified as "definitely," three others as not (2) or possibly (1) drug-related.[70]

A sub-analysis by Trebuchon of 736 pediatric patients included in a previous retrospective, observational, multicentre study reported a significant decrease in symptoms and medications with HDM SLIT drops.[67] In a prospective, open, parallel group, controlled study, the efficacy of three year of SLIT in addition to pharmacotherapy (62 children) was compared with pharmacotherapy alone (28 children).[71] Ozdemir and colleagues reported significant decreases in the dose and duration of ICS treatment in the SLIT group with 52.4% of subjects able to discontinue ICS.[72] Di Rienzo followed up over a 10-year period: 60 children, 35 receiving SLIT vs 25 who received pharmacotherapy only; in this open nonrandomized trial, the authors reported significant long-lasting effect on symptoms and medication at the end of 4- to 5-year SLIT.[73]

A health economic, piggyback analysis of SCIT was conducted based on a RCT performed by Allergopharma that enrolled 65 children and adolescents with controlled allergic asthma. Both costs and cost-effectiveness of HDM SCIT were evaluated based on total medication costs, incremental medication costs, and treatment effects (measured as lung function). A bootstrap analysis was performed to validate the results. Compared to the control group with standard asthma medication alone, a steady decline in medication costs was be observed in the intervention group (SCIT plus standard asthma medication) 1 year after commencing SCIT. This cost trend became statistically significant 3 years after starting SCIT. The calculated potential savings in the SCIT group correlated with an improved lung function. The distribution of the bootstrap results revealed that the probability of SCIT having a superior effectiveness (measured by changes in peak flow results) is around 90%.[74]

SQ-HDM SLIT-tablet cost-effectiveness was evaluated in a hypothetical cost utility analysis, based on the results of a European phase III randomized controlled trial in HDM allergic asthma uncontrolled by ICS.[67] The model included data collected from 559 patients from 13 countries. SQ-HDM SLIT-tablet plus pharmacotherapy was estimated to generate 6.16 quality-adjusted life years (QALYs) per patient at a cost of €5658, compared with 5.50 QALYs at a cost of €2985 for placebo plus pharmacotherapy. This equated to an incremental cost of €2673, incremental QALYs of 0.66, and an incremental cost-effectiveness ratio (ICER) of €4041. The ICER was, therefore, substantially lower than the €40 000 willingness-to-pay threshold per QALY adopted for the analysis. Deterministic sensitivity analyses indicate the results are most sensitive to the utility score of SLIT during years 2 and 3 of treatment.[75]

Another observational, retrospective, and multicentre study carried out in Spain on 419 adult patients diagnosed with HDM AR and/or asthma showed a significant decrease in all quantified resources after a single year of SCIT. Direct costs were decreased by 64% and indirect costs by 94%. Estimated savings for the public National Health System of using SCIT were 5.7 times the cost of immunotherapy.[76]

6 | RECOMMENDATIONS

We present recommendations for AIT in allergic asthma only for HDM since it is the major allergen for allergic asthma and it has the most robust evidence.

6.1 | HDM SCIT

Question: Is HDM SCIT recommended for children and adults with HDM-driven allergic asthma?

6.1.1 | Recommendations

1. HDM SCIT is recommended for children and adults with controlled HDM-driven allergic asthma as an add-on treatment to regular therapy to decrease symptoms and medication use.

   Conditional recommendation, low-quality evidence (Table 3).

2. HDM SCIT is recommended for adults with controlled HDM-driven allergic asthma as the add-on treatment to regular therapy to decrease allergen-specific AHR and to improve QoL.

   Conditional recommendation, low-quality evidence (Table 3).

6.1.2 | Values and preferences

This recommendation places a higher value on the risk of intervention with SCIT and a lower value on the benefit of decreasing symptom and medication use and decreasing allergen-specific AHR (Table 3).

