

# Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases

## Key words

allergen-specific immunotherapy; AIT; Hypo-sensitization; guideline; allergen; allergen extract; allergic disease; allergic rhinitis; allergic asthma

S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD)

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## Summary

The present guideline (S2k) on allergen-specific immunotherapy (AIT) was established by the German, Austrian and Swiss professional associations for allergy in consensus with the scientific specialist societies and professional associations in the fields of otolaryngology, dermatology and venereology, pediatric and adolescent medicine, pneumology as well as a German patient organization (German Allergy and Asthma Association; Deutscher Allergie- und Asthmabund, DAAB) according to the criteria of the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF).

AIT is a therapy with disease-modifying effects. By administering allergen extracts, specific blocking antibodies, tolerance-inducing cells and mediators are activated. These prevent further exacerbation of the allergen-triggered immune response, block the specific immune response and attenuate the inflammatory response in tissue.

Products for SCIT or SLIT cannot be compared at present due to their heterogeneous composition, nor can allergen concentrations given by different manufacturers be compared meaningfully due to the varying methods used to measure their active ingredients. Non-modified allergens are used for SCIT in the form of aqueous or physically adsorbed (depot) extracts, as well as chemically modified allergens (allergoids) as depot extracts. Allergen extracts for SLIT are used in the form of aqueous solutions or tablets.

The clinical efficacy of AIT is measured using various scores as primary and secondary study endpoints. The EMA stipulates combined symptom and medication scores as primary endpoint. A harmonization of clinical endpoints, e.g., by using the combined symptom and medication scores (CSMS) recommended by the EAACI, is desirable in the future in order to permit the comparison of results from different studies. The current CONSORT recommendations from the ARIA/GA<sup>2</sup>LEN group specify standards for the evaluation, presentation and publication of study results.

According to the Therapy allergen ordinance (TAV), preparations containing common allergen sources (pollen from grasses, birch, alder, hazel, house dust mites, as well as bee and wasp venom) need a marketing authorization in Germany. During the marketing authorization process, these preparations are examined regarding quality, safety and efficacy. In the opinion of the authors, authorized allergen preparations with documented efficacy and safety, or preparations tradeable under the TAV for which efficacy and safety have already been documented in clinical trials meeting WAO or EMA standards, should be preferentially used. Individual formulations (NPP) enable the prescription of rare allergen sources (e.g., pollen from ash, mugwort or

ambrosia, mold *Alternaria*, animal allergens) for specific immunotherapy. Mixing these allergens with TAV allergens is not permitted.

Allergic rhinitis and its associated co-morbidities (e.g., bronchial asthma) generate substantial direct and indirect costs. Treatment options, in particular AIT, are therefore evaluated using cost-benefit and cost-effectiveness analyses. From a long-term perspective, AIT is considered to be significantly more cost effective in allergic rhinitis and allergic asthma than pharmacotherapy, but is heavily dependent on patient compliance.

Meta-analyses provide unequivocal evidence of the efficacy of SCIT and SLIT for certain allergen sources and age groups. Data from controlled studies differ in terms of scope, quality and dosing regimens and require product-specific evaluation. Therefore, evaluating individual preparations according to clearly defined criteria is recommended. A broad transfer of the efficacy of certain preparations to all preparations administered in the same way is not endorsed. The website of the German Society for Allergology and Clinical Immunology ([www.dgaki.de/leitlinien/s2k-leitlinie-sit](http://www.dgaki.de/leitlinien/s2k-leitlinie-sit); DGAKI: Deutsche Gesellschaft für Allergologie und klinische Immunologie) provides tables with specific information on available products for AIT in Germany, Switzerland and Austria. The tables contain the number of clinical studies per product in adults and children, the year of market authorization, underlying scoring systems, number of randomized and analyzed subjects and the method of evaluation (ITT, FAS, PP), separately given for grass pollen, birch pollen and house dust mite allergens, and the status of approval for the conduct of clinical studies with these products.

Strong evidence of the efficacy of SCIT in pollen allergy-induced allergic rhinoconjunctivitis in adulthood is well-documented in numerous trials and, in childhood and adolescence, in a few trials. Efficacy in house dust mite allergy is documented by a number of controlled trials in adults and few controlled trials in children. Only a few controlled trials, independent of age, are available for mold allergy (in particular *Alternaria*). With regard to animal dander allergies (primarily to cat allergens), only small studies, some with methodological deficiencies are available. Only a moderate and inconsistent therapeutic effect in atopic dermatitis has been observed in the quite heterogeneous studies conducted to date. SCIT has been well investigated for individual preparations in controlled bronchial asthma as defined by the Global Initiative for Asthma (GINA) 2007 and intermittent and mild persistent asthma (GINA 2005) and it is recommended as a treatment option, in addition to allergen avoidance and pharmacotherapy, provided there is a clear causal link between respiratory symptoms and the relevant allergen.

The efficacy of SLIT in grass pollen-induced allergic rhinoconjunctivitis is extensively documented in adults and children, whilst its efficacy in tree pollen allergy has only been shown in adults. New controlled trials (some with high patient numbers) on house dust mite allergy provide evidence of efficacy of SLIT in adults.

Compared with allergic rhinoconjunctivitis, there are only few studies on the efficacy of SLIT in allergic asthma. In this context, newer studies show an efficacy for SLIT on asthma symptoms in the subgroup of grass pollen allergic children, adolescents and adults with asthma and efficacy in primary house dust mite allergy-induced asthma in adolescents aged from 14 years and in adults.

Aspects of secondary prevention, in particular the reduction of new sensitizations and reduced asthma risk, are important rationales for choosing to initiate treatment early in childhood and adolescence. In this context, those products for which the appropriate effects have been demonstrated should be considered.

SCIT or SLIT with pollen or mite allergens can be performed in patients with allergic rhinoconjunctivitis using allergen extracts that have been proven to be effective in at least one double-blind placebo-controlled (DBPC) study. At present, clinical trials are underway for the indication in asthma due to house dust mite allergy, some of the results of which have already been published, whilst others are still awaited (see the DGAKI table “Approved/potentially completed studies” via [www.dgaki.de/Leitlinien/s2k-Leitlinie-sit](http://www.dgaki.de/Leitlinien/s2k-Leitlinie-sit) (according to [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu))). When establishing the indication for AIT, factors that favour clinical efficacy should be taken into consideration. Differences between SCIT and SLIT are to be considered primarily in terms of contraindications. In individual cases, AIT may be justifiably indicated despite the presence of contraindications.

SCIT injections and the initiation of SLIT are performed by a physician experienced in this type of treatment and who is able to administer emergency treatment in the case of an allergic reaction. Patients must be fully informed about the procedure and risks of possible adverse events, and the details of this process must be documented (see “Treatment information sheet”; available as a handout via [www.dgaki.de/Leitlinien/s2k-Leitlinie-sit](http://www.dgaki.de/Leitlinien/s2k-Leitlinie-sit)). Treatment should be performed according to the manufacturer’s product information leaflet. In cases where AIT is to be performed or continued by a different physician to the one who established the indication, close cooperation is required in order to ensure that treatment is implemented consistently and at low risk. In general, it is recommended that SCIT and SLIT should only be performed using preparations for which adequate proof of efficacy is available from clinical trials.

Treatment adherence among AIT patients is lower than assumed by physicians, irrespective of the form of administration. Clearly, adherence is of vital importance for treatment success. Improving AIT adherence is one of the most important future goals, in order to ensure efficacy of the therapy.

Severe, potentially life-threatening systemic reactions during SCIT are possible, but – providing all safety measures are adhered to – these events are very rare. Most adverse events are mild to moderate and can be treated well.

Dose-dependent adverse local reactions occur frequently in the mouth and throat in SLIT. Systemic reactions have been described in SLIT, but are seen far less often than with SCIT. In terms of anaphylaxis and other severe systemic reactions, SLIT has a better safety profile than SCIT.

The risk and effects of adverse systemic reactions in the setting of AIT can be effectively reduced by training of personnel, adhering to safety standards and prompt use of emergency measures, including early administration of i. m. epinephrine. Details on the acute management of anaphylactic reactions can be found in the current S2 guideline on anaphylaxis issued by the AWMF (S2-AWMF-LL Registry Number 061-025).

AIT is undergoing some innovative developments in many areas (e. g., allergen characterization, new administration routes, adjuvants, faster and safer dose escalation protocols), some of which are already being investigated in clinical trials.

