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REVIEW ARTICLE

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Perspectives in allergen immunotherapy: 2019 and beyond

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Abbreviations: ACS, Allergy-Control Score; ACQ, Asthma Control Questionnaire; AEC, allergen exposure chamber; AHR, allergen-specific airway hyperreactivity; AIT, allergen immunotherapy; AR, allergic rhinitis; ARC, allergic rhinoconjunctivitis; Breg, B regulatory cell; CD4+ T cell, CD4 positive T cell; CRTH2+, chemoattractant receptor-homologous molecule expressed on Th2 lymphocytes; CSMS, combined symptom medication score; CTLA4, cytotoxic T-lymphocyte-associated protein 4; DAO, diamine oxidase; DC, dendritic cell; DRF, dose-response finding; dMS, daily medication score; dSS, daily symptom score; EAACI, European Academy of Allergy and Clinical Immunology; EFPIA, European Federation of Pharmaceutical Industries and Associations; EMA, European Medicines Agency; FAB, facilitated antigen binding; FASIT, Future of the Allergists and Specific Immunotherapy; FDA, US Food & Drug Administration; FV, folding variant; GMP, Good Manufacturing Practice; HDM, house dust mite; HTA, Health Technology Assessment; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; Id, intradermal test; Ig, immunoglobulin; IL, interleukin; IL-10R, interleukin 10 receptor; MA, marketing authorization; MAA, marketing authorization application; MCID, minimal clinically important difference; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction; PD1, programmed cell death protein 1; PEI, Paul-Ehrlich-Institut; PNIF, peak nasal inspiratory flow; QoL, Quality of Life; PIP, Pediatric Investigational Plan; RC-ACS, Rhino-conjunctivitis Allergy-Control Score; RUNX, runt-related transcription factor; SCIT, subcutaneous immunotherapy; sIg, specific Ig; SLIT, sublingual immunotherapy; SPT, skin prick test; TAO, Therapy Allergen Ordinance; TGF-ß, Transforming growth factor beta; TNSS, total nasal symptom score; Treg, T regulatory; VAS, visual analogue scale; VLPS, virus-like particles.

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Abstract

The seventh "Future of the Allergists and Specific Immunotherapy (FASIT)" workshop held in 2019 provided a platform for global experts from academia, allergy clinics, regulatory authorities and industry to review current developments in the field of allergen immunotherapy (AIT). Key domains of the meeting included the following: (a) Biomarkers for AIT and allergic asthma; (b) visions for the future of AIT; (c) progress and data for AIT in asthma and the updates of GINA and EAACI Asthma Guidelines (separated for house dust mite SCIT, SLIT tablets and SLIT drops; patient populations) including a review of clinically relevant endpoints in AIT studies in asthma; (d) regulatory prerequisites such as the "Therapy Allergen Ordinance" in Germany; (e) optimization of trial design in AIT clinical research; (f) challenges planning and conducting phase III (field) studies and the future role of Allergen Exposure Chambers (AEC) in AIT product development from the regulatory point of view. We report a summary of panel discussions of all six domains and highlight unmet needs and possible solutions for the future.

KEYWORDS
allergen exposure chamber, allergen immunotherapy, allergic asthma, biomarker, clinical trials

1 | INTRODUCTION

Allergic rhinitis (AR) is the most common immune disease and one of the most common chronic diseases worldwide—with an ever increasing prevalence. Almost one in three European citizens is affected by AR. This disease is still largely underestimated, underdiagnosed and undertreated. The socio-economic consequences of AR and its comorbidities are considerable for healthcare systems all around the globe.[1] Asthma is a serious global health problem affecting 1%-18% of the population in different countries and all age groups. Its prevalence is increasing in many countries, especially among children and it still imposes an unacceptable burden on healthcare systems, and on society. One of the most common phenotypes is "allergic asthma," which often commences in childhood.[2]

Although the number of patients with allergy increases, and the efficacy for allergen immunotherapy (AIT) in different indications like allergic rhinoconjunctivitis (ARC),[3] allergic asthma,[4] insect venom allergy[5] and IgE-mediated food allergy[6] is well established, the use of AIT decreases.[7] Reimbursement pressure across the EU adds uncertainty.[8-13] This is a critical time for patients and physicians as the known benefits of AIT, and current innovations in the field are to be effectively translated into routine clinical use.

The Future of the Allergists and Specific Immunotherapy (FASIT) workshop is organized and hosted by Allergopharma GmbH & Co. KG (Reinbek, Germany) to provide a platform to review developments in the field of AIT, highlight unmet needs and develop and discuss possible solutions. Attendees are drawn from academia, allergy clinics, regulatory authorities and industry. The first FASIT meeting was held in 2006 and has since been repeated at 2- to 3-year intervals and highlights of the discussion have been published in series of publications.[14] This seventh workshop took place in Hamburg in February 2019. We provide a review of the six domains. The keynotes of the expert panel's discussion are summarized in Table 1.

TABLE 1 Keynotes of the expert panel's discussion

Domain I: Biomarkers	There is a need for biomarkers of efficacy, safety, compliance and immune monitoring in AIT trials. Biomarker validation in responders/non-responders will require extensive molecular and omics research linked to the definition of efficacy and validation of efficacy parameters
Domain II: Future pathways for AIT development	Future pathways for AIT development include targeted prevention, biomarkers to select patients who are most likely to respond and predict success of AIT as early as possible and noninvasive diagnostic approaches
Domain III: AIT and asthma - a breakthrough?	AIT trials in house dust mite (HDM) allergic asthma have shown efficacy. Sublingual HDM tablet AIT reduced asthma exacerbations and enabled steroid reduction. These data have led to an update of the EAACI guideline on AIT for allergic asthma and of the GINA 2018 guideline. These now include HDM subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT) as add-on to controller treatment for controlled HDM-driven allergic asthma
Domain IV: Regulatory prerequisites in AIT: Ten years of Therapy Allergen Ordinance and outlook in the European Union	The implementation of the "Therapy Allergen Ordinance" (TAO) leads to a new generation of allergen therapy products, often of higher dosage than before, and the first market authorization (MA) was granted for two TAO products in 08-2018
Domain V: Clinical trial design in AIT trials: innovation through harmonization	Products for AIT must meet modern methodological standards for quality, efficacy and safety. Consequently, validated clinical endpoints and clinically justified and validated effect sizes are needed. A better understanding of the placebo effect in AIT is necessary
Domain VI: Allergen exposure chambers (AECs) in AIT studies	AECs are a promising tool for the evaluation of efficacy of AIT. For acceptance of AECs for a phase III trial, hybrid studies (AEC versus field) are necessary intermediates

2 | BIOMARKER (DOMAIN I)

2.1 | Biomarker for allergen immunotherapy

Biomarkers of disease can be grouped into those that highlight disease susceptibility/risk, support diagnosis, prognosis and can predict efficacy and safety. Despite our understanding of the current mechanisms of AIT,[15] there is unmet need for identifying those who are successfully desensitized, in whom AIT is effective during the course of 1-2 years and those who are likely to be hyporesponsive to the sensitized allergen after cessation of treatment.

Understanding the immune mechanisms of AIT is of paramount importance in order to identify potential biomarker targets of safety, efficacy and tolerance. In the mid 90', the induction of T regulatory (Treg) cells following AIT was reported. These cells utilize multiple suppressor factors like IL-10, IL-35, TGF-β, IL-10R, TGF-βR, CTLA4, PD1, HR2 and RUNX as transcription factor and downregulate the pro-allergic environment directly or indirectly. Restoration of tolerogenic dendritic cells has been shown to promote T cell tolerance. This is associated with the suppression of allergic effector such as mast cells, basophils and eosinophils and induction of B regulatory cells that secrete allergen-neutralising IgG4 antibodies that can prevent FcεRI and CD23-mediated IgE responses. Mechanisms of tolerance following AIT are similar to those seen during natural tolerance to bee keepers and cat owners (see Figure 1). Despite our understanding of the mechanisms of AIT, several challenges and important questions remain to be addressed (Box 1).

These important questions have been addressed in a longitudinal study including healthy and allergic patients and confirmation populations, where around 400 local and systemic molecules (some known and some not known) have been investigated after preseasonal SCIT AIT. Information about allergen-specific and nonspecific CD4+ T cells, transcriptomic profile, plasma proteome, nasal proteome, allergen-specific memory Treg cells, CRTH2+ CD4+ T cells was collected. The analysis of the 3rd year data is currently ongoing and will yield potential biomarkers of AIT (*personal statement*: Akdis CA, FASIT 2019).

At baseline, before immunotherapy, outside of pollen season, allergen-specific CD4+ T cells and Treg cells were more frequent in patients as compared to controls, but displayed profound gene and protein downregulation of immune response and cell activation pathways except type 2 immunity, TCR signalling, fatty acid and prostaglandin metabolism (Figure 2). Plasma and nasal untargeted and targeted proteome reflected specific cellular signatures with upregulation of proteins leading to lymphocyte proliferation, T-cell differentiation and fatty acid metabolism and downregulation of several anti-inflammatory pathways. After three months of AIT, allergen-specific CD4+ T cells and allergen-specific Treg cells increased parallel with a substantial decrease of total and allergen-specific CRTH2+ CD4+T cells. Moreover, AIT-induced extensive and precise changes in gene expression of several previously dysregulated immune and metabolic processes and led to induction of tolerance programmes in allergen-specific CD4+ T cells and Treg cells, persisting until 12 months of the therapy. The analysis of the 3rd year data is currently ongoing.

Importantly, AIT-induced gene expression profiles differed between clinical responders and nonresponders. At early time points,

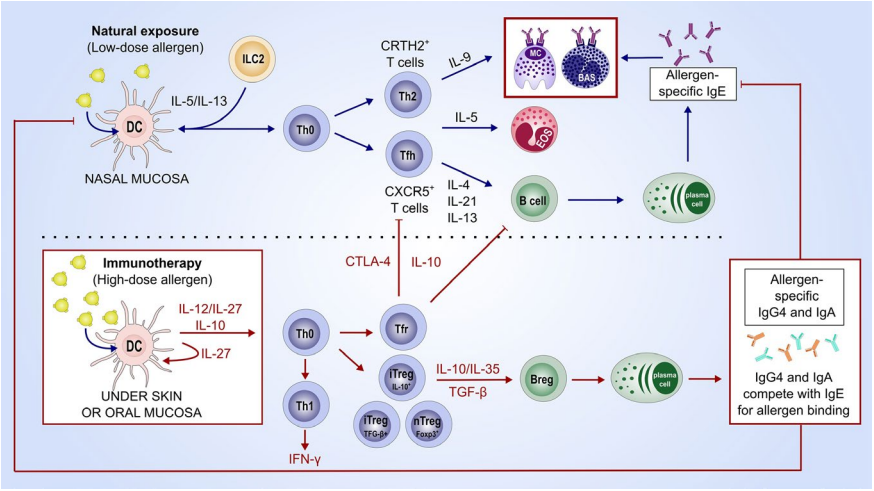

FIGURE 1 Pathophysiology of allergic rhinitis and mechanisms of AIT (based on ref.[15]). BAS: basophil; Breg: regulatory B; CRTH2: chemoattractant receptor-homologous molecule expressed on TH2 lymphocytes; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; CXCR5: C-X-C chemokine receptor type 5; DC: dendritic cell; EOS: eosinophil; Foxp3: Forkhead box P3; IFN: Interferon; Ig: Immunoglobulin; IL: Interleukin; iTreg: inducible regulatory T; MC: mast cell; nTreg: natural regulatory T; Tfh: follicular helper T; TGF: transforming growth factor; Th: T helper

Box 1 Challenges and questions in the mechanisms of AIT (Akdis CA, FASIT 2019).