TABLE 3 Judgment of HDM SCIT in decreasing asthma symptoms and medication in children or in adults as add-on treatment to regular asthma therapy in controlled asthma

Importance	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Desirable effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Undesirable effects	Large	**Moderate**	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
Certainty of evidence of resources required	**Very low**	Low	Moderate	High			No included studies
Cost-effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
Equity	Decreased	Probably decreased	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Bold value indicates the evaluation by the voting panel.

6.1.3 | Remarks

1. There is significant heterogeneity of HDM SCIT studies: different preparations (extracts and modified forms like allergoid), different delivery systems such as liposome-encapsulated allergen, different protocols included DBPC or non-DBPC studies, different end points, etc. Thus, product-by-product evaluation is recommended to inform the clinical judgment and only products with proof of efficacy should be used.
2. To date, no HDM SCIT study evaluated reduction in asthma exacerbations or improving asthma control as its primary outcome because they were performed before GINA guidelines promoted these end points as primary goals for asthma management. Additionally, EMA only published guidance on AIT in 2015. However, decreased symptoms and medication use can be considered as a surrogate for asthma control.[40] The decrease in specific AHR might lead to less allergen-driven asthma exacerbations.[77,78] Of note, the number of studies that demonstrated a significant effect on the early and, most importantly, the late phase of allergen-induced bronchial reaction is very limited.
3. There is limited evidence on potential direct or indirect cost-saving effect by adding HDM SCIT to regular asthma treatment.
4. Asthma control and lung function should be assessed regularly (preferably before each SCIT injection); a minimum 30 minutes of observation after therapy at the office is recommended; SCIT should be administered by healthcare professionals (HCPs) with proper training in AIT, under proper conditions to manage severe bronchospasm or a systemic anaphylactic reaction.

Due to lack of evidence, no recommendation can be provided for the use of HDM SCIT to decrease exacerbations, improve asthma control and lung function, or to decrease nonspecific AHR.

6.2 | HDM SLIT drops

Question: Are HDM SLIT drops preparations recommended in children or adults with HDM-driven allergic asthma?

6.2.1 | Recommendations

1. HDM SLIT drops are recommended for children with controlled HDM-driven allergic asthma as an add-on treatment to decrease symptoms and medication use

   Conditional recommendation, low-quality evidence (Table 4).

6.2.2 | Values and preferences

This recommendation places a high value on decreasing asthma symptoms and medication as well as on the ease of administration at home with potential of decreased resource utilization (Table 4).

6.2.3 | Remarks

1. Asthma control and lung function should be assessed regularly.
2. The subgroup of patients with moderate asthma might have a better benefit, but more safety data are needed.
3. In children, the potential benefits could include the ICS sparing effect.

Due to lack of evidence, no recommendation can be provided for the use of HDM SLIT drops in adults with HDM-driven allergic asthma to decrease exacerbations, improve asthma control, or to decrease specific and nonspecific AHR.

6.3 | HDM SLIT-tablets

Question: Are HDM SLIT-tablets recommended for children and adults with HDM-driven allergic asthma?

6.3.1 | Recommendations

HDM SLIT-tablets are recommended for adults with controlled and partially controlled HDM-driven allergic asthma as an add-on treatment to regular therapy to decrease exacerbations and to improve asthma control.

Conditional recommendation, moderate-quality evidence (Table 5).

6.3.2 | Values and preferences

This recommendation places the high value on decreasing asthma exacerbations and improving or maintaining asthma control while decreasing the ICS dose and on the ease of administration at home with potentially decreased resource utilization (Table 5).

6.3.3 | Remarks

1. Asthma control and lung function should be assessed regularly
2. Patients with partially controlled asthma or with a history of severe asthma exacerbations during the last 12 months should be carefully monitored

Due to lack of evidence, no recommendation can be provided for the use of HDM SLIT-tablets for children or for adults to improve asthma lung function or quality of life or to decrease specific and nonspecific AHR.