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## Abbreviations

AAAAI	American Academy of Allergy, Asthma & Immunology	HIV	Human immunodeficiency virus
ACE	Angiotensin converting enzyme	HMG	Medicinal Products Act (Switzerland), Heilmittelgesetz (Schweiz)
AD	Atopic dermatitis	HR	Hazard ratio
ADR	Adverse drug reactions	HRQL	Health-related quality of life
AGES	Austrian Agency for Health and Nutrition, Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH	ICER	Incremental cost-effectiveness ratio
AIT	Allergen-specific immunotherapy	IFN	Interferon
Al(OH) <sub>3</sub>	Aluminum hydroxide	IgA	Immunglobulin A
AMG	Arzneimittelgesetz, Medicinal Products Act	IgE	Immunglobulin E
APC	Antigen-presenting cells	IgG	Immunglobulin G
BASG	Austrian Medicines and Medical Devices Agency, Bundesamt für Sicherheit im Gesundheitswesen (Österreich)	IL	Interleukin
Baso	Basophile granulocyte	ILIT	Intralymphatic immunotherapy
BGB	Bundesgesetzbuch, german civil code	ITT	Intention to treat
BGR	professional association regulations, Berufsgenossenschaftsregeln	MPL	Monophosphoryl lipid A
Ca <sub>3</sub> (PO <sub>4</sub> ) <sub>2</sub>	Calcium phosphate	NaCl	Sodium chloride
CI	Confidence interval	NPP	Named patient product
CONSORT	Consolidated standards of reporting trials	NVL	National disease management guideline, Nationale Versorgungsleitlinie
CSMS	Combined symptom and medication score	O <sub>2</sub>	Oxygen
DAAB	German Allergy and Asthma Association, Deutscher Allergie- und Asthmabund	OAS	Oral allergy syndrome
DBPC	Double-blind placebo-controlled	PAT	Preventive allergy treatment
DC	Dendritic cells	PDCO	Paediatric Committee
DELBI	German instrument for methodological guideline appraisal, Deutsches Leitlinien-Bewertungsinstrument	PEF	Peak expiratory flow
EAACI	European Academy of Allergy and Clinical Immunology	PP	Per protocol
EMA	European Medicines Agency	QALY	Quality-adjusted life year
Eos	Eosinophile granulocyte	SCIT	Subcutaneous immunotherapy
EPIT	Epidermal immunotherapy	SCORAD	Scoring Atopic Dermatitis
FAS	Full analysis set	SLIT	Sublingual immunotherapy
FEV1	Forced expiratory volume in 1 second	SMD	Standardised mean difference
GCP	Good clinical practice	TAV	Therapy allergen ordinance, Therapieallergene-Verordnung
GINA	Global Initiative for Asthma	TGF	Transforming growth factor
GKV	Statutory health insurance, Gesetzliche Krankenversicherung	Th	T helper cell
GMP	Good manufacturing practice	TRBA	Technical regulations for biological agents
HAART	Highly active antiretroviral therapy	T <sub>reg</sub>	Regulatory T cell
		TSS	Total symptom score
		VAS	Visual analogue scale
		WAO	World Allergy Organization
		WHO	World Health Organization



## 1. Objectives and development of the guideline

The present guideline was developed on behalf of and financed by the German Society for Allergology and Clinical Immunology (Deutsche Gesellschaft für Allergologie und klinische Immunologie, DGAKI) and replaces the S2 guideline published in 2009 [1]. It has been conceived as a S2k guideline according to the methodological requirements set out by the German Working Group of Scientific Medical Societies (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF). A detailed guideline report in line with AWMF policy (DELBI criteria 1–7) can be found on the AWMF website ([www.awmf.org/leitlinien/detail/II/061-004.html](http://www.awmf.org/leitlinien/detail/II/061-004.html))

In summary, it was decided by the board of the DGAKI in 2012 that the corresponding author should take over the task of coordinating the revision of the guideline. In addition to members of the DGAKI (Oliver Pfaar, Jörg Kleine-Tebbe, Eckard Hamelmann, Bettina Wedi, Claus Bachert and Margitta Worm), representatives of the following bodies were involved in drawing up the guideline: the Medical Association of German Allergologists (Ärzteverband Deutscher Allergologen, AeDA: Thomas Fuchs, Hans Merk, Uta Rabe), the Society for Pediatric Allergy and Environmental Medicine (Gesellschaft für Pädiatrische Allergologie und Umweltmedizin, GPA: Albrecht Bufer, Matthias Volkmar Kopp, Antje Schuster), the Austrian Society for Allergy and Immunology (Österreichische Gesellschaft für Allergologie und Immunologie, ÖGAI: Christof Ebner, Isidor Huttegger, Stefan Wöhr), the Swiss Society for Allergy and Immunology (Schweizerische Gesellschaft für Allergologie und Immunologie, SGAI: Peter Eng, Peter Schmid-Grendelmeier), the German Society of Dermatology (Deutsche Gesellschaft für Dermatologie, DDG: Joachim Saloga), the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie, DGHNO-KHC: Ludger Klimek), the German Society of Pediatrics and Adolescent Medicine (Deutsche Gesellschaft für Kinder- und Jugendmedizin, DGKJ: Ulrich Umpfenbach), the Society for Pediatric Pneumology (Gesellschaft für Pädiatrische Pneumologie, GPP: Nikolaus Schwert), the German Respiratory Society (Deutsche Gesellschaft für Pneumologie, DGP: Roland Buhl), the German Association of ENT Surgeons (Berufsverband der HNO-Ärzte, BV-HNO: Doris Hartwig-Bade), the Professional Federation of Paediatricians and Youth Doctors (Berufsverband der Kinder- und Jugendärzte, BVKJ: Frank Friedrichs), Federal Association of

Pulmonologists (Bundesverband der Pneumologen, BdP: Thomas Hering) and the German Dermatologists Association (Berufsverband der Deutschen Dermatologen, BVDD: Kirsten Jung). The Paul-Ehrlich Institute (PEI: Susanne Kaul) and the German Allergy and Asthma Association/Patient Organization (Deutscher Allergie- und Asthmabund, DAAB: Anja Schwalfenberg) were involved in the consensus process in an advisory capacity.

The guideline was updated at a consensus conference in Wiesbaden, Germany, in April 2013, as well as by written consent and using a web-based guidelines portal especially set-up and authorized by the AWMF ([www.leitlinienentwicklung.de](http://www.leitlinienentwicklung.de)). The final consensus process took place on July 18<sup>th</sup> 2014. The guideline was then presented to all responsible board members to be authorized and recommended for adoption. This final authorization process was formally completed by October 1<sup>st</sup> 2014.

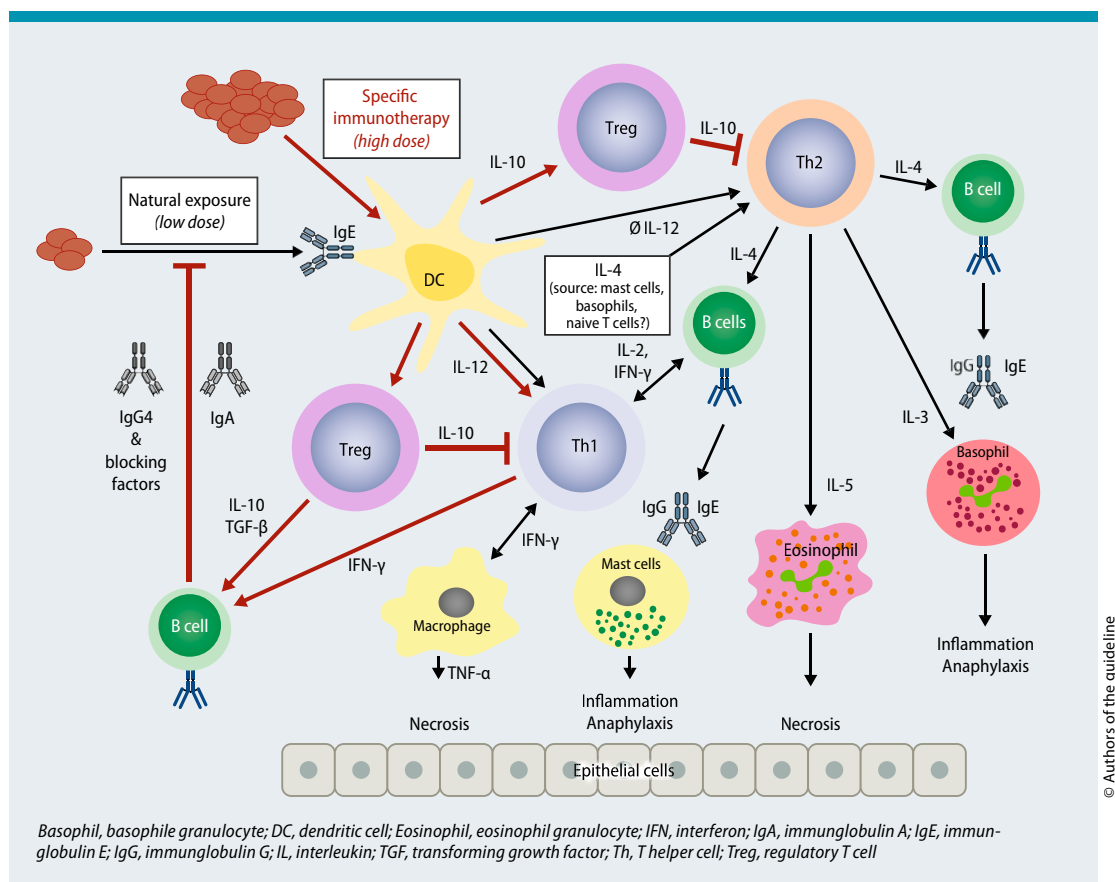
The guideline is addressed to all physicians with a board certification or subspecialty in allergy as well as all physicians that treat and/or monitor allergic patients in the context of AIT, and can be used for all patient groups with allergic rhinoconjunctivitis with/without allergic asthma and allergic sensitization to inhaled allergens.