Challenges

- Extremely rare cell populations in vivo in humans in periphery
- MHC II restriction
- In vitro re-stimulation experiments
- No predictive biomarkers of clinical response

Questions

- What are molecular mechanisms of abnormal type 2 immune responses in allergen-specific T cells and T regs in allergy?
- What are molecular mechanisms of AIT in allergen-specific T cells?
- What is the role of Breg cells and dendritic cell subsets?
- What are the local or systemic biomarkers of AIT?

allergen-specific Treg cells of allergic patients displayed profiles suggesting dysregulated suppressive functions. The increase in the frequency of these cells observed after AIT, correlated with the upregulation of survival programmes and correction of immune regulatory functions. However, allergen-specific Treg cells in nonresponders still displayed aberrant type 2 gene, protein and metabolic profiles, coupled with the corresponding plasma and nasal inflammatory milieu.

In conclusion, these data suggest that in allergy there is a systemic and local aberration of immune signalling, leading to dysfunctional transcriptomic reprogramming and subsequent functional impairment of allergen-specific effector and regulatory T cells. AIT causes profound changes in the frequency, gene and protein expression profiles of allergen-specific T cells as well as in protein expression profiles of plasma and nasal tissue. These profiles are abnormal in allergic patients, but AIT is skewing them towards the levels of immune tolerant controls.

2.2 | Blocking antibodies

Different clinical studies and a recent study with grass pollen-allergic patients comparing SCIT, SLIT and placebo[17] showed that peripheral and local immune reactive and functional IgG4 antibodies are induced by AIT. Both active treatments showed significant improvement in total nasal symptom score (TNSS) and peak nasal inspiratory flow (PNIF) during the 2-year treatment period, but this effect diminished in the follow-up year after AIT, even though IgG4 levels and IgE-FAB to B cells persisted through this 3rd year of investigation. When looking locally in the organ using nasal fluid (ISAC-chip array, IgE-FAB) and serum samples (IgE-FAB, Immuno-CAP, ISAC-chip) in and out of grass pollen season in allergic individuals, in SCIT-treated patients and nonatopics a more dramatic suppression of IgE-FAB in nasal fluid compared to serum could be demonstrated, especially in season. The nasal inhibitory activity for IgE-FAB to B cells is IgG-dependent and the nasal inhibitory antibodies correlate more closely with symptom scores.[18]

During AIT also other novel biomarkers of efficacy and tolerance of AIT like the intracellular fluorochrome-labelled diamine oxidase in basophils or dendritic cell (DC)2 cells, the conductor of the orchestra (CD141, GATA3 and RIPK4) and DCreg (C1QA and FcγRIIIA) cell markers are expressed. Details are reported in the FASIT 2017 report.[14] The findings indicated that histamine bound to labelled diamine oxidase (DAO) may be useful for monitoring treatment for AR and using quantitative polymerase chain reaction (PCR) from

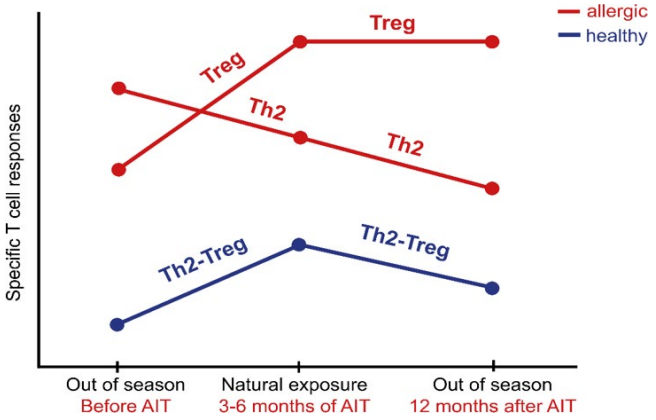

FIGURE 2 Allergen-specific T cell numbers show a relatively high frequency in allergic individuals, which shows a significant decrease in Th2 cells and their cytokines during the course of allergen immunotherapy (AIT). A skew from T helper 2 (Th2) to T regulatory (Treg) cells occurs at the time of 3 to 6 months and during natural allergen exposure. Treg responses increase after 3 months of AIT and at the time of natural exposure and stay high at the end of one year. For comparison, healthy individuals show very limited allergen-specific immune responses outside the season, which increases and becomes visible during natural allergen exposure and is under the control of Treg cells and decreases back to baseline levels at the end of one year (based on ref.[16], *personal statement*: Akdis CA, FASIT 2019)

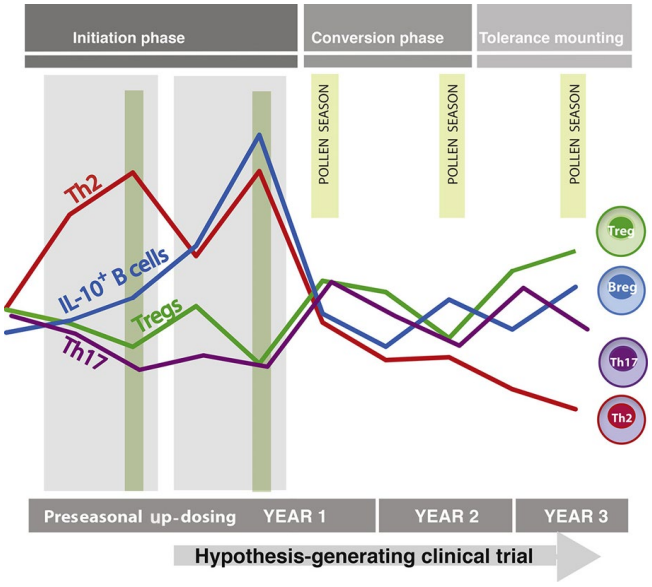

FIGURE 3 Competition in immune system after one year of AIT.[16] Reprinted from EBioMedicine, 36, Zissler U M, Jakwerth C A, Guerth F M, Pechtold L, Aguilar-Pimentel J A, Dietz K, Suttner K, Piontek G, Haller B, Hajdu Z, Schiemann M, Schmidt-Weber C B, Chaker A M, Early IL-10 producing B-cells and coinciding Th/Tr17 shifts during three year grass pollen AIT, 475-488, Copyright 2018, with permission from Elsevier. Breg: regulatory B; IL: interleukin; Th: T helper; Treg: regulatory T

peripheral blood it could be shown that the expression of CD141, GATA3 and RIPK4 was downregulated in responders compared to the nonresponders or placebo. C1QA and FcγRIIIA were upregulated in active responders and downregulated in the active nonresponders or placebo. There was a correlation between these five biomarkers and efficacy, already after two months, after initiation of AIT with a sensitivity of 90% and a specificity of 61%.[19]

The prospective allergy immune function cohort (PACIFIC), an open clinical cohort of patients undergoing AIT and controls (untreated and nonallergic) involved sampling of local nasal secretion, sputa, peripheral blood mononuclear cells (PBMCs) in more than 200 individuals and was performed during up-dosing and during maintenance phase (antigen-specific window 4-6 hours post-AIT) and up to an observation period of 10 years.[16] This was a hypothesis generating framework, not a confirmatory study. Data showed differential shifts in a "hierarchy of tolerance" in three distinct phases of AIT characterized by conversion of regulatory against pro-inflammatory mechanisms, of which the Breg/Th17 ratio after initial treatment emerges as potential early prediction of AIT efficacy.

The preseasonal up-dosing in AIT leads to an increase in all kind of different cells, and during the two years afterwards, there is a kind of competition within the immune system between the pro-tolerogenic and the allergic part (Figure 3).

In summary, for successful AIT, allergen-neutralizing IgG4-associated blocking antibodies are necessary but not sufficient. The presence of blocking antibodies may be used as a marker of compliance and FAB adds information in the correlation to clinical response. A lack of correlation between both may indicate ineffectiveness of the investigated product. Basophil activation and histamine release at single-cell level appear to be potential biomarker of clinical response. The DC markers are able to be measured by use of PCR on peripheral blood.[19] All of the above need thorough investigation in the future.

2.3 | Biomarkers in allergic asthma

Due to high heterogeneity in pathophysiology, clinical presentation and therapeutic responses the treatment of asthma patients is sometimes suboptimal. The goal is a stratification of patients on the basis of plausible biomarkers for better diagnosis, prognosis and prediction of treatment response, but the sensitivity and/or specificity for asthma pathology is limited and biomarkers are influenced by other factors.[20,21] While traditionally clinicians have focused on phenotyping, it will be increasingly more important to stratify by endotype or theratype (see definition and details in the FASIT 2017 report[14]). 50% of asthmatic patients have a type 2-high asthma, but with different predominant pathways, with or without IgE and eosinophils, and several inflammatory phenotypes have been identified (Figure 4).[22]

Endotype classification remains elusive due to the complexity of these phenotypes; rather than a single endotype associated with a particular disease mechanism, asthma is believed to have a number of sub-endotypes associated with each mechanism. Table 2 gives an overview about possible biomarkers in blood, induced sputum and exhaled breath of type 2 (T_2)-high endotype. Exhaled breath

condensate provides useful material, underestimated so far and mediators like leukotrienes, lipoxines, arachidonic acid metabolites, nitrogen oxides and related products, cytokines, ammonia, oxidative stress markers, H_2O_2 or adenosine can very precisely be measured.[23] Eosinophils are another important marker used recently in clinical trials and cut-points to diagnose eosinophilic inflammation and are recommended to be used in clinical trials.[24,25]

A growing field is the study of biomarkers in type 2-low endotypes (Table 3). INOS induced by Th1/Th17 cells is a marker of general inflammation in the airways, not only T_2 inflammation. For the TH1/TH17 endotype in asthma (around 50%), pathophysiological events are not clear and biomarkers not available so that long-term follow-up is necessary. Periostin is not a T_2 biomarker as such, but 50% of asthmatics have measurable periostin. These periostin/T_2-high asthmatics respond better to anti-IL-13 therapy in comparison with periostin low patients.[26]