7 | SAFETY, PRECAUTIONS, CONTRAINDICATIONS

HDM AIT is a safe adjunct treatment for controlled HDM-driven allergic asthma in children and adults. However, it should be noted

TABLE 4 Judgment of HDM SLIT drops in decreasing asthma symptoms and medication in children while added to regular asthma treatment for controlled asthma

Importance	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	**Small**	Trivial		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
Certainty of evidence of resources required	Very low	Low	Moderate	High			**No included studies**
Cost-effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
Equity	Decreased	Probably decreased	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Bold value indicates the evaluation by the voting panel.

TABLE 5 Judgment of HDM SLIT-tablets for decreasing asthma exacerbations and improving asthma control while added to regular asthma treatment

Importance	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable effects	Large	Moderate	**Small**	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	**Moderate**	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
Certainty of evidence of resources required	Very low	Low	Moderate	High			**No included studies**
Cost-effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies
Equity	Decreased	Probably decreased	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Bold value indicates the evaluation by the voting panel.

that most of the safety data are derived from AR studies enrolling patients with controlled asthma and with FEV_1 >70% predicted. Limited data for adverse events are available for patients only with allergic asthma or for patients with moderate or severe asthma.

Uncontrolled asthma is the major independent risk factor for both severe and fatal adverse reactions and is therefore a major contraindication for both HDM SCIT and SLIT. Patients with severe but controlled HDM severe asthma may be eligible for HDM AIT in selected cases with careful monitoring. Other contraindications and precautions are listed in Tables 6 and 7. The summary of product characteristics (SmPC) should also be checked for product specific precautions and contraindications that may differ between preparations.

8 | SPECIAL CONSIDERATIONS

8.1 | Provocation tests for selecting patients with HDM-driven allergic asthma for HDM AIT or efficacy assessment

In some AIT trials, bronchial allergen provocation tests with HDM were used as the inclusion criteria or as the end points (primary or secondary).[38] Based on the concept of "united airways," nasal and conjunctival allergen provocations can be performed under some circumstances, especially in high-risk patients.[79,80] The drawback of provocation testing is that it may not reflect natural exposure. Standardization and availability for daily practice (including safety issues) still need to be refined.[79,81]

8.2 | Duration of AIT

Although there is evidence for efficacy after the first year of HDM AIT,[65,67,82,83] the current practice is three years of treatment for both SCIT and SLIT aiming at achieving long-term efficacy. In asthma, there does not appear to be an additional benefit of five-year therapy compared to three-year therapy.[84,85]

8.3 | Criteria for HDM AIT cessation

After one year of AIT, the efficacy for HDM-driven allergic asthma should be evaluated. Unfortunately, there is no consensus on efficacy criteria specific for allergic asthma. Thus, the same approach as for asthma controller medication should be applied.[40,43] If efficacy is not proven after one year, cessation of AIT therapy should be considered. The indication for treatment, allergic status of patients, association between HDM sensitization and asthma

TABLE 6 Contraindications and precautions for HDM AIT in patients with HDM-driven allergic asthma