The validity of the guideline shall be reviewed by the authors 5 years following its publication. The guideline coordinator shall be responsible for this task. Further details can be found in the separate guideline report.

The guideline will be published and distributed by the allergy societies in their official associated journals; it will also be published (in German language) in the AWMF guideline register, recommended for adoption by other involved societies and made available for reprint to interested journals with allergy-related content.

## 2. Immunological mechanisms of action

With AIT, allergen extracts in the form of molecule mixtures are presented to the immune system either subcutaneously (SCIT) or sublingually (SLIT). The patient is already sensitized to the allergens and reacts upon renewed exposure to allergens with inflammation of the skin and mucosa. The allergen extracts first diffuse into local tissue, where they are taken up by antigen-presenting cells (APC) [2]. The speed of this process depends on the dose and composition of the extracts, particularly when depot preparations are used [3]. Following administration, the allergens are found in local lymph nodes. They arrive there either unbound via free diffusion or are taken up by dendritic (DC) or B cells [4]. At the same time, immunocomplexes made up of allergens



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**Fig. 1:** Complex model of the immunological effects during AIT

and IgE antibodies may form in the tissue, by which allergens can be intercepted, mast cells activated or allergens transported to lymph nodes. At present, the literature [4, 5, 6, 7, 8, 9] favors the following immunological mechanisms to explain the effect of AIT (**Fig. 1**):

1. Activation of new and boosting of existing antibodies that block the allergen-antibody-mediated immune response. In particular, these include IgG antibodies that are able to prevent binding of IgE-allergen complexes to B cells and DC. An increase in these antibodies correlates to a certain extent with the success of treatment, an effect that cannot be seen when measuring the total fraction of IgG and IgG4 serum-antibodies.
2. Activation of regulatory T cells ( $T_{regs}$ ) that inhibit the T cell-mediated activation of B cells and the specific T-cell response to the allergen.  $T_{regs}$  migrate from their site of formation in the lymph nodes back to the area of inflammation and release IL-10 and TGF- $\beta$ , thereby reducing local inflammation. These effects can only be measured

after 6 months of treatment and have not as yet been confirmed in all studies.

3. Induction of mediators and cytokines that attenuate local allergic inflammation. Allergens primarily activate local APC (e.g., DC). These release IL-10 and TGF- $\beta$  in particular. Both cytokines can have a local anti-inflammatory effect and are able to inhibit T-cell proliferation. In addition, the release of IL-10 serves to reinforce the above-mentioned production of blocking IgG antibodies. Cytokines released locally also attenuate local mast cell activity and the activation of other effector cells that contribute to allergic inflammation.

**Conclusion:** AIT is a therapy with disease-modifying effects. By administering allergen extracts, specific blocking antibodies, tolerance-inducing cells and mediators are activated. These prevent further exacerbation of the allergen-triggered immune response, block the specific immune response and attenuate the inflammatory response in tissue.

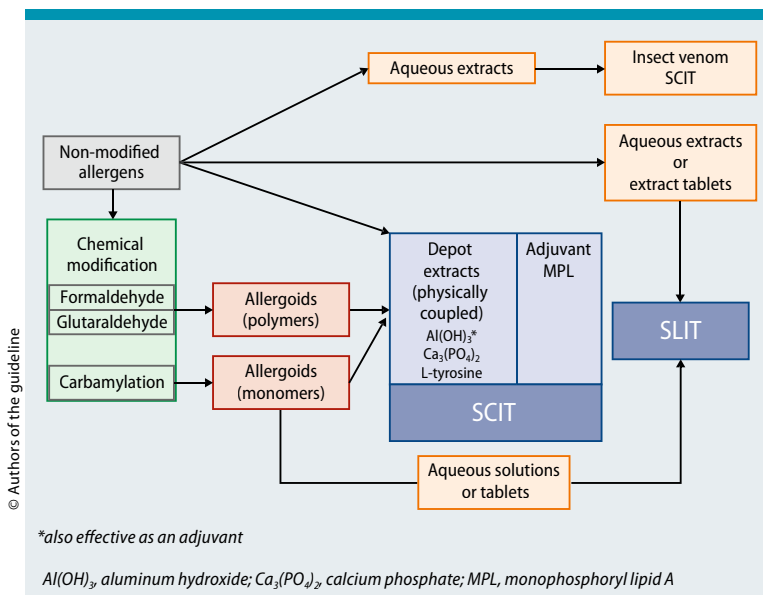


Fig. 2: Allergen extracts available for AIT (see Sect. 3.1 for more details)

### 3. Allergen extracts: assessment and marketing authorization

#### 3.1. Production and composition of allergen extracts

Due to manufacturer-specific processing, the allergen extracts produced differ in terms of composition and allergen activity and are therefore not comparable even if the same allergen sources are used. Standardized allergen extracts should preferentially be used for AIT, as otherwise extracts vary significantly in their biological activity [10]. The total activity of the extracts is determined using in-vitro methods [11]. Determining individual allergens (e.g., major allergens) using standardized, validated methods is endorsed in international guidelines [12]. Two recombinant major allergens, rBet v 1 from birch pollen (*Betula verrucosa*, <http://crs.edqm.eu/db/4DCGI/View=Y0001565>) and rPhl p 5a from timothy grass pollen (*Phleum pratense*, <http://crs.edqm.eu/db/4DCGI/View=Y0001566>), were adopted as reference preparations by the European Pharmacopoeia Commission in 2012. These reference preparations are intended for the determination of the Bet v 1 and Phl p 5a content in corresponding allergen preparations (native and recombinant) [13].

The use of these references is voluntary until suitable ELISA systems are available and requested by the European Pharmacopoeia. Thus, it is not possible at present to compare the allergen concentrations in various preparations, as manufacturers use different antibodies and measuring systems to determine major allergens.

Non-modified (native) extracts with unaltered allergen conformation and chemically modified extracts (allergoids) can be used for SCIT. The concept is that allergoids possess less reactive B-cell epitopes and thus reduced IgE binding, while their T-cell epitopes and their immunogenic effect remain unaltered [14]. In addition to aqueous extracts, which are commonly used as the initial treatment in insect venom allergy, depot extracts are primarily used in Europe for SCIT. Here, allergens or allergoids are physically adsorbed to a carrier, such as aluminum hydroxide, tyrosine or calcium phosphate (Fig. 2).

Preparations for SLIT are available with allergens in unmodified conformation or as chemically modified extracts in the form of aqueous solutions or tablets (Fig. 2). Some preparations need to be refrigerated, others can be stored at room temperature.

**Conclusion:** Products for SCIT or SLIT cannot be compared at present due to their heterogeneous composition, nor can allergen concentrations given by different manufacturers be compared meaningfully due to the varying methods used to measure their active ingredients. Non-modified allergens are used for SCIT in the form of aqueous or physically adsorbed (depot) extracts, as well as chemically modified allergens (allergoids) as depot extracts. Allergen extracts for SLIT are used in the form of aqueous solutions or tablets.

#### 3.2. Criteria for evaluating subcutaneous or sublingual administration of specific immunotherapy in clinical studies

The efficacy of AIT is measured using symptom scores [e.g., individual symptoms, total symptom score (TSS)], medication scores, combined symptom and medication scores, health-related quality of life (HRQL) as well as other methods (e.g., visual analog scales, “well” or “severe days”) [15, 16, 17]. It is essential to record allergy exposure over time (e.g., using pollen counts) as well as to collect safety data; moreover, recording laboratory data on IgE, IgG and IgG4 is recommended.

Combined symptom and medication scores are frequently used as primary endpoints in AIT trials and proposed in multiple variations [18, 19, 20]. The lack of validation of primary and secondary efficacy parameters represents a considerable problem in terms of the comparability of study results [15, 16, 17].