Factors modulating the disease endotype include innate and adaptive immune responses, genetic and epigenetic factors, the exposome (allergen, pollutant, irritants), type of nutrition and metabolic pathways.[27] This illustrates the importance of patient stratification according to endotype for the purpose of biomarker evaluation and for inclusion of participants in clinical trials.[28]

A substantial subgroup of asthmatics have comorbidities with a complex network of interactions between immune and metabolic pathways.[29] Especially the gut immune system is influenced by microbiota and its metabolites like histamine. This is very important for regulating the immune response. For example, *Morganella morgana* is increased in asthma patients and this increase correlated with disease severity[30]. In contrast, asthma in obese individuals represents a distinct endotype[30]. In these patients, *Bifido* and *Faecali* bacteria are commonly associated with a healthy gut microbiome and negatively correlated with BMI.[31] The gut microbiota composition has been shown to predict an "obese phenotype" and gut enterotype to correlate with serum biomarkers.[31] Systemic inflammatory mediators in obese patients are primarily driven by obesity, but not by asthma.[31] An obese asthma patient obviously needs to be treated differently than a nonobese asthma patient and changes in the microbiota may provide an important missing link in the stratification and selection of patients for specific therapies. The "*One size does not fit all*," phenotyping, endotyping and theratyping (response to treatment) will select the right patient, and for this, we need validated biomarkers to guide a precision medicine approach to treatment and to allow their translation into practice in the clinical management of allergic disease.

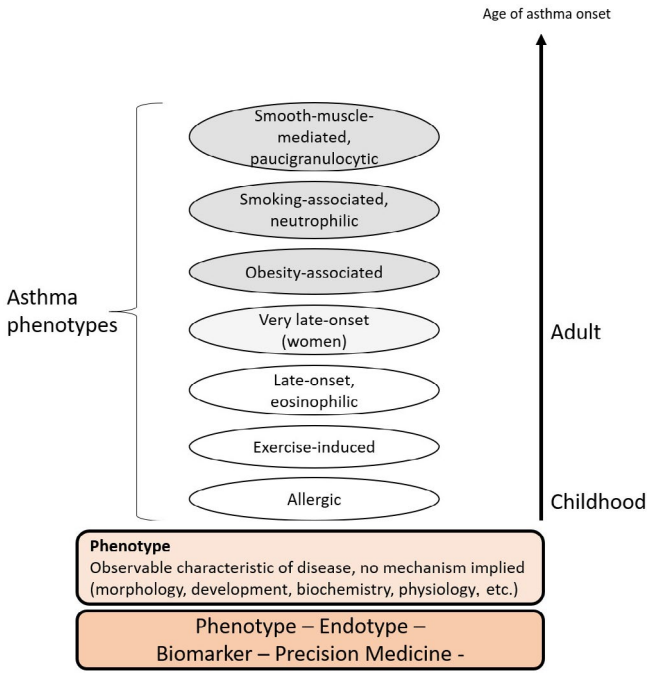

FIGURE 4 Asthma phenotypes (Renz H, FASIT 2019, based on ref.[22])

2.4 | Conclusion/Outlook (domain I)

In the discussion about the most promising biomarker candidates for prediction of AIT efficacy, it is important to understand the different phases of AIT that include desensitization with onset of efficacy, sustained efficacy during maintenance treatment and "tolerance" that refers to persistence of clinical benefit that is accompanied by long-term changes in the adaptive immune response following discontinuation of treatment. It is not clear whether this long-term tolerance resides within T cells or the B cells or possibly both compartments with persistence of blocking antibodies as a major component of tolerance after stopping treatment.

To validate, a biomarker information on responders and nonresponders and a definition of efficacy and validation of efficacy parameters is necessary. Studies like PACIFIC might be an option to combine clinical outcome and biomarker research and clinical and immunological parameters can be clustered so that stratification might be possible. In allergy a huge number of variances influence the outcome, mixed endotypes increase complexity and the question is whether parameters that change after AIT are the markers of response. Or is induction of immune tolerance sufficient? Here we might learn from oncology clinical trials with high throughput, larger patient groups, deep endotyping linked with bioinformatics and microbiomics and the acceptance of immune response as outcome. Currently, there is no validated and simple marker for daily clinical practice predicting efficacy of AIT.

Key message 1

There is a need for biomarkers of efficacy, safety, compliance and immune monitoring in AIT trials. Biomarker validation in responders/nonresponders will require extensive molecular and omics research linked to the definition of efficacy and validation of efficacy parameters.

TABLE 2 Biomarkers in the type 2-high asthma endotype[25]

Biomarker	Treatment expected to produce a response	Associations	Comments (point of case, variability/fluctuation)
Blood			
Eosinophils	Anti-IL-5 Anti-IgE Anti-IL-4/IL-13 Corticosteroids CRTH2 antagonists	Exacerbations LF decrease Fixed airway obstruction	Easily available Significant fluctuation
Specific IgE	Anti-IgE AIT	Exacerbations AHR (AIT)	
Periostin DPP-4	Anti-IL-13	LF decline Exacerbations	Research type Assay dependent
Induced sputum			
Eosinophils	Anti-IL-5 ICS	Exacerbations	Research type Significant fluctuations
IL-13	Anti-IL-13	Unknown	Research type
Exhaled breath			
FENO	Anti-IL-5 Anti-IgE Anti-IL-13 ICS	Exacerbations, LF decrease	Easily available Significant fluctuation
Metabolomics (VOC)	ICS	Unknown	Research type

Reprinted from J Allergy Clin Immunol, 137/5, Muraro A, Lemanske R F, Hellings P W, Akdis C A, Bieber T, Casale T B, Jutel M, Ong P Y, Poulsen L K, Schmid-Grendelmeier P, Simon H-U, Seys S F, Agache I, Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology, 1347-1358., Copyright 2016, with permission from Elsevier.
There is significant overlap between biomarkers used to predict response to different endotype-driven strategies. In addition, few biomarkers are easily available, most are subject to fluctuation, and none are validated and qualified. AIT: Allergen immunotherapy; DPP-4: dipeptidyl peptidase 4; FENO, Fraction of exhaled nitric oxide; ICS: inhaled corticosteroids; IL: Interleukin; LF: lung function; VOC: volatile organic compounds

TABLE 3 Biomarkers in the type 2-low asthma endotype (Jutel M, FASIT 2019)

Biomarker	Treatment expected to produce a response	Surrogate endpoint value	Comments
Sputum neutrophils	Anti-IL-17 ICS resistant	Exacerbations LF decline Fixed airway obstruction	Associated with severe asthma and can be indicative for non-T2-mediated asthma. Wide range of cut-off values varying between 40% and 60%
IL-17	Anti – IL-17	Concentrations in BAL fluid, sputum, serum and biopsies correlate with asthma severity	Holds possible diagnostic value for the identification of non-Th2-mediated asthma
YKL-40		Serum concentrations of YKL-40 appear to correlate with sputum neutrophilia	Serum and sputum levels of YKL-40 increased in severe asthma and correlate with disease severity, airway obstruction and membrane thickness
IL-6	Anti-IL-6	Serum concentrations of IL-6 correlate with disease activity and severity	Possible indicator for metabolic dysfunction and tissue damage in asthma patients. IL-6 is not specific for asthma

ICS: inhaled corticosteroids; IL, Interleukin; LF: Lung function; BAL: bronchoalveolar lavage.

3 | FUTURE PATHWAYS FOR AIT DEVELOPMENT (DOMAIN II)

AIT products are leading to an allergen-specific immune modulation, with the aim of preventing and relieving allergic symptoms. Traditionally, the active ingredients of AIT products are mixtures of allergens and other proteins extracted from biological sources (such as pollen and mites), used unmodified or treated with aldehydes and then formulated (with or without an adjuvant such as aluminium salts) for SCIT or (without adjuvants) for SLIT administration.[11,32,33]

3.1 | New developments and technologies

Several next generation AIT concepts possibly rely on recombinant or synthetic proteins or DNA rather than biological allergen extracts for their active ingredients. After identification of a large number of potentially interesting genome sequences or major allergens, the resulting candidates are then tested extensively by in vitro assays and selected animal models to give information about their allergenicity and immunogenicity.

The concept of peptides, B or T cell targeted, showed conflicting results.[34-36] Whereas use of small T-cell peptides has demonstrated evidence of efficacy at phase II in environmental chamber studies, these have not translated into success at phase III in trials of T-cell peptide immunotherapy for cat or mite allergy (Circassia press release, unpublished). The development of recombinant allergen linear B-cell peptides is still under investigation and has not been finally evaluated. According to current knowledge, medium chain hydrolyzed peptides have shown efficacy at phase III, but comparison with currently available effective extracts are required. Recombinant linear peptides that selectively promote IgG rather than IgE antibody responses are currently in development[36] and have shown evidence of modest efficacy accompanied by IgG antibody responses, marked decreases in IgE and selective increase in IL-10 production in peripheral blood mononuclear cultures.