	Remarks	Key reference
HDM AIT is contraindicated in uncontrolled asthma	Due to safety concerns.	Epstein 2016,[90] Calderon 2017,[91] Rodriguez del Rio 2017,[92] Normansell 2015,[59] Pitsios 2015,[93] Cox 2011,[94] Lockey 2001,[95] Bernstein 2004[96]
HDM SLIT-tablet may be considered with caution in partially controlled asthma	HDM AIT might be beneficial especially in patients with partly controlled HDM-driven allergic asthma with studies demonstrating improved asthma control and quality of life. HDM SLIT-tablet in adults with asthma not well controlled by ICS or combination products did not increase the risk of major adverse events (AEs)[65]; however, FEV_1 less than 70% of predicted value or severe asthma exacerbation within 3 months before randomization were key exclusion criteria.	Mosbech 2014[65] Virchow 2016[67]
AIT should not be initiated in pregnancy (but can be continued in pregnancy)	Safety of initiation and continuation of SCIT and SLIT during pregnancy analyzed in 4 studies totaling 422 women demonstrated no increased incidence of prematurity, hypertension/proteinuria, congenital malformations or perinatal deaths during pregnancy, and no fetal complications following systemic AEs while receiving AIT[94]	Pitsios 2015[93] Oykhman 2015.[97]
AIT should not be initiated in patients with active or uncontrolled autoimmune disorders (AID)	The CONSIT survey reported on patients undergoing AIT with AID. Major problems were infrequent[78]	Pitsios 2015[93] Rodriguez del Rio 2017[92]
AIT should not be initiated in patients with active malignancies		Pitsios 2015[93]
AIT may be considered with caution in patients with controlled asthma under treatment with beta-blockers (BB) or ACE inhibitors (ACEI)	Only in specialized settings due to increased refractoriness to treatment of anaphylaxis with epinephrine. The CONSIT survey reported on patients undergoing AIT under BB or ACEI. Major problems were infrequent[78]	Rodriguez del Rio 2017[92]
AIT is not recommended in patients with immune deficiencies, active infections, and infestations and uncontrolled diseases such as diabetes, inflammatory bowel disease, gastric ulcer, etc.	The CONSIT survey reported on patients with immune deficiencies or under immune suppressants receiving AIT. Major problems were infrequent[78]	Pitsios 2015[93] Rodriguez del Rio 2017[92]

symptoms, treatment compliance, etc. should be re-analyzed to assess the nonresponsiveness to AIT. There is no evidence to allow any recommendations to be made on a shift to another product neither with regard to route of administration, protocol of desensitization, nor company specific preparations.

8.4 | Categories not covered by recommendations

This Guideline formulated recommendations only for HDM AIT. All the other allergens, including polysensitized and polyallergic patients, will be covered in a second paper.

8.5 | Biomarkers

To date, there are no biomarkers that sufficiently predict response to HDM AIT that can be used to decide on initiation or cessation of HDM AIT in HDM-driven allergic asthma.

8.6 | Combination with biologics

Several trials have been performed with pre-administration or co-administration with omalizumab to improve the safety of SCIT up-dosing.[86] Evidence is lacking to recommend co-administration of biologics and HDM AIT for HDM-driven allergic asthma.

9 | DISCUSSION

9.1 | Unmet needs for HDM AIT in HDM-driven allergic asthma

9.1.1 | Measuring outcomes

Most of the clinical trials of AIT in asthma evaluated clinically relevant parameters such as symptom and medication scores (with an emphasis on the corticosteroid-sparing effect). A limited number of

TABLE 7 Recommendations for risk management of HDM AIT in HDM-driven allergic asthma

HDM SCIT for HDM-driven allergic asthma	• Signed informed consent • Supervised administration by a healthcare professional (HCP) trained in the evaluation of patients with allergic conditions in a setting facilitating proper management of systemic reactions • Assessment of the patient's current health status before the administration of SCIT to determine whether there have been any recent changes in the patient's health that may require modifying or withholding treatment (eg, uncontrolled/symptomatic asthma or exacerbation of allergy symptoms • Observation for at least 30 minutes after injection • Patient education for management and reporting late reactions
Home based HDM SLIT for HDM-driven allergic asthma	• Signed informed consent • Supervised initiation by a HCP trained in the evaluation of patients with allergic conditions in a setting facilitating proper management of systemic reactions • Observation for at least 30 minutes after the first dose • Patient education and written instructions on how to recognize and manage adverse reactions and when to contact the HCP for adverse reactions, treatment gaps, or other events that may affect treatment (eg, new medication or illness), how to manage missed doses and the situations when they should withhold SLIT • In cases of oral inflammation, such as mouth ulcers, lichen planus, stomatitis aphthous, or dental extractions, administration of SLIT should be temporarily discontinued until there is complete healing of the oral cavity. Dental flossing and gum hygiene can be associated with gum bleeding. It is recommended that the patient delay the administration of SLIT for a few hours after cessation of gum bleeding. It is suggested to resume SLIT 24 hours after a dental cleaning procedure. • Recommendations for when to withhold SLIT dose to avoid potential situations when systemic allergic reactions may be more likely should also be provided. • Regular follow-up care with a HCP trained in the evaluation of patients with allergic conditions to monitor safety.