The European Medicines Agency (EMA) primarily recommends combined symptom and medication scores for the primary endpoint in AIT trials and accepts (in justified exceptional cases) a positive study result for both scores, as the consumption of rescue medication also affects the symptoms. Therefore, the score should reflect both, severity of symptoms as well as the need for medication [21].

However, the EMA does not provide a precise definition for this parameter [21, 22].

A task force working group of the EAACI recently published specific recommendations on clinical endpoints in AIT trials [17]. Particularly worthy of note is that the EAACI Position Paper provides a definition of a homogeneous, standardized combined symptom and medication score (CSMS) as primary endpoint with the aim of harmonizing this outcome measure in future AIT trials [17].

It is essential that study results are evaluated, represented and published in an appropriate manner. To this end, standards have been established (Consolidated Standards of Reporting Trials [CONSORT]) which, by the use of checklists, are intended to guarantee minimal yet transparent reporting of studies ([www.consort-statement.org](http://www.consort-statement.org) [23]). This includes the evaluation of clinical data in an intention-to-treat (ITT) analysis, which takes all patients included in a study (even those that withdraw early) into account, illustrating the actual effects of AIT under practical conditions [23, 24]. The per-protocol (PP) analysis, on the other hand, is well suited to estimating maximum efficacy under optimal standard conditions. In addition, data on all patients – even those included in the study without fulfilling the specified inclusion criteria or whose treatment deviated from the study protocol – are recorded in the analysis of full-analysis-sets (FAS) in order to depict the safety profile of the treatment.

**Conclusion:** The clinical efficacy of AIT is measured using various scores as primary and secondary study endpoints. The EMA stipulates combined symptom and medication scores as primary endpoint. A harmonization of clinical endpoints, e.g., by using the CSMS recommended by the EAACI, is desirable in the future in order to permit the comparison of results from different studies. The current CONSORT recommendations from the ARIA/GA<sup>2</sup>LEN group specify standards for the evaluation, presentation and publication of study results.

### 3.3. Relevance of marketing authorization for allergen preparations

In Germany, marketing authorization is required for allergen preparations in accordance with the German Medicinal Products Act (Arzneimittelgesetz, AMG). However, there is an exemption excluding individual formulations (named patient products, NPP) of therapy allergens from marketing authorization. Irrespective of this, all preparations are finished medicinal products according to the AMG (Tab. 1).

Both types of product can be prescribed and are tradeable. Individual formulations have been regulated in Germany since 2008 in addition by the

Table 1

#### Important terms in the German Medicinal Products Act (Deutsches Arzneimittelgesetz, AMG)

[www.gesetze-im-internet.de/bundesrecht/amg\\_1976/gesamt.pdf](http://www.gesetze-im-internet.de/bundesrecht/amg_1976/gesamt.pdf), as well as particular features of the Austrian and Swiss drug laws

##### Finished medicinal products

Section 4 Sub-section 1, AMG § 4 (1): „Finished medicinal products are medicinal products which are manufactured beforehand and placed on the market in packaging intended for distribution to the consumer or other medicinal products intended for distribution to the consumer, in the preparation of which any form of industrial process is used or... are produced commercially“.

##### Marketing authorization

Section 21 Sub-section 1, AMG § 21 (1): „Finished medicinal products which are medicinal products as defined in Section 2 sub-section 1 or sub-section 2 number 1, may only be placed on the market within the purview of the present Act, if they have been authorised by the competent higher federal authority...“

##### Individual formulations (NPP)

Section 21 Sub-section 2, AMG § 21 (2): “A marketing authorization (*Zulassung*) shall not be required for medicinal products which ... No. 1g: ... are therapeutic allergens manufactured to order for individual patients...”

##### Important Terms in the Austrian Drug Law (Österreichisches Arzneimittelgesetz)

AMG § 7a(1): “Medicinal products containing antigens or half-antigens intended for the detection of specific antibodies and protective substances for desensitization or hyposensitization, provided they are not always produced in the same composition and under the same designation in a defined form intended for distribution to the consumer or user, are only permitted to be distributed domestically or held ready for domestic distribution if the Federal Office for Safety in Healthcare has approved by notification the manufacturing process including chemical/pharmaceutical documentation, for this medicinal product.”

##### Situation in Switzerland

Under the terms of the Swiss Federal Law on Medicinal Products [Heilmittelgesetz, HMG; Art. 9 (1)] dated December 15<sup>th</sup> 2000, allergen preparations intended for AIT are considered as medicinal products requiring marketing approval (SR812.21, [www.admin.ch/opc/de/classified-compilation/20002716/index.html#a9](http://www.admin.ch/opc/de/classified-compilation/20002716/index.html#a9)). Allergen preparations used under the terms of the exemption clause [HMG Art. 9 (2)], for example as individual formulations (patient-specific mixture of allergens, NPP), are exempt from marketing authorization.

A new regulation came into force in 2010 to simplify the marketing approval process for allergen preparations (Allergenverordnung, AllergV SR812.216.2, [www.admin.ch/opc/de/classified-compilation/20060055/index.html](http://www.admin.ch/opc/de/classified-compilation/20060055/index.html)). The simplification of the marketing approval procedure consists of the fact that the market authorization documentation can be based on published literature (from scientifically recognized sources) or on documentation for other allergen preparations (a reference preparation of the same manufacturer). Allergen preparations containing recombinant allergens or genetically modified organisms are excluded from this simplified marketing authorization procedure.

In cases where marketing authorization has already been granted in a country with comparable medicinal drug regulations and a comparable marketing authorization process, it is possible, under the terms of Art. 13 of the Swiss HMG to take these results into consideration with regard to marketing authorization in Switzerland.

Therapy Allergen Ordinance (Therapieallergene-Verordnung, TAV) [25]. According to the TAV, individual formulations containing at least one extract of an allergen source that frequently triggers allergies (Tab. 2) require a marketing authorization.

At present, there are marketing authorization applications for 96 individual formulations of this kind



Table 2

**A list of therapy allergens requiring marketing authorization in Germany\* [25]**Species of the *Poaceae* family excluding *Poa mays* (grasses excluding maize)*Betula* sp. (species of the birch genus)*Alnus* sp. (species of the alder genus)*Corylus* sp. (species of the hazel genus)*Dermatophagoides* sp. (species of the house dust mite genus)

Bee venom

Wasp venom

\*A list of therapy allergens requiring marketing authorization according to the German Therapy Allergen Ordinance [25] and which, once transitional regulations have expired, may not be marketed either as individual preparations or as mixtures without marketing authorization.

Table 3

**Examples of individual formulations (NPP) for specific immunotherapy using allergen sources not subject to the German Therapy Allergen Ordinance\* [25]**Mugwort pollen (*Artemisia vulgaris*)Ash pollen (*Fraxinus excelsior*)Alternaria (*Alternaria alternata*)Animal allergens, e.g., from the cat (*Felis domesticus*)Storage mites (e.g., *Acarus siro*)

\*Not mixed with allergen groups subject to the Therapy Allergen Ordinance (Tab. 2), otherwise they would be subject to the ordinance.

Table 4

**Marketing authorization procedures\* for medicinal products in the European Union (EU)**

National procedure, when marketing authorization is granted for a medicinal product in the respective member state only

Mutual recognition procedure, when a preparation already has marketing authorization in one EU member state and this authorization should be extended to other member states

Decentralized procedure, when a medicinal product does not yet have national marketing authorization and seeks parallel marketing authorization in several EU member states

Central procedure (simultaneous marketing authorization in all EU member states), necessary in the case of medicinal products cited in the Appendix to EU Regulation 726/2004 (e.g., medicinal products which are manufactured by using biotechnological processes); can also be used for other medicinal products under certain conditions

\*All procedures resulting in marketing authorization in several or all European countries are coordinated by the European Medicines Agency (EMA).

pending at the Paul-Ehrlich-Institute (PEI) (as of December 2014, PEI communication). These preparations remain equivalent to approved preparations in terms of being prescribable and tradeable until the decision on their application for marketing authorization. All preparations (more than 6,400) contain-

ing allergens of this kind and for which no approval was sought needed to be reported to the PEI, remained tradeable until November 2011 at the latest for the treatment of patients already on treatment and were then removed from the market [26]. New regulations related to batch release also came into force with the TAV. Before the TAV became effective, only authorized allergen preparations were subject to governmental batch release; with the TAV, batch release became mandatory for all reported individual preparations. In the case of individual formulations (NPP), testing is performed on the bulk allergen extracts from which the individual formulations are produced (bulk allergen extract batch release), whereas for all other preparations testing is performed primarily on the end product.

All other therapy allergens produced as individual formulations (NPPs that do not contain allergens listed in the TAV appendix; see **Tab. 3** for examples) are still exempt from mandatory marketing authorization and are thereby neither subject to official monitoring on quality, efficacy and safety nor governmental batch release. With regard to manufacture, however, according to the AMG, a manufacturing license that fulfills all the criteria of good manufacturing practice (GMP) is required.