A number of companies have tested recombinant (Bet v 1, a cocktail of Phl p 1, 2, 5.01, 5.02 and 6) or hypoallergenic recombinant allergens (rBet v 1 folding variant (FV)) in rhinitis/ rhinoconjunctivitis with or without asthma. The concept involves replacement of the crude extract by the relevant major allergens with a view to patient-tailored therapy. The expectation was better efficacy due to defined high amounts of relevant components in equimolar concentration avoiding potential new sensitization to further components due to high allergen concentrations. After promising in vitro data[37] and good safety profiles in dose range finding trials[38,39] these products showed clinical effect in some of the phase III trials,[40-43] but not in others (Tables 4 and 5). Furthermore, the successful trials have not shown overall treatment effect sizes that were greater than those achieved with conventional extracts and more comparative head to head trials are needed. Nonetheless benefit of shortened treatment regimens compared to those with conventional extracts were achieved.[38]

A recognized problem with AIT products during the marketing application process is the difficulty of replicating results of phase II studies in multinational, multicentre phase III trials with different endpoints.[44] So, the proof of concept for AIT with recombinant allergens in patients with rhinitis/ rhinoconjunctivitis with or without asthma could be shown and a single hypoallergenic recombinant birch allergen (rBet v1 FV) could replace a complete extract.[40,42]

TABLE 4 Overview on clinical results in studies conducted by Allergopharma with a recombinant hypoallergenic Bet v 1 folding variant (Nandy A, FASIT 2019)

Study code/Publication	Year	Phase of study	Tested dose/No. of patients	Results primary endpoints	Results secondary endpoints; clinical parameters
AL0303rB[42]	2003-2005	II	Active comparator* n = 24 Active (80 µg) n = 27	SMS: both treatments effective compared to baseline evaluation in study AL0103rB in same centres; recombinant treatment effect more pronounced in year 1; similar treatment effect in year 2	NPT ↑
AL0103rB[40]	2003-2010	III	Placebo n = 98 Active (80 µg) n = 104	SMS ↑	SMS (1st year) ↔ VRS ↔
AL0702rB Study report EudraCT 2007-001029-84	2007-2010	III	Placebo n = 127 Active (80 µg) n = 128	SMS ↔	RC-SMS ↔ RQLQ ↔ CPT ↔ Well days ↓ RC well days ↔
AL0903rB[39]	2010-2011	II	Placebo n = 6 Active (20 µg) n = 6 Active (80 µg) n = 6 Active (160 µg) n = 6 Active (320 µg) n = 8	ICT – no result (only 6 of 32 patients showed an ICT reaction)	In AEC: TSS ↑ TNSS ↑ TNNSS ↑ TOSS ↑

SMS: Symptom medication score; TNNSS: Total non-nasal symptom score; TNSS: Total nasal symptom score; TOSS: Total ocular symptom score; TSS: Total Symptom Score; CPT: Conjunctival provocation test; ICT: Intracutaneous provocation test; NPT: Nasal provocation test; RQLQ: Rhinitis quality of life questionnaire; VRS: Visual rating scale; AEC: allergen exposure chamber; RC: rhinoconjunctivitis. Symbols: ↑ statistically significant superiority of active treatment; ↔ trend in favour of active treatment but no statistical significance; ↓ no effect of active treatment; *active comparator: Novo-Helisen® Depot Birch Pollen, Allergopharma GmbH & Co. KG, Reinbek.

TABLE 5 Overview on clinical results in studies conducted by Allergopharma with a recombinant 5 Phleum allergens cocktail (Nandy A, FASIT 2019)

Study code/Publication	Year	Phase of study	Tested dose/No. of patients	Results primary endpoints	Results secondary endpoints; clinical parameters
AL0301rP[41]	2002-2003	II	Placebo n = 28 Active (40 μg) n = 29	SMS (FAS) ↔	SMS (PP) ↑ RQLQ ↑ CPT ↔
AL0403rP	2004-2006	III	Placebo n = 98 Active (40 μg) n = 103	SMS (FAS) ↓	VRS ↔
AL0701rP[38]	2007-2008	II	Placebo n = 10 Active (20 μg) n = 10 Active (40 μg) n = 10 Active (80 μg) n = 10 Active (120 μg) n = 10	Safety: all doses well tolerated	CPT ↔
AL0704rP Study report EudraCT 2007-003208-37	2008-2012	III	Placebo n = 84 Active (80 μg) n = 86 Active (120 μg) n = 86	RC-SMS (FAS; 2nd year) 80 μg ↓; 120 μg ↔	CPT 80 μg ↔; 120 μg ↑ RQLQ 1st year 80 μg ↑; 120 μg ↑ RQLQ 2nd year 80 μg ↔; 120 μg ↑ Well days 80 μg ↔; 120 μg ↔
AL0906rP Study report EudraCT 2009-011504-36	2010-2013	III	Placebo n = 102 Active (120 μg) n = 90	ma-RC-SS (FAS; 2nd year) ↔	CPT ↑ ma-RC-SS (2nd year; adults) ↑ RC-SS (2nd year) ↔

SMS: Symptom medication score; RC: Rhinoconjunctivitis; ma-RC-SS: Medication adjusted RC-Symptom Score; CPT: Conjunctival provocation test; RQLQ: Rhinitis quality of life questionnaire; VRS: Visual rating scale; PP: Per protocol set; FAS: Full analysis set. Symbols: ↑ statistically significant superiority of active treatment; ↔ trend in favour of active treatment but no statistical significance; ↓ no effect of active treatment.

During the last years, the regulatory situation concerning personalized approaches has changed a lot and new doors are open now: Regulators have learned from oncology where single molecules are produced according to Good Manufacturing Practice (GMP) and mixed afterwards for a single patient (personalized medicine) often applied within basket and umbrella studies.[45] Similar approaches in the field of allergy now hypothetically seem possible from a regulatory point of view. According to the participants, a "toolbox" of molecules of reduced allergenicity and increased immunogenicity would be very interesting, if they could be mixed according to the sensitization profile of a single patient. To prove, not only sensitization but also the clinical relevance of the molecules it should also be possible to use them individually for diagnosis and provocations tests. Modified recombinant allergen derivatives might be of interest and are currently in clinical development for peanut allergy for example.[46]

Adjuvants act as enhancers or potentiators of AIT and are very important. The current adjuvants like aluminium salts (alum) are widely used. Adjuvant selection needs a new mindset and according to the participants adjuvants from the vaccine field may not be optimal for the intended immunological modification in allergic diseases and need to be individually investigated. The goal is to induce suppression of inflammation and induction of tolerance. But a strong unspecific adjuvant might be problematic from the regulatory point of view because of the possible safety issues (ie severe adverse events with "Swine Flu"). With regard to virus-like particles (VLPs), the question arises whether the immune deviation pathway is sufficient for tolerance.[47]

Other concepts like combination treatments, passive immunization or antibody approach need further evaluation. Prophylactic vaccination might be possible as well, that is, HDM allergy prophylaxis in infants and children at high risk of allergy. Clinically, first attempts with AIT have not been successful.[48,49]

The prerequisites for entering clinical trials are good preclinical data, in vitro models, and proof of concept before entering the clinical development phase using good patient selection. Provocation tests in AR might be useful,[50,51] as well as phenotyping/endotyping to randomize the right patients. Furthermore, it might be possible to combine phase I and proof of concept trials in one study.

3.2 | Conclusion/outlook (domain II)

Biomarkers and improved diagnostic techniques which help to identify the likely best responders to a particular intervention would be preferable, and new therapeutic antigens and formulations which might help to optimize the patient's response are desirable. Both these targets need further research. Future pathways for AIT development include targeted prevention and biomarkers to select patients most likely to respond and predict success of AIT after 3 years.

Key message 2

Future pathways for AIT development include targeted prevention and biomarkers to select patients most likely to respond and predict success of AIT after 3 years.

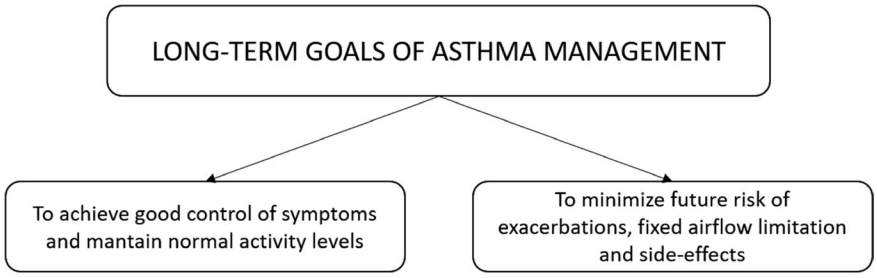

FIGURE 5 Goals of asthma management (based on ref.[2])

4 | AIT AND ASTHMA—A BREAKTHROUGH? (DOMAIN III)

4.1 | What generated the mind change?

According to the GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION (known as the GINA guidelines),[2] the long-term goals of asthma management are to achieve good asthma control and minimize future risk (see Figure 5). It is also important to consider the patients' own goals regarding their asthma, as these may differ from conventional medical goals.

The available asthma therapy of reliever and controller treatment is very effective in the majority of cases, but prevention can neither be achieved with reliever nor with controller treatment and preventive approaches are not well established.

Recent data from AIT in HDM allergic asthma from phase II[52] and phase III trials[53] have led to a revision of the GINA guidelines.

With regard to the inclusion criteria (see Box 2) and the 31%-34% reduction in moderate/severe asthma exacerbations during the time of inhaled corticosteroid (ICS) reduction in the HDM AIT-treated groups,[53] a relevant respiratory clinical parameter, convinced the respiratory specialists that HDM AIT can maintain (some) of the anti-inflammatory (controller) effects of ICS in allergic asthma, can improve control of asthma with AR and should be considered as add-on treatment for HDM-driven allergic asthma phenotype with concomitant AR.

According to GINA 2018[2] AIT may be an option if allergy plays a prominent role, for example asthma with ARC. Considerations for subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) in allergic asthma are as follows:

SCIT: In patients with asthma and allergic sensitization, the majority of SCIT studies included in a Cochrane review showed that SCIT is associated with a reduction in symptom scores and medication requirements and improved allergen-specific and non-specific airway hyper-responsiveness.[54] Adverse effects include uncommon systemic anaphylactic reactions or severe bronchospasm which may both be life-threatening.

SLIT: Another Cochrane review and a meta-analysis on sublingual immunotherapy in allergic asthma found modest benefits in adults and children when added to low-dose ICS.[55,56] A study of HDM SLIT in patients with HDM-allergic asthma and rhinitis demonstrated a modest reduction of ICS with high-dose SLIT.[52] In patients sensitized to HDM, with AR and persistent asthma requiring ICS, with FEV1 > 70% predicted, SLIT for HDM showed benefit in decreasing mild to moderate asthma exacerbations.[53] In such patients with exacerbations despite taking Step 2 therapy, SLIT can be considered as an add-on therapy (Evidence B). Adverse effects include mild oral and gastrointestinal symptoms.[55]

Box 2 Relevant inclusion criteria and demographic data in Eudra CT 2010-018621-19 study design.[53]

Mean duration of asthma: 13 years
66% sensitized to other allergens in addition to HDM
Use of inhaled corticosteroids (ICS) as listed in GINA-guidelines step 2-4 (ICS dose after switch: budesonide 400–1200 μg)
Documented reversible airflow obstruction (no hyper-reactivity test)
Level of asthma control corresponding to "partial control" at randomization
Asthma Control Questionnaire (ACQ) Score 1.0-1.5
72% had partially controlled asthma and 28% had uncontrolled asthma as defined by GINA guidelines at randomization

4.2 | Data in children

One in seven children suffers from asthma.[57] In a randomized placebo-controlled trial in 3-16 years old grass pollen-allergic asthmatics,[58] a significant reduction in symptom medication score ($P < .04$), as well as a significant reduction in bronchial allergen reactivity ($P < .01$) after SCIT (Roberts G. FASIT 2019) could be observed. A systematic review[4] supported these findings so that it can be concluded that grass AIT is effective in paediatric asthma and pooled safety data from 38 studies (SCIT = 29, SLIT = 9) have shown that it is also safe (Roberts G, FASIT 2019). But guidelines give a biased view of modern AIT therapy in asthmatic children. The reason might be that guideline methodology is often based on systematic review of all literature including older studies using inferior products and study designs. There is a need for more evidence using modern endpoints like asthma control or exacerbations and to rethink the approach to AIT guidelines and take a