trials have used established asthma outcomes such as validated asthma control questionnaires (eg, ACQ), lung function parameters besides FEV_1, or exacerbation rates (generally defined by requirement for oral corticosteroids or hospitalizations); they have showed negative or mixed results. There is a clear need for better designed studies of HDM AIT in HDM-driven allergic asthma using harmonized and validated clinical outcomes. Respiratory physicians should be included in the trial design.

The frequency and the number of exacerbations, decreased need for controller medication and possibly lung function with a special focus on small airways, should be considered as primary end points. Co-primary end points such as corticosteroid sparing and decrease in exacerbations should also be considered.

9.1.2 | Methodological difficulties

Several challenges were encountered in developing this guideline.

Firstly, we faced different patient population (pediatrics vs adults) and different allergens with significant variations in standardization and potency and routes for HDM AIT. Thus, a decision was made to formulate separate research questions for each patient population and HDM AIT route according to biological plausibility and pharmacological effects.

Secondly, guideline panel members identified multiple outcomes to assess desirable and undesirable effects of HDM AIT. Although, guideline panel members rated the importance of the outcomes in HDM-driven allergic asthma, additional work needs to be continued to define patient important outcomes for patients.

Thirdly, multiple RCT reported findings using different approaches. For instance, while some RCTs reported findings in mean and standard deviation, other reported results as median and interquartile ranges. Prespecified outcomes varied hugely. Ideally, a meta-analysis should have access to individual patient data. To summarize the body of evidence, data were transformed using validated approaches and available data.

9.2 | Barriers, facilitators, gaps, and audit criteria

A subgroup of patients with HDM-driven allergic asthma may benefit most from HDM AIT. The important prerequisites for successful HDM AIT are (a) use of allergen extracts of proven efficacy and (b) selection of patients most likely to respond to this causal therapy. The major barriers and facilitators as well as audit criteria are presented in Table 8. Generally, a holistic approach to patients is required with joint commitment of various stakeholders to offer the patients optimal care.[87–89]

9.3 | HDM AIT positioning in the context of general asthma management

The administration of HDM AIT should not interfere with or substitute for pharmacological asthma treatment as recommended by various asthma guidelines. It should be considered only when asthma is driven by HDM allergy and is controlled providing the perspective of stepping-down controller treatment while decreasing the future risk of asthma exacerbations and drug-related adverse events. Another option that needs further exploration is whether adding AIT to pharmacological treatment in partially controlled asthma can facilitate achieving asthma control. More safety data are required to support this approach (Figure 2).

TABLE 8 Barriers, facilitators, and audit criteria for HDM AIT in HDM-driven allergic asthma