Authorized preparations ([www.pei.de/DE/arzneimittel/allergene/allergene-node.html](http://www.pei.de/DE/arzneimittel/allergene/allergene-node.html)) can be distinguished from individual formulations (NPP) by their authorization number on the outer packaging and in the summary of product information.

In Germany, the PEI is responsible for the marketing authorization of allergen preparations (**Tab. 4**) for therapeutic and diagnostic purposes and for batch release. Authorization in Austria is regulated by the Federal Office for Safety in Health Care (Bundesamt für Sicherheit im Gesundheitswesen), which serves the Austrian Agency for Health and Nutrition (Österreichische Agentur für Gesundheit und Ernährung, AGES-PharmMed). Marketing authorization for allergens is supervised in Switzerland by the Swiss Agency for Therapeutic Products Swissmedic. The above-mentioned regulations apply only partially to Austria and Switzerland, especially the TAV applies only for Germany.

The application for marketing authorization at the competent authority shall include among others information on the production process of the drug, its quality control, the results of all pre-clinical and clinical studies as well as further medical testing. Medicinal products must fulfil the state of the art requirements valid at the time of authorization [27]. Today, these include, e.g., GMP, good clinical practice (GCP), the European pharmacopoeia as well as the relevant EMA guidelines ([www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003333.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003333.pdf) [11], [www.ema.europa.eu](http://www.ema.europa.eu)).

europa.eu/docs/en\_GB/document\_library/Scientific\_guideline/2009/09/WC500003605.pdf [21]).

Preparations are only authorized for those indications and patient groups for which safety and efficacy have been proven in clinical trials.

Since 1993, and with the exception of bee and wasp venom preparations, marketing authorization has only been granted if at least one double-blind placebo-controlled (DBPC) trial complying with the relevant state of the art has been successfully carried out. Placebo control is not required for hymenoptera venom preparations for ethical reasons; in such cases, an established equivalent preparation is generally used for comparative testing. In the case of older authorizations – in accordance with requirements valid at that time – open studies were sometimes also accepted as evidence of efficacy.

Increased requirements set more recently have resulted in a significant improvement in the quality of data obtained in clinical studies and thus also in the evidence of safety and efficacy of preparations authorized on the basis of these studies. Although individual formulations that come under the TAV (**Tab. 2**) are subject to governmental batch release on bulk allergen extracts for quality assurance purposes, no official inspection of the production process or examination of efficacy and safety is carried out prior to the authorization process.

In the opinion of the authors, authorized allergen preparations with documented efficacy and safety, or preparations tradeable under the TAV for which efficacy and safety have already been documented in clinical trials meeting WAO or EMA standards, should be preferentially used. A current overview intended as a guide for most of the current clinical trials on AIT approved for implementation can be found in the European Clinical Trials Register at: [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu).

Manufacturers have the opportunity to report results on efficacy from relevant studies in the summary of product information under Article 5.1; however, study quality may vary significantly, given the differences in requirements between 1990 and today. In the case of authorized preparations, this information is also examined by the authorities. In the case of current marketing authorizations, manufacturers use this opportunity, which also offers physicians a good chance to inform themselves about the preparation.

Since authorized finished medicinal products are not able to cover the full spectrum of allergen extracts required for AIT, the use of individual formulations (named patient products, NPP) is justified in cases where the extract needs to be individually tailored to the allergy needs of a particular patient [28] (see **Tab. 3**).

**Conclusion:** According to the TAV, preparations containing common allergen sources (pollen from grasses, birch, alder, hazel, house dust mites, as well as bee and wasp venom) need a marketing authorization in Germany. During the marketing authorization process, these preparations are examined regarding quality, safety and efficacy. In the opinion of the authors, authorized allergen preparations with documented efficacy and safety, or preparations tradeable under the TAV for which efficacy and safety have already been documented in clinical trials meeting WAO or EMA standards, should be preferentially used.

Individual formulations (NPP) enable the prescription of rare allergen sources (e.g., pollen from ash, mugwort or ambrosia, mold *Alternaria*, animal allergens) for specific immunotherapy. Mixing these allergens with TAV allergens is not permitted.

#### 3.4. AIT from a socio-economic perspective

Allergic diseases, such as allergic rhinoconjunctivitis, have a significant impact on the individual patients as well as on the national economy as a whole [29, 30, 31].

The healthcare system is burdened not only by the costs caused directly by disease, but also by the indirect costs that are often challenging to measure [32]. One in ten doctors' certificates for work absence can be attributed to allergy symptoms. The direct disease costs for allergic rhinoconjunctivitis already totalled several hundred million euros in the 1990s [31]. Treatment options consist of symptomatic treatment and allergen avoidance, as well as disease-modifying therapy in the form of AIT. Since AIT is both a somehow curative and a preventive approach, it is able to affect the individual disease course positively (disease modifying effect). Allergic rhinitis patients have a 3.5-fold higher relative risk of developing bronchial asthma within less than 10 years [33]. In this context, AIT is deemed to have a preventive effect in terms of allergic progression (to allergic bronchial asthma) or new sensitizations [24, 34].

The scientific socio-economic evaluation of therapeutic agents is carried out using cost-benefit and cost-effectiveness analyses, which enable healthcare policymakers to compare different methods and products, as well as to identify the advantages and disadvantages of treatment methods from a socio-economic perspective. The results of this kind of analysis are taken into consideration in the evaluation of medicinals and play an important role today in decision-making on the coverage of the treatment costs by state health institutions.

The gain in quality of life per year following intervention with AIT is measured using the standardized quality-adjusted life year (QALY) and em-

ployed for incremental cost-effectiveness analysis [35]. Every year of life in perfect health is expressed with a QALY of 1, diminishing according to disease burden to a QALY of 0.0 for death. By dividing the disease course, the difference in costs for various methods or time points in treatment (in this case AIT) by the relevant QALY, one obtains the incremental cost-effectiveness ratio (ICER). Recent examples show that the ICER for AIT, irrespective of the route of administration, falls within the range of treatments accepted in healthcare policy for the treatment of chronic diseases [36, 37]. Another cost-effectiveness analysis carried out in Germany underscores the potential of AIT to save costs [38].

If one takes the cumulative ICER per year as a basis, it becomes clear that the significant investment made in AIT at the beginning of treatment proves to be cost-neutral after 7 years on average [39]. This is consistent with the fact that the principal advantage of AIT lies in its long-term effects. It must be pointed out, however, that these effects depend to a great extent on treatment compliance.

Generally speaking, the prices of individual products valid at the time (according to the official drug price list (LAUER-TAXE®) and at dosage according to the manufacturer's recommendations) for a treatment period of 3 years should be used to compare the costs of SCIT and SLIT.

**Conclusion:** Allergic rhinitis and its associated comorbidities (e.g., bronchial asthma) generate substantial direct and indirect costs. Treatment options, in particular AIT, are therefore evaluated using cost-benefit and cost-effectiveness analyses. From a long-term perspective, AIT is considered to be significantly more cost effective in allergic rhinitis and allergic asthma than pharmacotherapy, but is heavily dependent on patient compliance.

#### 4. Efficacy in clinical studies

##### 4.1. Systematic reviews and meta-analyses for the evaluation of AIT

Systematic reviews and meta-analyses are often referred to as the highest form of statistical evaluation of multiple studies. The reliability of their conclusions depends on the study selection criteria and on quality control measures as the studies evaluated are usually highly heterogeneous [40]. Although numerous meta-analyses on AIT have been carried out, recent ones were able to include more studies with large numbers of cases and of higher quality. Reviews of published meta-analyses carried out up to and including 2009 can be found in [41] and [42].

One way to reduce the effect of heterogeneity on study results, while enabling conclusions that are relevant in routine practice, is to select the studies to be included strictly according to predefined cri-

teria. As an example one could only include studies with a minimum of 100 subjects per arm or studies on commercially available products. In their analysis through 2009, Calderon et al. evaluated 33 clinical studies on AIT in grass-pollen allergic patients that fulfilled predefined criteria [43]. 28 recent trials were used for a more up-to-date meta-analysis of studies on SCIT and SLIT in patients with seasonal allergic rhinitis [44]. Another recent systematic review of the efficacy and tolerability of SCIT and SLIT in patients with house dust mite allergy included 44 studies published up to 2013 [45].

In summary, these meta-analyses and reviews demonstrate a well-documented efficacy for AIT. However, due to the heterogeneity of individual studies described in all analyses, the authors stress that it is not possible to make a generic recommendation about the route of application, but rather that evidence of efficacy and tolerability is required for individual AIT preparations.

It is anticipated that, under the TAV (see Sect. 3.3), a large number of studies combined with adequate evidence on various preparations will be available.