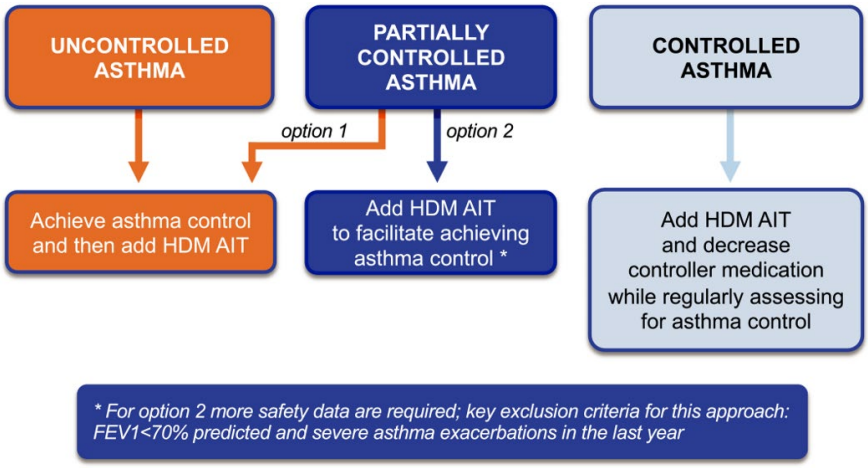

FIGURE 6 Integration of house dust mite (HDM) allergen immunotherapy (AIT) in the stepwise management of HDM-driven allergic asthma based on the level of asthma control.[59] Copyright 2019. Reprinted with permission from Wiley

product-specific approach to appraise the evidence before making guideline recommendations.

4.3 | EAACI asthma guideline

The EAACI guidelines for HDM AIT for allergic asthma have recently been published.[59] A GRADE assessment of the existing evidence of HDM AIT in asthma was used complemented by individual assessment of major randomized controlled trials (RCTs), previous meta-analyses for HDM AIT in asthma and open studies, real-life and observational studies and surveys.

HDM SCIT is recommended for children and adults with controlled HDM-driven allergic asthma (Figure 6) as an add-on treatment to regular therapy to decrease symptoms and medication use (conditional recommendation, low-quality evidence) as well as to decrease allergen-specific airway hyperreactivity (AHR) and to improve quality of life (QoL) (conditional recommendation, low-quality evidence).[59] According to the participants of the workshop, SCIT products with proven evidence for this effect as demonstrated in marketing authorisation application (MAA) studies should preferentially be used.

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.[59]

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).[59] According to the participants of the workshop, SLIT-drop-products with proven evidence for this effect as demonstrated in MAA studies should preferentially be used.

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).[59] According to the participants of the workshop, SLIT-tablet-products with proven evidence for this effect as demonstrated in MAA studies should preferentially be used.

HDM should be the major driver of asthma symptoms and control, and well-characterized vaccines with proof of efficacy should be used. It is axiomatic that demonstration of efficacy with a single allergen extract should not imply a "class" effect and each individual product should be subjected to an evidence-based evaluation prior to use in clinical practice. Box 3 describes what is expected from HDM AIT in HDM-driven allergic asthma. Patients with HDM-driven allergic asthma and concomitant AR will benefit following HDM AIT from treatment of both the upper and lower airways; thus, the association of AR is a strong recommendation for HDM AIT in controlled allergic asthma. Neither atopic dermatitis nor food allergy is contraindication for HDM AIT in asthma.

Box 3 HDM AIT expected impact when added to regular controller treatment for integrated HDM-allergic asthma management (Agache I, FASIT 2019).

HDM AIT should be integrated in the general frame of HDM-allergic asthma management aiming to:
Reduce symptoms
Improve QoL
Improve asthma control
Minimize future risk by:
Decreasing exacerbation rate,
Improving lung function (including AHR),
Decreasing adverse reactions to medication (steroid and beta-2 agonist sparing effect)

4.4 | Meaningful endpoints in AIT asthma studies

Established and standardized outcome measures are required. The aim of AIT includes long-term remission and future risk reduction as well as improvement in symptoms and reduced requirements for medications. Clinically relevant endpoints in AIT for allergic asthma trials include the following:

- Future risk reduction
- Exacerbation frequency or better "time to first exacerbation" (ensures that participants are counted only once for the primary study endpoint)
- Quality of life
- Symptom score/medication reduction (composite score)
- Reduction of inhaled and oral corticosteroids
- FEV_1 is not a good marker of efficacy; however, the effect on specific AHR and on small airways disease in asthma should be considered.

Trials of AIT in asthma prevention are necessary. Those trials could use a step-down design with exacerbations or asthma control as clinical parameters. HDM is the best allergen for these trials because it is the gate keeper for asthma induction. Multi-sensitization and AIT to other allergens do not influence the clinical outcome.[53]

From the view of competent authorities, a good study design with a clear rational and seeking for combined advice of medical agencies and Health Technology Assessment (HTA) bodies would be the best way forward.

4.5 | Conclusion/Outlook (domain III)

New data from double-blind, randomized, placebo-controlled AIT trials in HDM-allergic asthma patients with convincing respiratory parameters has led to an update of the GINA 2018 guideline and the EAACI asthma guidelines. Patients with HDM-driven asthma and AR will benefit from HDM AIT for both the upper and lower airways; thus, the association of AR is a strong recommendation for HDM AIT in controlled allergic asthma, considering that prevention can neither be achieved with current asthma treatment of reliever or controller treatment.

Key message 3

AIT trials in HDM-allergic asthma showing a reduction in moderate/severe exacerbations, a decrease in inhaled corticosteroid use in the HDM AIT-treated groups and an improvement in relevant respiratory clinical parameters have led to an update of the GINA 2018 guideline and the EAACI asthma guideline. The association of AR is a strong recommendation for HDM AIT in controlled allergic asthma.

5 | REGULATORY PREREQUISITES IN AIT: TEN YEARS OF THERAPY ALLERGEN ORDINANCE AND OUTLOOK IN THE EUROPEAN UNION (DOMAIN IV)

According to the European Directive 2001/83/EC, products for AIT are medicinal products (drugs) and require individual marketing authorizations (MAs). MAs are granted on the basis of proven quality, efficacy and safety according to current state of knowledge.[60,61] This directive and the "Therapy Allergen Ordinance" (TAO) in Germany, with the aim to ensure that the quality, efficacy and safety of specific frequent therapeutic allergens (sweet grasses w/o maize, birch/alder/hazel, HDM, bee/wasp venom) are documented and assessed in a marketing authorization procedure, have changed—and will continue to change—the environment in AIT (Figure 7).

In the two-step process of TAO deficiency letters, all quality letters were sent, and responses were received and are under review; all clinical letters were sent (thereof last in April 2018) and 45 responses were received and are under review.

Frequent quality deficiencies of TAO products are lack of comparability of the drug due to extensive changes in the manufacturing process during the clinical development programme; insufficient or missing stability data and process validation, analytical methods not or insufficiently validated; internal reference preparations (IHRP) not suitable for ensuring consistent quality and strength of the medicinal product and specifications and/or in-process controls inadequate or not in concordance with applicable requirements.

Twenty-eight clinical studies are completed for TAO allergens, 16 dose-response finding studies (DRF), 7 phase III studies and 25 study reports have been submitted to the Paul-Ehrlich-Institut (PEI). In the DRF studies, the market dose showed positive benefit/risk balance but was not always the "optimal" dose. In 7 cases, a higher dose showed a better benefit/risk balance, and in 9 cases, the results were not clear. If no efficacy was demonstrated in clinical studies, the PEI declined further batch release until the MA can be rejected (Figure 8).

With the TAO, the quality of AIT products increased, firstly, due to a reduction in the number of nonlicensed mixtures of questionable efficacy (eg mixtures of seasonal and perennial allergen sources), and secondly, more products are optimally dosed based on scientific evidence reviewed by the authorities. Marketing authorizations are always granted based on the current state of scientific knowledge at time of approval. Therapeutic allergens with active MAA under the development programme of the TAO are legally marketable in Germany. Rare therapeutic allergens are still available without the need for MA. New applications for MA for diagnostics are very rare and existing MAs are frequently withdrawn by the manufacturers—mainly concerning rare allergen sources. In order to keep existing diagnostics for rare allergen sources available on the German market, a fee reduction to a quarter for all official acts of the federal agency in connection with rare test allergens is granted upon application by the pharmaceutical companies.

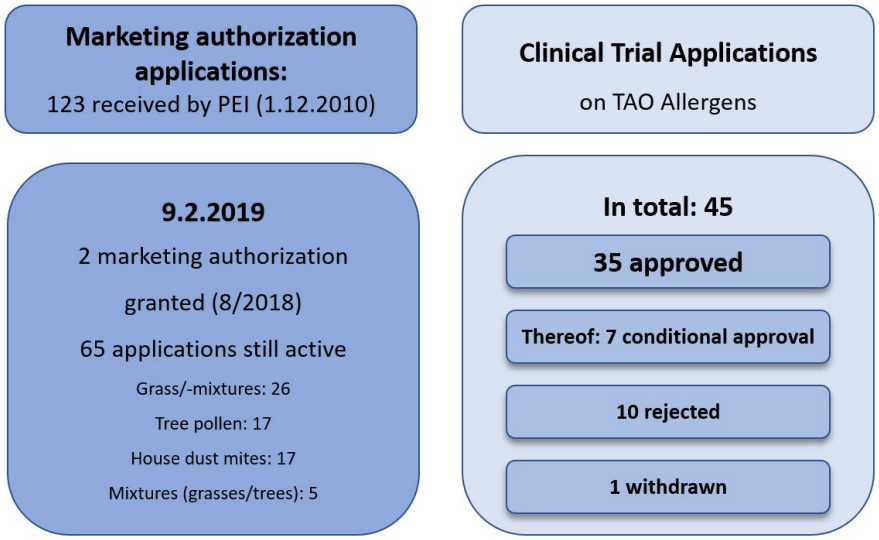

FIGURE 7 Therapy Allergen Ordinance (TAO) in Germany. Status marketing authorization and clinical trial applications 02-2019 (Mahler V, FASIT 2019). PEI: Paul-Ehrlich-Institut

In the EU, the authorities are working together within two guideline projects (i) to define scientifically, that is what is a rare allergen in a special region and (ii) the regulatory requirements for rare versus frequent allergens; corresponding position papers are in preparation. While the TAO strengthens the evidence level of existing products and their indications, the quality and clinical requirements represent a high workload and expenditure for companies, and also bear the risks of product failure.