Barriers	Facilitators	Audit criteria	Resource implications
Insufficient evidence primarily for asthma population	Large RCTs and real-life studies focused on HDM-driven allergic asthma population	Updated AIT indications based on new evidence.	Joint efforts and harmonization of different stakeholders
Insufficient evidence for the pediatric population	Large RCTs and real-life studies focused on pediatric population	Updated AIT indications based on new evidence.	Revised, realistic pediatric investigation plan (PIP)
Differences in the evidence for efficacy and safety between different HDM AIT products due to product quality and standardization and study designs	Improved product standardization. Harmonization of production process and study design. Head-to-head comparison between products.	Proportion of patients treated with products for which there is product specific evidence of efficacy and safety	Joint efforts and harmonization of different stakeholders
The application of HDM AIT in asthma is limited due to efficacy and safety concerns	Higher quality large phase 3 DBPC trials with validated outcome measures, patient centered outcomes, and postmarketing data	Proportion of patients with HDM-driven allergic asthma successfully treated with HDM AIT Proportion of patients treated with HDM AIT for HDM-driven allergic asthma who suffer from an adverse event	Joint efforts and harmonization of different stakeholders
Definition of HDM-driven allergic asthma as a lower airways condition, ignoring the frequent association with AR and/or AD and disease endotypes	Revised definition of HDM-driven allergic asthma to include the one airways disease concept and asthma endotypes	Proportion of patients prescribed HDM AIT for the one airways disease (AR and allergic asthma) Proportion of patients with HDM-driven allergic asthma treated according to their endotype	More research for better understanding of the disease mechanism and implementing a new disease taxonomy
Low awareness and knowledge of AIT potential by the general public and healthcare professionals outside allergy speciality, for example, pediatricians, respiratory physicians, ENT, dermatology, and primary care physicians	Joint commitment and coordinated actions among academia, patient organizations, regulators, industry to find solutions that properly answer the health expectations of the allergic patients	Proportion of patients prescribed AIT for allergic asthma	Alignment between various stakeholders
Availability and affordability	Pharmacoeconomics studies and implementation of better reimbursement policies	Prescription and reimbursement rate	Change in priority perception of healthcare system
Improved patient selection	Better selection of responders using diagnostic tools for accurate identification of clinically relevant patient's sensitization profile	Proportion of patients who do not benefit from HDM AIT	More research in disease mechanisms and diagnostic tools
Adherence to HDM AIT	Educational programs, more convenient HDM AIT regimens	Proportion of patients who dropout from HDM AIT	Allocation of funds for education. Harmonization between stakeholders
Outcomes reporting in individual RCTs	Randomized controlled trials reported findings as, for instance, median and interquartile rank.	Transform data using properly formulas and approaches	Harmonization between researchers.

10 | KEY POINTS AND CONCLUSION

The treatment of HDM-driven allergic asthma both in adults and children relies on the use of corticosteroids and other controllers recommended to achieve and maintain asthma control and to prevent exacerbations, loss of lung function, and improve quality of life. The addition of the first HDM AIT product approved specifically for asthma, the HDM SLIT-tablet, has fueled optimism for the potential benefits of HDM AIT in some patients with HDM-driven allergic asthma, especially if appropriate responder phenotypes can be identified. However, in some countries where there is no reimbursement for HDM AIT, economic constraints may mean that these options are not accessible. It is important to explore the short- and long-term health economic effect of AIT in asthma due to its potential disease-modifying effect.

10.1 | Conclusion. Key points

1. Patients with HDM-driven allergic asthma not adequately controlled on available pharmacotherapy present an unmet health need.

TABLE 9 Gaps in evidence for HDM AIT in HDM-driven allergic asthma and plan to address