Tables providing a preparation-specific list of AIT products on the market in Germany, Switzerland and Austria can be found on the DGAKI website via [www.dgaki.de/Leitlinien/s2k-Leitlinie-sit](http://www.dgaki.de/Leitlinien/s2k-Leitlinie-sit). This list includes all preparations with certain features for some products:

- a) studies are available fulfilling five efficacy criteria that are modified to conform to the recommendations in the WAO consensus paper on the standardization of clinical AIT studies [46]. Since the efficacy of AIT in view of potential side effects and treatment costs should at least be comparable to that of pharmacotherapy, a threshold in efficacy of 20% above placebo has been selected as acceptable [46]. The currently most effective pharmacotherapy (MP29-02) has an efficacy of 19% above placebo, thereby justifying this threshold value [47].
- b) marketing authorization has been granted in Germany.
- c) the authorities have granted consent to perform clinical trials and the positive vote of the relevant ethics commission has been submitted to the competent authorities (from [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu)).

The table lists studies in adults and children separately, the year of marketing authorization, the clinical endpoints used as a basis, the number of patients randomized and evaluated, the evaluation method used (ITT, FAS, PP) for grass pollen – and birch pollen allergens and house dust mite allergens, as well as the status of consent to conduct clinical trials.

It is important to note that the quality of evidence of efficacy differs according to the year in which approval was granted (in accordance with the PEI criteria applied in the year of approval) and that approval is independent of the five efficacy criteria discussed here (e.g., a fixed percentage improvement above placebo is not endorsed for marketing authorization).

**Conclusion:** Meta-analyses provide unequivocal evidence of the efficacy of SCIT and SLIT for certain allergen sources and age groups. Data from controlled studies differ in terms of scope, quality and dosing regimens and require product-specific evaluation. Therefore, evaluating individual preparations according to clearly defined criteria is recommended. A broad transfer of the efficacy of certain preparations to all preparations administered in the same way is not endorsed.

## 4.2. Efficacy of SCIT in inhalant allergies

### 4.2.1. Efficacy of SCIT in allergic rhinoconjunctivitis

The documentation on the clinical efficacy of SCIT in allergic rhinoconjunctivitis is based on numerous DBPC trials of heterogeneous size and quality and which were summarized for seasonal allergens (e.g., grass pollen, birch pollen) in a systematic review and meta-analysis in 2007 [48]. This analysis evaluated 15 studies on SCIT that demonstrated a reduction in the symptom score (Standardized Mean Difference (SMD) -0.73; 95 % Confidence Interval (CI) -0.97 to -0.50;  $p < 0.00001$ ) and in the medication score (SMD -0.57; 95 % CI -0.82 to -0.33;  $p < 0.00001$ ; in 13 studies).

A current meta-analysis (2013) evaluated 17 clinical trials (up to April 2011) for efficacy of SCIT in patients with seasonal allergic rhinitis [44]. This analysis found a reduction in the symptom scores (SMD -0.65; 95 % CI -0.85 to -0.45;  $p < 0.00001$ ; all 17 studies), the medication scores (SMD -0.55; 95 % CI -0.75 to -0.34;  $p < 0.00001$ ; 16 studies), the combined symptom and medication scores (CSMS) (SMD -0.48; 95 % CI -0.67 to -0.29;  $p < 0.00001$ ; 8 studies) as well as an improvement in the quality-of-life scores (SMD -0.53; 95 % CI -0.66 to -0.39;  $p < 0.00001$ ; 8 studies).

An evidence-based review of SCIT efficacy based on results from 7 studies on house dust mite-allergic patients was also published in 2013, wherein strong heterogeneity in data on the major allergen doses used, the evaluation parameters selected and the actual study results was seen [45].

A comparison of meta-analyses of DBPC SCIT trials published to date with meta-analyses of pharmacotherapy only in seasonal allergic rhinitis showed that, even in the first year of treatment, SCIT resulted in a reduction in allergic symptoms

that was at least equivalent to (purely symptomatic) drug treatment [49].

Despite new, methodologically sound DBPC trials (for example [50]), there is less data to support evidence of the clinical efficacy of SCIT in children.

### 4.2.2. Efficacy of SCIT in allergic bronchial asthma

In contrast to the use of SCIT in allergic rhinoconjunctivitis, the decision to use SCIT in allergic bronchial asthma is generally made with greater caution [51, 52, 53, 54, 55, 56, 57]. SCIT is not a substitute for adequate anti-asthmatic treatment. On the basis of numerous studies, SCIT can be recommended in intermittent (severity according to the National disease management guideline (NVL) for asthma /Global Initiative for Asthma (GINA) I) and mild persistent bronchial asthma (severity according to NVL/GINA II) [51, 52, 54, 58]. These recommendations are based on data from a meta-analysis in the Cochrane Library [59], which evaluated 88 randomized controlled – yet methodologically heterogeneous – SCIT studies including altogether 3,459 patients with allergic asthma to house dust mite allergens (42), pollen allergens (27), animal dander allergens (10) and other allergens. An analysis of all the articles evaluated showed a significant reduction in both symptom score and medication use. Furthermore, a slight yet significant reduction in non-specific bronchial hyperreactivity was seen. The marked reduction in allergen-specific bronchial hyperreactivity to house dust mite allergens as well as pollen allergens and animal dander allergens in patients treated with SCIT compared with control groups can be considered as evidence of a lower risk of asthma exacerbation on renewed exposure to the relevant allergen. However, the 20 studies that included the measurement of lung function parameters showed only a trend towards improved lung function, without statistical significance [59]. As, there is generally no significant reduction in lung function parameters in patients with intermittent or mild persistent asthma, this clinical endpoint is not suitable for evaluating the efficacy of AIT.

The incidence of systemic side effects was 19.9 % in the actively treated group versus 8.1 % in patients receiving placebo injections. One in nine actively treated patients developed systemic reactions of varying severity to the allergen injections. Unfortunately, this particular Cochrane review did not conduct a separate analysis for children.

The relatively small group of patients with insufficiently controlled asthma represents a high-risk group for systemic side effects, which explains why here particular caution is required when assessing the indication for AIT and its practical implementation [60].



A recent evidence-based analysis of 19 studies (three of which were in children) on the efficacy of SCIT in patients with (house dust mite) allergic asthma found a statistically significant benefit in SCIT compared with placebo in terms of symptom score or symptom-related scores in only 9 studies [45]. Moreover, there was significant heterogeneity in terms of (major allergen) doses used as well as the evaluation parameters and time periods selected [45].

One study conducted solely in children with allergic asthma in which SCIT was employed using an allergoid extract of house dust mite showed improved asthma control as well as significant reduction in the required doses of inhaled corticosteroids compared with the control group not treated with SCIT [61].

#### 4.2.3. Efficacy of SCIT relative to allergen source

##### 4.2.3.1. Grass pollen

Numerous clinical studies in the literature highlight the efficacy of AIT in grass pollen allergic adult patients (amongst others [62, 63, 64, 65, 66]). Not all approved grass pollen extracts available on the market have been tested according to the WAO and EMA efficacy criteria, and specific pediatric studies are lacking for most preparations (see DGAKI table “Trials showing evidence of treatment efficacy: grass pollen” via [www.dgaki.de/Leitlinien/s2k-Leitlinie-sit](http://www.dgaki.de/Leitlinien/s2k-Leitlinie-sit)). A DBPC trial in 35 children and adolescents with seasonal grass pollen-induced asthma aged 3 to 16 years showed that SCIT using a non-modified (native) allergen extract can significantly reduce asthma symptom-medication scores [67].

##### 4.2.3.2. Tree pollen

A number of efficacy studies on birch pollen allergies have shown a reduction in symptoms and/or medication use (e.g., [68, 69, 70, 71, 72, 73, 74]). The efficacy and safety of most early-flowering (fagales) tree extracts available on the market have not been proven in DBPC trials, and relevant specific pediatric studies are lacking (see the DGAKI table “Trials showing evidence of treatment efficacy: tree pollen” via [www.dgaki.de/Leitlinien/s2k-Leitlinie-sit](http://www.dgaki.de/Leitlinien/s2k-Leitlinie-sit)).

##### 4.2.3.3. House dust mites

The evaluation of the efficacy of SCIT in house dust mite-induced rhinoconjunctivitis is based on a number of studies (e.g., [75, 76, 77, 78, 79]), but it is true also in this indication that many of the commercially available dust mite extracts have not been investigated for efficacy or safety in DBPC trials, and only scant specific pediatric studies (e.g., [80]) are available (see the DGAKI table “Trials showing evidence of treatment efficacy: house dust mites” via [www.dgaki.de/Leitlinien/s2k-Leitlinie-sit](http://www.dgaki.de/Leitlinien/s2k-Leitlinie-sit)).