5.1 | Conclusion/Outlook (domain IV)

TAO led to a reduction in the number of therapy allergen preparations, especially mixtures of questionable efficacy. A new generation of allergen therapy products may result, often of higher dosage than before, and first MA were granted for two TAO products in 08-2018. Products which failed to prove efficacy are no longer released in batch testing. The European harmonization is being sought and for rare allergen sources individual formulations are still useful and important.

Key message 4

The Therapy Allergen Ordinance led to a new generation of AIT products, often with higher dosage than before, and the first MA was granted for two TAO products in 08-2018.

6 | CLINICAL TRIAL DESIGN IN AIT TRIALS: INNOVATION THROUGH HARMONIZATION (DOMAIN V)

6.1 | Endpoints in rhinoconjunctivitis AIT trials

According to the European Medicines Agency (EMA) "Guideline On The Clinical Development Of Products For Specific Immunotherapy For The Treatment Of Allergic Diseases",[62] the primary endpoint in phase III pivotal rhinoconjunctivitis AIT studies has "*to reflect both symptom severity as well as the intake of*

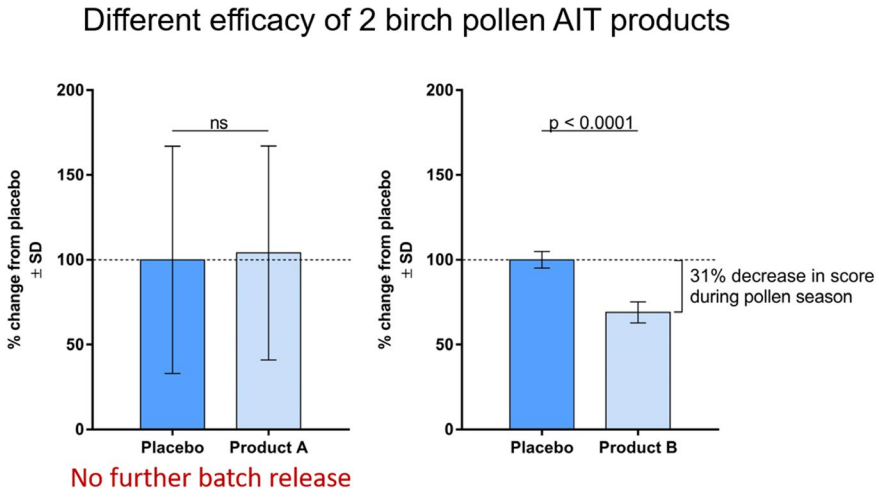

FIGURE 8 Results of phase III studies of 2 birch products in the same birch pollen season (Mahler V, FASIT 2019). AIT: allergen immunotherapy

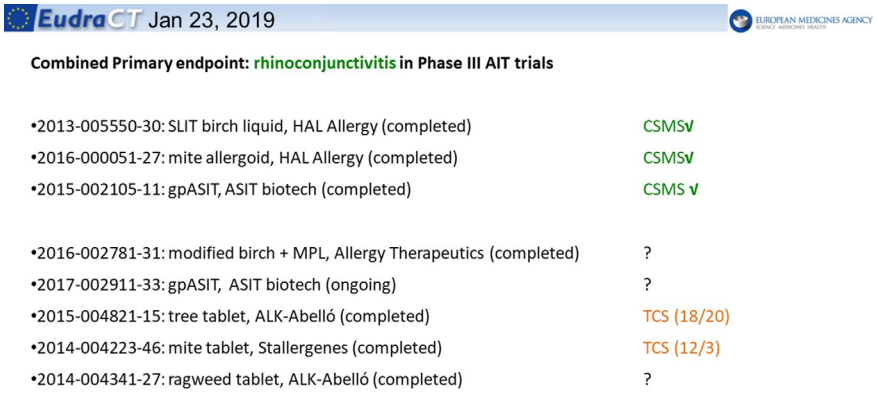

FIGURE 9 Combined symptom and medication score (CSMS) and total combined score (TCS) in phase III allergen immunotherapy (AIT) trials (Pfaar O, FASIT 2019)

rescue medication," because rescue medication has an impact on symptom severity. The method to combine both scores has to be *"pre-specified and justified."*

But up to now only one company has prospectively validated a Rhino-Conjunctivitis Allergy-Control Score© (RC-ACS©)[63] and an Allergy-Control-Score© (ACS©)[64] for rhinoconjunctivitis plus asthma, showing a significant correlation between RC-ACS© and the global severity of allergy (r = 0.691; P < .0001), quality of life (r = 0.757; P < .0001), allergy-related medical consultations (r = 0.329; P = .0019), a good retest reliability (r = 0.813; P < .001) and discriminating capacity between allergic patients and healthy controls, with a sensitivity of 93.8% and a specificity of 92.5% at a score value of 0.786 and good feasibility. Otherwise, combined symptom medication scores (CSMS) are not validated and different primary endpoints are currently used in clinical phase III trials[65] with huge heterogeneity.[3] This heterogeneity in approaches used to assess outcomes limits the comparability of clinical data.[44] Meta-analyses use random-effects modelling and pooled data using standardized mean differences, which can be difficult to interpret[3]; it is not possible to pool data from all trials or undertake all the planned subgroup analyses.

To overcome these problems, an EAACI taskforce proposed a CSMS for trials on AIT in ARC with a homogeneous terminology for nasal and conjunctival symptoms using the six organ-related categories in the daily symptom score (dSS), a stepwise use of rescue medication summed in the daily medication score (dMS); the CSMS is based on an equal weight of the dSS and of the dMS: CSMS = dSS (0-3) + dMS (0-3) = 0-6.[66] This score has already been used successfully in clinical rhinoconjunctivitis trials (see Figure 9)[67,68] and a strong positive correlation with the RQLQ-S during pollen season (r = 0.68; P < .0001) could be shown in preliminary post hoc analyses.[69]

The EAACI CSMS for rhinoconjunctivitis is standardized and harmonized, but study results could differ if different scores were used, so that there is a clear unmet need of a prospective validation of this standardized endpoint (see Box 4).

The participants discussed what might convince regulators to authorize an AIT product and agreed that a validated endpoint is required. Maybe a validated tool can be used as anchor or post hoc analyses of existing data can be used. The use of oral corticosteroids in the medication score of CSMS should be deleted. The rationale for this recommendation is that oral corticosteroids are taken only very rarely in trials of ARC such that the effective medication component of the CSMS is 0-2 and not 0-3 as originally intended, thereby reducing the impact of medication use in the CSMS. Pragmatically, the group felt that the combined use of a corticosteroid and an antihistamine or a combination topical corticosteroid/antihistamine should score 3 and the occasional use of oral corticosteroid recorded but not included in the rhinoconjunctivitis CSMS. Other possible clinical parameters should be investigated to find the best tool to show efficacy of AIT in clinical trials.

The optimal outcome parameters are likely to be different in children and adults, an important factor for PIP (paediatric investigational plan) trials. For example, a CSMS in 6- to 9-year-old children performed by the parent might not be valid and could be replaced by a visual analogue scale (VAS) completed by the child and the parent independently.[70] Regulatory authorities would accept other plausible parameters as well if clinical benefits could be shown. Looking at group mean differences at the end of trial is critical, a better approach might be having a baseline and looking at changes in the different groups so that changes for an individual patient can be seen, a more relevant parameter; but a placebo group is still needed, because of the individual season as confounder in trials without placebo.

Box 4 Unmet needs for further validation of primary endpoints (Pfaar O, FASIT 2019).

- Anchor based? Which (validated) endpoint to use as anchor?
- Reliability and reproducibility
- Discrimination capacity
- Feasibility
- Hybrid endpoints, for example subjective scores with objective parameters/biomarkers

Consideration should be given to using within-individual absolute differences rather than results expressed as % changes. However, comparisons of absolute differences are only relevant if identical scoring systems are employed so use of both approaches is complementary.

6.2 | Treatment effect in rhinoconjunctivitis AIT studies

In AIT trials, the minimal clinically important difference (MCID) is subject to ongoing discussions based on a WAO taskforce statement published in 2007; this relevant efficacy should be at least 20% or higher than placebo.[71] In 1998, the so-called "Malling criteria" for rhinoconjunctivitis trials were published[72] on the basis of a study from Varney VA et al[73] proposing ≥ 30% for efficacy. Both statements are empirical and based on expert consensus (ie category D evidence) and therefore unreliable.

The available clinical studies including big studies in patients with rhinitis/rhinoconjunctivitis more likely reflecting real world are very heterogeneous[74-80] with a huge variability and relative scales are used whereas the absolute differences are even more important.

Different factors have an influence on the treatment effect size in AIT (see Box 5) like pretreatment,[81] seasonal variations and different exposure during the study,[82] the sample size and a robust power calculation[83] and the right parameter.[66]

So, the assumptions on relative AIT treatment effects remain arbitrary and the relative effects should always be provided with absolute treatment effects.

6.3 | Placebo effect in rhinoconjunctivitis AIT studies

A placebo is an inert substance without pharmacological effect according to the current state of science, the placebo response is a neurobiological and psychophysical reaction of an individual to a placebo treatment and the placebo response in clinical trials is any change in the placebo arm.[84]

Allergic diseases are fluctuating conditions, in randomly fluctuating conditions it is more likely that one seeks advice when the condition is flaring up or at high level and when the condition is at high level, it is more likely, that it is flaring down by itself (regression to the mean). The endpoints in AIT trials (CSMS) are largely subjective.

A placebo effect is influenced by different factors like the colour of the placebo, the size, quantity, type, brand, price, packaging and geographical region. More invasive procedures and more painful placebos induce higher placebo effects and placebos applied by doctors have higher placebo effects than those applied by nurses.[85]

The placebo effect in AIT rhinoconjunctivitis studies was investigated by different authors [84,86] and showed a high variability. A longitudinal investigation of the placebo effects in AIT trials with comparable designs, different allergens and a baseline year as well as 2 treatment years in each of the trials[84] (see Figure 10) showed a placebo effect of up to 52% and an influence of the allergen exposure in different years on the effect size (low exposure increased the placebo effect, high exposure deceased the effect).

If placebos cannot fully be blinded or contain adjuvants like with SCIT treatment, this could have an influence on the placebo effect as well. So, a high placebo effect in AIT trials is a good indication that the study has been properly blinded.

As learned from pain relief studies, placebos have effects on the immune system and molecular level as well.[87] It might be good to have a group without intervention or to use different allergens in one trial[88] to get more information on the placebo effect. In SLIT trials, placebos with local effects are not available, so a complete blinding is not possible, which may influence the placebo effect and thus on the threshold for effect sizes of SLIT AIT products. In SCIT trials, local effects at the injection side may be produced by adding histamine. There is a clear unmet need of understanding the underlying mechanisms of placebo effects in AIT better by better characterizing psychological, biochemical, immunological, neural and even genomic effects of the placebo response in AIT.[44]

Box 5 Factors influencing the treatment effect size in AIT (Kleine-Tebbe J, FASIT 2019).