Gaps in evidence	Plan to address	Priority
Identifying and standardizing relevant outcome measures (control, exacerbation, lung function, composite scores)	Investigate and validate optimal outcome measures in adults and children.	High
Stratification of patients (HDM as driver of asthma control, adherence, severity)	Well-designed RCT, example for personalized medicine	High
Determining long-term efficacy of HDM AIT in HDM-driven allergic asthma (after treatment cessation)	Well-designed RCT and real-life studies focusing on long-term efficacy of AIT in asthma	High
Cost-effectiveness of HDM AIT in HDM-driven allergic asthma	Sectoral and generalized cost-effectiveness analysisLong-term perspective as HDM AIT can modify the disease and thereby influence long-term cost	High
Alignment of studies with guidance from regulatory bodies.	Work in partnership with regulatory bodies to continually review trial methodology and outcomes.	High
Identification of clinically relevant biomarkers of sensitization beyond SPT/IgE in order to select responders to HDM AIT	Proof-of-concept studies evaluating patient selection based on provocation tests and/or biomarkers including components and other measures	High
Impact of allergic multi-morbidities (allergic rhinitis, atopic dermatitis, etc.)	Studies evaluating the global effect of HDM AIT on allergic multi-morbidities	High
Impact of multi-morbidity (autoimmunity, diabetes, obesity, smoking) and the impact of age (>60 and <5) and age of onset (early onset (childhood; <18 years); adult onset (between 18 and 40 years) or late onset (>40 years).	Well-designed RCT and real-life studies focusing on HDM AIT in asthma with comorbidities	Medium
Impact of severity of asthma including suboptimal lung function	Well-designed RCT and real-life studies focusing on HDM AIT in HDM-driven allergic asthma stratified by severity, including severe and uncontrolled asthma	High
Impact of observational period after HDM AIT dose on safety	Well-designed RCT and real-life surveys assessing impact of different observational periods	Medium
Validation of different regimens	RCTs and real-life studies testing different approaches in HDM AIT in terms of dose, duration, and route	Medium

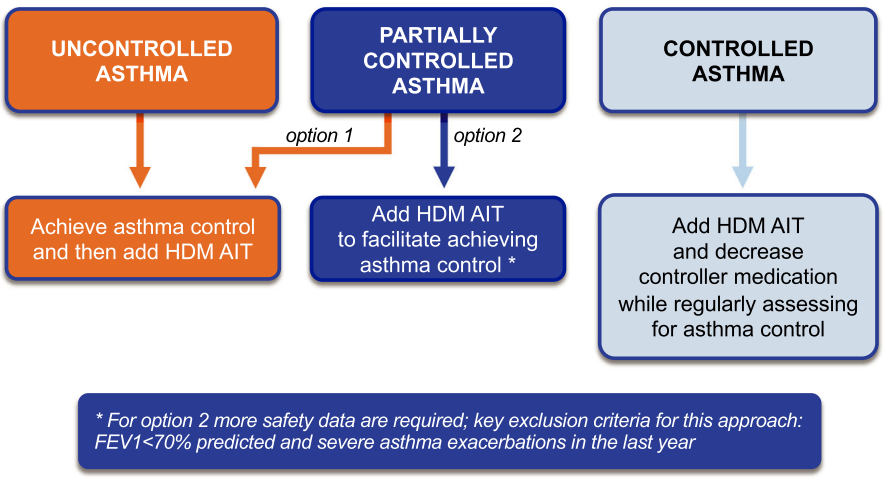

FIGURE 2 Integration of HDM AIT in the stepwise management of HDM-driven allergic asthma based on the level of asthma control. HDM AIT is recommended for controlled HDM-driven allergic asthma with the expectation to be able to step-down controller treatment while maintain asthma control, given the fact, that the HDM allergen is identified as relevant trigger. For partially controlled asthma, adding HDM AIT while stepping-up pharmacological treatment might facilitate achieving asthma control. Due to safety concerns, HDM AIT should not be used for uncontrolled asthma. Caution is necessary if HDM AIT treatment decisions are made in patients with severe controlled HDM-driven allergic asthma

2. AIT targets the underlying mechanisms in allergic asthma by modifying the immunological response to allergen toward tolerance.
3. HDM AIT may add to the anti-inflammatory action of ICS to promote asthma control and decrease the risk of exacerbations.
4. Success of HDM AIT in HDM-driven allergic asthma is largely dependent on proper selection of patients with HDM sensitization and symptoms driven by specific allergen exposure plus the use of allergen extracts of proven efficacy.
5. To date, only AIT with HDM SLIT-tablet has been demonstrated to show robust effects in adults on critical end points (exacerbations, asthma control, and safety).
6. AIT should only be initiated and monitored by healthcare professionals with the appropriate competencies which will require an investment in training.

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