Studies on SCIT using mite extracts in patients with perennial allergic asthma and house dust mite allergy found less symptoms [75, 81, 82, 83], lower medication use [75, 81, 83, 84], a reduction in allergen-specific bronchial hyperreactivity [75, 83] and improved quality of life [75, 83] compared with placebo. These findings were also confirmed in children; SCIT with an allergoid extract of dust mite resulted in improved asthma control with a significant reduction in the dose of inhaled corticosteroids required compared with the non-SCIT control group (see Sect. 4.2.2 [61]).

#### 4.2.3.4. Animal allergens

To date, a small number of studies have provided evidence of efficacy primarily for cat allergen extracts (with only few for dog allergen extracts) [85, 86, 87, 88, 89]. Only isolated reports are available on AIT with allergens from other furry animal species.

#### 4.2.3.5. Other allergen sources

Evidence of clinical efficacy in mold allergy is limited to a small number of studies using *Alternaria alternata* and *Cladosporium herbarum* extracts [90, 91, 92]. A 3-year DBPC trial in children with *Alternaria alternata* allergy showed SCIT to be effective from the second year of treatment onwards [50].

#### 4.2.4. Efficacy of AIT in other indications

Data on the efficacy of AIT with pollen allergens to treat oral allergy syndrome (OAS) are as yet insufficient [93], meaning that further studies are needed before a conclusion is possible. A randomized controlled trial (on 40 tree pollen allergic patients, 20 of whom were treated with SCIT and 20 treated with SLIT) demonstrated an improvement of the OAS in some of the patients [94]. At present, AIT is not indicated in exclusively pollen allergen-associated OAS without airway symptoms.

Recent studies show AIT to have clinical effects in patients with extrinsic atopic dermatitis (AD) as well as corresponding and likely clinically relevant type-I sensitization (e.g., eczema triggered by airborne allergens; reviews in [95, 96]). One randomized double-blind dose-range-finding SCIT trial on 89 adult patients with a chronic form of AD and sensitization to house dust mites revealed a significant improvement of the SCORAD (Scoring Atopic Dermatitis) over a one-year therapy-course [97]. In a more recently published DBPC-Phase-III study (SCIT) on 168 adult patients a significant improvement in the SCORAD was only demonstrated in a subgroup with severe forms of AD [98].

A 2013 meta-analysis on the efficacy of AIT in AD, in which eight randomized and controlled (six SCIT, two SLIT) trials were included, found a positive effect [99]. The authors stress, however, the consider-

able heterogeneity between the studies conducted, some of which had small patient numbers, thus limiting the validity of this meta-analysis. However, AD is not a contraindication for AIT in patients with allergic airway diseases requiring treatment.

**Conclusion:** Strong evidence of the efficacy of SCIT in pollen allergy-induced allergic rhinoconjunctivitis in adulthood is well-documented in numerous trials and, in childhood and adolescence, in a few trials.

Efficacy in house dust mite allergy is documented by a number of controlled trials in adults and few controlled trials in children. Only a few controlled trials, independent of age, are available for mold allergy (in particular *Alternaria*). With regard to animal dander allergies (primarily to cat allergens), only small studies, some with methodological deficiencies are available. Only a moderate and inconsistent therapeutic effect in atopic dermatitis has been observed in the quite heterogeneous studies conducted to date.

SCIT has been well investigated for individual preparations in controlled bronchial asthma (GINA 2007 [56]) and intermittent and mild persistent asthma (GINA 2005 [55]) and it is recommended as a treatment option, in addition to allergen avoidance and pharmacotherapy, provided there is a clear causal link between respiratory symptoms and the relevant allergen.

#### 4.3. Efficacy of SLIT in inhalant allergies

##### 4.3.1. Efficacy of SLIT in allergic rhinoconjunctivitis

Due to new controlled trials in adults [100, 101, 102, 103, 104, 105, 106] and children [107, 108, 109], some with high patient numbers, good data on the efficacy of SLIT is also available. As with SCIT, there are significant differences in the documentation of clinical efficacy depending on the product used. While for certain products no randomized and large controlled trials have been published, extensive data is available for individual preparations and allergens, which have been taken into consideration in a recent Cochrane meta-analysis on SLIT ([110] intended as an update of [111]). The analysis conducted up to August 2009 included for the symptom scores 23 studies in grass pollen allergic patients (SMD -0.35; 95 % CI -0.45 to -0.24;  $p < 0.00001$ ), 9 studies (including 2 using birch pollen extract) in tree pollen allergic patients (SMD -0.42; 95 % CI -0.77 to -0.06;  $p = 0.02$ ) and 9 studies in house dust mite allergic patients (SMD -0.97; 95 % CI -1.80 to -0.13;  $p = 0.02$ ).

A meta-analysis published in 2013 on the efficacy of SLIT in patients with seasonal allergic rhinitis found a reduction in the symptom scores (SMD -0.33; 95 % CI -0.42 to -0.25;  $p < 0.00001$ ; 42 studies), in the medication scores (SMD -0.27; 95 % CI -0.37

to -0.17;  $p < 0.00001$ ; 35 studies), the combined symptom and medication scores (SMD -0.40, 95 % CI -0.55 to -0.25;  $p < 0.00001$ ; 6 studies) as well as improved quality of life scores (SMD -0.37, 95 % CI -0.52 to -0.22;  $p < 0.00001$ ; 7 studies) in SLIT-treated patients compared with placebo [44].

An evidence-based review of SLIT efficacy in patients with (house dust mite-induced) allergic rhinitis found a significant difference in the respective symptom score or symptom-related scores in only two of the eight studies considered, whereby (as with the analysis of SCIT studies in the same publication) the authors described significant heterogeneity in terms of the (major allergen) doses used as well as the evaluation parameters and time periods selected [45].

Although head-to-head comparisons of studies between SLIT and SCIT in adults show both treatment methods to be clinically effective, these studies are methodologically inadequate ([112], reviewed in [41, 44]). Due to scant data and/or methodological deficiencies, it is not possible to draw conclusions either from meta-analyses on the differences between SLIT and SCIT in terms of efficacy [41, 44].

In a recent comparison of DBPC trials in seasonal allergic rhinitis on SLIT grass tablets and pharmacotherapy-only studies published to date, a reduction in allergic symptoms by SLIT at least equivalent to purely symptomatic drug treatment was found [113].

##### 4.3.2. Efficacy of SLIT in allergic bronchial asthma

Compared with allergic rhinoconjunctivitis, there are only a limited number of studies on the efficacy of SLIT in patients with allergic bronchial asthma. A grass tablet study showed efficacy for SLIT in bronchial asthma in a subgroup of children with seasonal allergic asthma [107]. With regard to immunotherapy using dust mite extracts, heterogeneous results were found in clinical trials with methodological limitations [114, 115, 116, 117].

A recent study included 604 house dust mite-allergic patients at least 14 years of age with mild to moderate asthma treated for a 1-year period with SLIT with house dust mite tablets. Compared with placebo, actively treated patients exhibited a significant reduction in the dose of inhaled corticosteroids required to maintain asthma control over the course of the study period [118].

##### 4.3.3. Efficacy of SLIT relative to allergen source

###### 4.3.3.1. Grass pollen

The efficacy of SLIT with grass pollen extracts in allergic rhinoconjunctivitis with or without concomitant asthma has been documented in a number of large studies conducted in Europe [102, 104] and the US [119] (reviewed in [120]) (see the DGAKI table

Factors that increase the clinical efficacy of AIT <sup>a, b</sup>	Table 5
Short duration of disease	
Minor involvement of the lower airways	
Age (the EMA PDCO recommends that therapy not be commenced before the age of 5 years)	
Good compliance and adherence	
A high cumulative AIT dose	
<sup>a</sup> The more of these points that apply, the higher the probability that administration of AIT will reduce symptoms and medication use, as well as decrease the likelihood of allergic march – the development of bronchial asthma and broadening of the allergen spectrum. <sup>b</sup> only valid for inhalant allergens	

Indications for AIT with allergens <sup>a</sup>	Table 6
Verification of an IgE-mediated sensitization (preferably <sup>b</sup> from skin testing and/or <sup>d</sup> in vitro diagnostics) with a clear relationship to clinical symptoms (if indicated, challenge testing)	
Availability of standardized or high-quality allergen extracts	
Proof of efficacy of the planned AIT for the respective indication and age group	
Allergen avoidance not possible or inadequate	
Patient age ≥ 5 years	
<sup>a</sup> All points should be fulfilled. <sup>b</sup> In Switzerland, verification of sensitization preferably by skin testing. <sup>c</sup> “And” refers to rare allergens or uncertain results. <sup>d</sup> “Or” refers to situations in which skin testing is not possible and to diagnostic work-up in children below 5 years.	