AIT treatment effect size depends on:
Severity of disease (eg baseline CSMS in enrolled subjects)
Level of IgE sensitization (skin prick test (SPT)/sIgE)
Expectations, interventional and placebo effect
Allergen exposure
Allergen dose
Duration of pretreatment
Size of the study

6.4 | Conclusion/Outlook (domain V)

The introduction of Directives designed to bring AIT into line with the requirements for pharmacological interventions has met a number of difficulties. Products for AIT must thoroughly meet modern methodological standards for proving quality, clinical efficacy and safety.

In this era of evidence-based medicine, there is a need for validated clinical endpoints and clinically meaningful and validated effect sizes, being reported as relative and absolute changes compared to placebo treatment.

A thorough understanding of (neuro-psychological) placebo effects in AIT will help to better discriminate between the specific

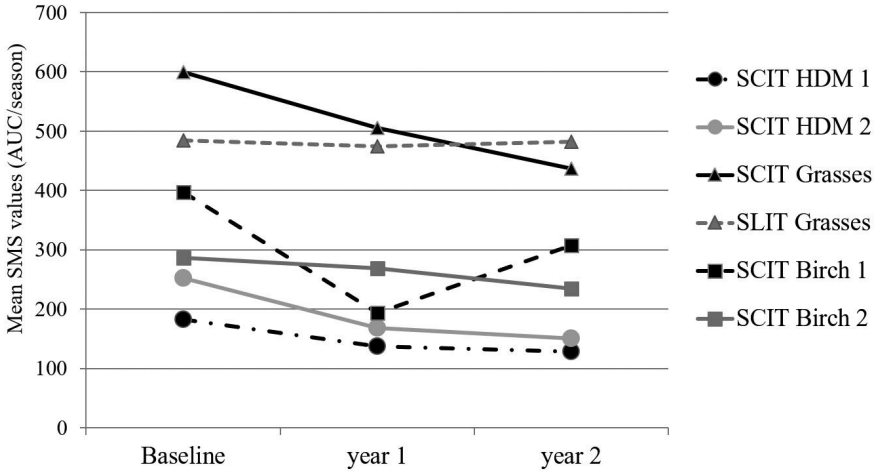

FIGURE 10 Placebo effect in allergen immunotherapy (AIT) trials. Mean area under the curve (AUC) of symptom medication score (SMS) at baseline after the first and the second treatment year in the placebo groups of the different trials.[84] HDM: house dust mite; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy

effects of AIT and unspecified effects. Missing local effects in placebos for SLIT trials may affect blinding.

Key message 5

Products for AIT have to meet modern methodological standards for proving quality, clinical efficacy and safety. Validated clinical endpoints and clinically justified and validated effect sizes and an understanding of placebo effects in AIT are required.

7 | ALLERGEN EXPOSURE CHAMBERS IN AIT STUDIES (DOMAIN VI)

7.1 | The regulatory view

The allergen exposure chamber (AEC) is currently viewed as promising alternative methodology for the evaluation of efficacy in AIT trials. Supportive evidence includes several high-quality phase II AIT rhinoconjunctivitis studies that have demonstrated clear dose-response effects and enabled informative time-to-onset of action information. In the current EMA Guideline on the Clinical Development of Products for Specific Immunotherapy for The Treatment of Allergic Diseases,[62] use of AEC provocation is an acceptable primary endpoint for dose-finding studies (phase II) and an acceptable secondary endpoint in phase III studies. As primary endpoint for phase III rhinoconjunctivitis studies only symptom medication scores based on natural allergen exposure is acceptable to this point. With regard to the US Food & Drug Administration (FDA), the role for AEC was publicly discussed at the meeting for the Allergenic Products Advisory Committee in May 2011.[89] Based on the discussion among committee members, FDA reviewers and representatives of AEC facilities, the FDA has considered AEC rhinoconjunctivitis data for phase II dose ranging and efficacy studies and to support efficacy data from pivotal field studies for two of the four SLIT products recently licensed in the United States. Overall, the FDA and the EMA agree that for phase III studies, AEC data are supportive, but field data are necessary to prove efficacy of a product for AIT.

AECs in phase III trials have pros and cons (for more detail see FASIT 2017 report[14]). Regulatory authorities welcome appraisal of new approaches, although they require proper validation of methodology and comparison with currently used clinical outcomes. For example, aeroallergen levels in AECs are relatively high compared to field exposure (see Table 6) and there is no priming effect of seasonal or even perennial exposure. Field studies under real-world conditions (ie variable pollen counts over time and by region, poly-sensitization, behavioural and environmental factors) may obscure the therapeutic effect of AIT leading to a TYPE II ERROR (false negative), whereas AEC studies have an artificial setting with allergen levels typically greater than natural exposure that might lead to a TYPE I ERROR (false positive). This could be most useful for identifying products with no therapeutic benefit early in clinical development ("if it don´t work in the chamber, it ain´t gonna work nowhere"), but in phase III pivotal trials this might be an issue. To explore optimization in terms of acceptability, safety, power and effect size as part of the validation process of AECs, one should compare high and low level AEC exposures.

An interdisciplinary EAACI task force initiative comprising clinicians, regulators and AEC vendors has been initiated and is working with the different stakeholders to decide which gaps need to be filled and provide a didactic strategy to achieve that.[90] Some clinical validation parameters have already been addressed for AEC units and technical validation parameters for different AECs worldwide have been published by several groups,[91-93] but full clinical validation of AEC study outcomes is required for their classification as an appropriate alternative to natural allergen exposure for AIT product efficacy assessment.[90] The reliability of provoked symptoms in repeated AEC sessions is high, but the predictive power of AEC settings for the clinical response on natural exposure and the impact of seasonal priming on test results still have to be validated, as does the inter-AEC variability.[93] The proof has yet to be delivered that the treatment outcome obtained in the AEC setting correlates with effects found after natural exposure, elucidated whether the magnitude of the treatment effect is biased by the time point of allergen challenge (in-season versus out of season) and which AEC exposure

TABLE 6 Levels of aeroallergen in allergen exposure chambers (AEC) and field (Rabin RL, FASIT 2019)

Aeroallergens levels in AECs compared to the field			
Aeroallergen	**Levels in AEC in facilities worldwide**		**Measure levels in field setting**
Orchard grass pollen	Germany	1000, 2000, 4000, 8000 ± 300 grains/m^3	30 to 170 grains/m^3 in Washington DC from 1998 to 2010 (Kosisky et al, 2010)
Timothy grass pollen	Canada	2500 and 3500 grains/m^3 (Ellis et al, 2015)	
Timothy grass pollen	Austria	1500 ± 120 grains/m^3	
Ragweed pollen	Texas and Canada	3500 ± 500 grains/m^3	20 to 60 grains/m^3 10 000 grains/mm^3 (1967 in NYC)
Birch pollen	Canada	3500 ± 500 grains/m^3 (Ellis et al, 2016)	20 to 400 grains/m^3 (Zhang et al, 2013) 4696 (2014 in Denmark) 4290 (2016 in Alaska)
Der p 1 (major allergen of North American dust mite *Dermatophagoides pteronyssinus*)	Austria Denmark	40 ng/m^3 50 or 100 ng/m^3	15 ng/g (floor in US urban homes) to 30 ng/g (beds in US urban homes) (Morgan et al, 2004)

timing correlates best with natural exposure and confirm reproducible treatment outcomes on repetitive AEC sessions between different AEC facilities applying the same study population and protocol.[93]

A possible way forward might be "Hybrid studies" that integrate field and AEC studies to assess ideally the same population in both settings.[90] Currently, very few phase II hybrid rhinoconjunctivitis studies with SMS and AEC have been performed. It is not required that both approaches show same SMS results, but robust findings like clinically relevant and significant findings in both are necessary which are mutually supportive.

7.2 | Correlation of AEC and field results for pharmacologic agents

Findings from collaborative, parallel studies, one conducted in North America and one in Europe, provide evidence of consistent efficacy for combination of cetirizine + pseudoephedrine between different factors: *AECs*, *patients*, *pollens and exposures*, *In* and *out* of season, *with* and *without* priming (see Figure 11). Results from North America (Cliantha Research, Mississauga, CA, Figure 11A) showed similar, significant treatment effect over placebo both *in* and *out* of season, results from European AEC[94] (Fraunhofer ITEM, Hannover, Germany Figure 11B) showed similar, significant treatment effect over placebo both *in* and *out* of season. Notably, the study in Canada was conducted in ragweed allergic patients in a ragweed AEC while the study conducted in Germany was done in grass allergic patients in a grass AEC. This shows that in different populations North America and Germany, with different seasonal allergies, *with* and *without* priming, and *in* and *out* of season provided for similar improvement in Total Nasal Symptom Scores (TNSS).

As shown in Table 7, studies with nasal antihistamines and corticosteroids using different AECs and comparing the results with field data (shown in parentheses) could prove that results and effect

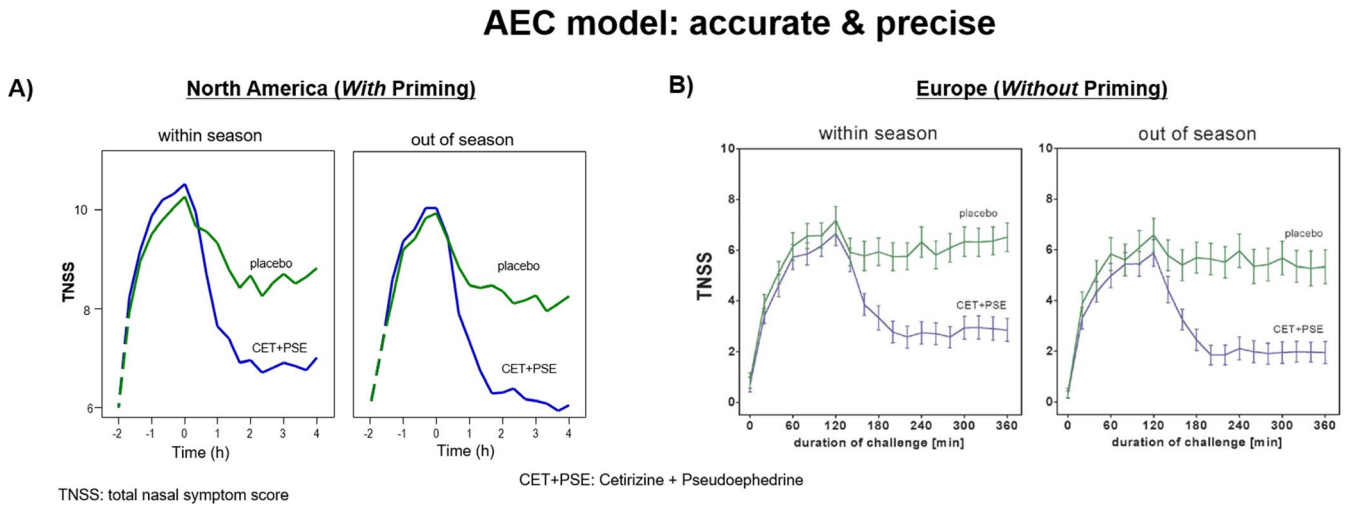

FIGURE 11 Comparison of different allergen exposure chamber (AEC) models: (A) the Canadian AEC using ragweed pollen (Salapatek AM, FASIT 2019); (B) the European AEC using grass pollen (ref.[94]). Reprinted from Ann Allergy Asthma Immunol, 106/4, Badorrek P, Dick M, Hecker H, Schaumann F, Sousa A R, Murdoch R, Hohlfeld J M, Krug N. Anti-allergic drug testing in an environmental challenge chamber is suitable both in and out of the relevant pollen season, 336-341, Copyright 2011, with permission from Elsevier

TABLE 7 Precision and reproducibility using different allergen exposure chamber models and comparability to field data (based on refs.[95-102])

Design (all double-blind, placebo-controlled)	Drug	Maximum mean change from baseline		
		Placebo	Treatment	Treatment difference
AEC Study, TNSS[95] *C-02-37*[96]	Olopatadine 0.4% spray	−2.25 (*−2.5*)	−3.3 (*−3.2*)	1.05 (*0.70*)
	Olopatadine 0.6% spray		−3.5 (*−3.5*)	1.25 (*1.00*)
AEC Study, TNSS[97] *C-93-013*[98]	Mometasone 50 µg spray	−1.5 (*−1.5*)	−2.25 (*−2.3*)	0.75 (*0.8*)
AEC Study, TNSS[99] *Study 401 SAR*[100]	Ciclesonide 200 µg spray	−1.75 (*−1.03*)	−2.25 (*−1.87*)	0.5 (*0.84*)
AEC Study, TNSS[101] *Study MP-4004*[102]	Mometasone 50 µg spray	−2.25 (*−2.45*)	−2.75	0.5
	Azelastine 137 µg spray		−4.75 (*−4.23*)	2.5 (*1.78*)

Comparable effect sizes for nasal spray antihistamines and corticosteroids in the AEC compared to the field (shown in parentheses).

TNSS: total nasal symptom score; SAR: seasonal allergic rhinitis.

sizes were remarkably similar and reproducible over multiple studies, chambers and field data. Similar comparative studies for AIT trials would be informative.

7.3 | Correlation of symptoms in the AEC and the field (no treatment)

A study performed in 2014-2015, grass allergy season in Mississauga, Canada (Clantha Research, *data-on-file*) for grass allergic patients including 100 grass allergic and 20 nonallergic patients was conducted in two parts. The first part was to study the patients for one entire grass season both in the AEC and the field. Patients reported on their TSS in the AEC and CSMS in the field. A moderate and significant correlation was seen of $r = 0.31$ and $P < .05$. It was postulated that there were many instances where patients had much less symptoms in the field than in the chamber and particularly for those patients who spent little time outdoors or had low grass pollen exposure in their everyday lives.

As might be expected, the correlation between AECs results and field data is markedly influenced by the hours that patients spent outside and accordingly the level of exposure. It is expected that those patients who are spending more time indoors in an air conditioned environment might have a lower exposure to pollen than a patient who works outdoors. This was supported by an AEC study performed in Mississauga, Canada (Clantha Research) in which the same grass allergic patients were studied in both the AEC and in the field. Patients were provided with the same ePRO device used in the AEC as in the field. Patients were also asked to report on the number of hours that were spent outdoors. For those patients who reported less than 3 hours outdoors, there was a low correlation (nonsignificant) between their symptom scores at home (in the field) and their symptom scores in the AEC ($r = 0.2131$; $P > .05$), whereas in the same study, there was a strong correlation which was highly significant between TSS recorded in the AEC and the field for those patients who spent greater than 3 hours outdoors ($r = 0.51$, $P < .0001$).[103]

7.4 | Correlation between symptoms recorded in the AEC and the field (after treatment)

7.4.1 | AIT for grass pollen allergy

In a recently completed phase II dose-finding trial in grass pollen-allergic patients with a sublingual liquid *Phleum pratense* extract performed in Mississauga, Canada, a *post hoc* analysis assessing the correlation between patient reported post-treatment TSS as assessed in an AEC and the CSMS in the field as proposed by the EAACI task force during grass pollen season, showed a strong positive and statistically significant correlation between the CSMS during the pollen season in the field and the TSS in the AEC ($r = 0.62$ and $P < .0001$).[104]

7.4.2 | AIT for house dust mite allergy

In a meta-analysis of a double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of intradermal HDM AIT the total rhinoconjunctivitis symptom score (TRSS) over the course of each AEC session was compared to symptoms collected in the morning and in the evening over two weeks at home and showed a correlation of $r = 0.56$ and a highly significant result ($P < .0001$) for the total nasal symptom score (TNSS) and an even better correlation for the TRSS ($r = 0.79$, $P < .0001$) when the TRSS maximum scores were compared in the field and AEC. Looking at the single components "itchy nose," "itchy eyes," "watery eyes," "red eyes" and "ear/palate itching" all had a $r \geq 0.60$, $P < .0001$.[105]

So, in grass pollen allergy the CSMS correlates highly with AEC TSS, time spent outdoors is important information to make comparisons possible, and in HDM allergy a high correlation between AEC and field could be observed. The comparison variables need to be carefully considered, symptom max. may be more helpful and tools to ensure compliance to treatment and symptom reporting are required.

7.4.3 | Missing link for market authorization

In the discussion how to provide the missing links for market authorization via AEC studies, it is important to think about: "*What is necessary for clinicians?*", "*What is doable?*", "*What is acceptable for patients?*" and "*What is necessary for regulators?*" The participants touched different topics: Maybe the EAACI could provide a platform for the hybrid study and different companies can perform the study together? Or the "*Innovative Medicine Initiative*" of the European Federation

of Pharmaceutical Industries and Associations (EFPIA) could be involved and regulatory authorities should give advice. One AEC could be validated first and other AECs could come on board later. The first step is to publish all available validation data in a position paper.

For ocular drugs, the FDA accepts AECs data without field studies. In contrast, for AIT products field studies are required and AEC data are supporting information. A possible approach in the EU for the acceptance of AECs in phase III trials could be providing convincing data (before possibly an update of the existing guideline for clinical development of AIT products could be discussed); for example, in case of one pivotal study (CSMS in the field) with compelling results and one AEC study with similar results a national advice could be requested, then EU advice in different countries, to find out whether in the specific case this can exceptionally be accepted for MA (instead of a second pivotal study).

7.4.4 | Possible hybrid study designs

After discussion in different working groups, the participants provided potential study designs for a potential hybrid study in patients with rhinoconjunctivitis as formerly requested by the task force Position Paper.[90] The consensus expert proposal suggests the following two solutions: (1) A dose-finding trial in the AEC with half-log increments (for example 3 active arms with target maintenance doses of 2, 6 and 20 µg major allergen). Such a trial should also include a placebo arm in parallel. In a single trial this should enable determination of the optimal dose ('don't miss the peak') whilst evaluating safety at higher doses. Symptoms could be evaluated before and after the AEC challenge along with measurements of biomarkers and the results compared in the same individuals during the natural pollen season. The study could be powered for equivalence or noninferiority, but a good clinical difference versus placebo should be shown in both parts of the study and the study needs maximal power to detect a difference to see good results. If the pollen count was too low, the study could run for a second season; (2) A 1-year (predefined option for second year) study incl. biomarker analysis. If the dose is known, one could start immediately with study 2. Study 2 has a placebo arm and the primary endpoint is CSMS in the field (information about hours outside, adjustment for pollen count, e-diary) and symptoms over 6 hours for the AEC at start (after placebo run-in) and end of trial.

The proposed trial designs will be discussed in advance with input from regulatory authorities. During this session, the participants were asked to vote if they would prescribe a preparation with efficacy proven only by allergen exposure chambers (AECs). 69% of the experts voted with "yes" and 31% with "no"; after discussion, the values were even higher: 73% "yes," 27% "no."

7.5 | Conclusion/Outlook (domain VI)

The AECs are a promising tool for the evaluation of efficacy. Some validation data are available and comparisons and reproducibility studies as for pharmacologic agents could be applied to trials of AIT.

An interdisciplinary EAACI task force including clinicians, regulators, patients and AEC vendors has been initiated and it is planned that the available data and unmet needs will be the topic of a position paper. Hybrid studies are necessary, and a possible design was proposed by the experts.

Key message 6

The allergen exposure chamber is seen as a promising tool for the evaluation of efficacy of AIT.
In order to assess whether AECs represent a valid endpoint for phase III trials of AIT, reproducibility studies and hybrid studies (AEC versus field) should be performed.
The design should include all stakeholders, including representatives from regulatory authorities, industry and patients.

8 | CONCLUSIONS AND UNMET NEEDS FOR THE FUTURE

The FASIT Workshop 2019 provided a platform for extensive discussion and debate among representatives of all stakeholders in the field of AIT, with global representation. Topics covered included biomarker research, regulatory issues, progress of AIT trials in AR and asthma and future strategies to improve AIT. Clinical topics in AIT research included study endpoints, effect size, placebo effect and the use of AECs in clinical development. The workshop highlighted the EAACI guidelines for HDM AIT in HDM-driven allergic asthma. This supplement provides insights into those discussions, highlights unmet needs and possible solutions for the future.

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FASIT participant contributions: MJ, JKT, OP, CBSW, MVK and PZ developed the topics to be discussed during the FASIT meeting and proposed the experts to participate in the meeting. CAA, CBSW, IA, MJ, OP, SV, RLR, PZ, and UW chaired the two half-day sessions of the FASIT meeting. MHS, GR, JKT, SRD, PH, and SV chaired the five panel discussions. SRD, AMC, CAA, HR, MJ, IA, JCV, GR, AN, CBSW, VM, OP, LK, JKT, RLR, AMS, and CW gave introductory lectures to the topics to be discussed during the meeting. CAA, AMC, SRD, MJ, HR, CBSW, IA, RG, MVK, JCV, LK, AN, OP, SV, PZ, JKT, VM, RLR, GJS, FdB, SB, RvR, and AMS took part in the panel discussions.

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