“Trials showing evidence of treatment efficacy: grass pollen” via [www.dgaki.de/Leitlinien/s2k-Leitlinie-sit](http://www.dgaki.de/Leitlinien/s2k-Leitlinie-sit)). The strongest evidence of clinical efficacy (in terms of the size and methodology of studies) is for the sublingual tablets already approved [43, 102, 104]. In a randomized controlled study in 80 children comparing the clinical efficacy of a co-seasonal versus a perennial (continuous) schedule, SLIT with an aqueous grass pollen extract demonstrated better efficacy of the continuous SLIT during the first year, but the clinical effects of both schedules were comparable in the second and third year of treatment [121].

Studies in grass pollen allergic children at least 5 years of age the course of one season showed comparable efficacy with grass tablet products to the previously conducted adult studies [107, 108, 122]. As a result, both preparations were approved for use in children from the age of 5 years. In addition, a carry-over effect could be shown for both grass tablets in adults: clinical efficacy was confirmed 1 year [123, 124] to 2 years [125] following completion of a 3-year treatment course.

In addition, large DBPC trials showed aqueous grass SLIT preparations to be clinically effective in

children as well as in adults [103, 109, 126, 127]. With regard to other grass SLIT preparations, either conflicting study results are available or they have not yet been investigated in DBPC trials.

#### 4.3.3.2. Tree pollen

A handful of efficacy studies also showed a reduction in symptoms and/or medication use in tree pollen allergic patients (e.g., [105, 112, 128, 129]). An early DBPC trial with a birch pollen extract demonstrated a significant reduction in symptom and medication scores after 1 year of treatment compared with placebo [112]. A recent study in over 570 birch pollen allergic adults found a statistically significant advantage with aqueous tree pollen extract compared with placebo in pre/co-seasonal SLIT over a 2 year period [105] (see the DGAKI table “Trials showing evidence of treatment efficacy: tree pollen” via [www.dgaki.de/Leitlinien/s2k-Leitlinie-sit](http://www.dgaki.de/Leitlinien/s2k-Leitlinie-sit)).

However, for numerous aqueous tree pollen (birch or birch/alder/hazel mixtures) SLIT preparations, either heterogeneous study results are available or they have not yet been investigated in DBPC trials. Efficacy data for birch tablets in SLIT are not available.

#### 4.3.3.3. House dust mites

Data on the efficacy of SLIT with house dust mite allergens are conflicting. A number of SLIT dust mite products currently available have not as yet been subjected for efficacy in clinical studies.

Most studies have been conducted in patients with mild to moderate asthma (with concomitant dust mite-induced rhinitis). Besides several positive study results (e.g., [130, 131, 117, 114, 132, 133, 134]), negative study results also exist (e.g., [116, 135]) (see the DGAKI table “Trials showing evidence of treatment efficacy: house dust mites” via [www.dgaki.de/Leitlinien/s2k-Leitlinie-sit](http://www.dgaki.de/Leitlinien/s2k-Leitlinie-sit)). A DBPC trial with a modified dust mite allergen tablet product proved efficacy in mild dust mite-induced rhinitis [134].

A recently published study in 509 adults with house dust mite allergic rhinitis demonstrated a significant improvement in symptom scores following 1-year SLIT with dust mite tablets with a carry-over effect even in the second year of the trial without immunotherapy [106]. Another recently published study on house dust mite tablets in adolescent (aged from 14 years) and adult patients with bronchial asthma also showed clinical efficacy for SLIT (see Sect. 4.3.2. [118]).

#### 4.3.3.4. Efficacy of SLIT with other allergen extracts

While individual studies on other inhalant allergen sources (animal dander, molds, weed pollen) are

available, they do not permit a conclusive evaluation of treatment efficacy.

**Conclusion:** The efficacy of SLIT in grass pollen-induced allergic rhinoconjunctivitis is extensively documented in adults and children, whilst its efficacy in tree pollen allergy has only been shown in adults. New controlled trials (some with high patient numbers) on house dust mite allergy provide evidence of efficacy of SLIT in adults.

Compared with allergic rhinoconjunctivitis, there are only few studies on the efficacy of SLIT in allergic asthma. In this context, newer studies show an efficacy for SLIT on asthma symptoms in the subgroup of grass pollen allergic children, adolescents and adults with asthma and efficacy in primary house dust mite allergy-induced asthma in adolescents aged from 14 years and in adults.

#### 4.4. Prevention of asthma and new sensitizations

For individual products controlled, open studies have shown that, in addition to its primary allergen-specific effect, AIT also has secondary preventive characteristics, thus the potential to have a positive effect on the long-term course of allergic disease. Therefore, young patients with early manifestations of allergic symptoms are an important target group for AIT intervention.

A SCIT preparation containing birch or grass allergens, or a birch–grass mixture in allergic rhinoconjunctivitis was shown to reduce the risk of developing allergic asthma in an open prospective study (“Preventive allergy treatment (PAT) study” [136, 137]). Moreover, this effect was detectable 7 years following discontinuation of SCIT compared with the control group that received symptomatic treatment only [34].

The development of new sensitizations can be reduced in the case of mono- and oligosensitizations [138, 139, 140, 141].

Evidence of these and other secondary preventive effects were described in an open study up to 12 years following discontinuation of SCIT with a modified allergen preparation compared with an untreated control group [139].

A recent SLIT study was able to show a reduction in new sensitizations, whereas this effect was not observed in another (also open) study [142, 143].

The preventive effect of SLIT on lower respiratory tract involvement (asthma onset) has also been demonstrated, but mainly in open studies [142, 144, 145]. A multinational prospective DBPC trial is currently being conducted in over 800 children with grass pollen allergic rhinitis but no evidence of asthma, on whether early intervention using grass pollen tablets can prevent the development of asthma during the 3 years of treatment, as well as during 2

Table 7

#### Allergen components helpful in establishing the indication for AIT (major allergens<sup>a</sup> versus panallergens<sup>b</sup>)

##### Major allergens<sup>a</sup>

Bet v 1	⇒ Birch, <i>Betula pendula</i> (formerly <i>Betula verrucosa</i> )
Phl p 1/5	⇒ Grasses, <i>Phleum pratense</i> (timothy grass)
Der p 1/2	⇒ House dust mites, <i>Dermatophagoides pteronyssinus</i>
Alt a 1	⇒ Alternaria, <i>Alternaria alternata</i>
Ole e 1	⇒ Ash – no actual components instead due to high cross-reactivity: olive tree: <i>Olea europaea</i>
Art v 1	⇒ Mugwort, <i>Artemisia vulgaris</i>
Amb a 1	⇒ Ragweed, <i>Ambrosia artemisiifolia</i> (common ragweed)

##### Components that explain positive skin tests but are not valid in the indications for AIT (panallergens<sup>b</sup>)

Profilins: e.g.: Amb a 8 (ragweed), Ara h 5 (peanut), Bet v 2 (birch), Cor a 2 (hazelnut), Hev b 8 (latex), Phl p 12 (grass), Tri a 12 (wheat)
Polcalcins: e.g.: Aln g 4 (alder), Amb a 9 (ragweed), Art v 5 (mugwort), Bet v 4 (birch), Phl p 7 (grass)

<sup>a</sup>The name of an allergen component is derived from the first three letters of the genus and the first letter of the species names, e.g., timothy grass *Phleum pratense* ⇒ Phl p 1. The numbering often follows the chronological order of first description; thus, identical numbers unfortunately do not automatically signify cross-reactivity. Cross-reactivity is so high in some allergen-families that it is not necessary to determine the individual components separately: Beech-like (PR10 proteins): Bet v 1 (birch) ⇔ Aln a 1 (alder) ⇔ Cor a 1 (hazelnut); Grasses (grass group 1 allergen): Phl p 1 (timothy) ⇔ Cyn d 1 (Bermuda grass) ⇔ Lol p 1 (ryegrass) ⇔ Tri a 1 (wheat); House dust and flour mites: cysteine proteases, Der p 1 ⇔ f1, NPC2 family: Der p 2 ⇔ f2. The up-to-date, international WHO/IUIS list of all allergen components is available at: [www.allergen.org](http://www.allergen.org).

<sup>b</sup>Definition: a major allergen is an allergen component to which more than 50% of sensitized allergy sufferers exhibit specific IgE (e.g., in grass allergy: major components, Phl p 1, 2, 5, 6; minor component: Phl p 11). Panallergens are found in many species and are generally clinically insignificant, but nevertheless explain irrelevant positive extract-based skin and/or blood tests, e.g., profilins from 48 plant species are currently described, and new ones are being added daily; for an up-to-date list see: [www.meduniwien.ac.at/allergens/allfam](http://www.meduniwien.ac.at/allergens/allfam).

subsequent follow up-years [146]. Preliminary data are expected in 2016.

**Conclusion:** Aspects of secondary prevention, in particular the reduction of new sensitizations and reduced asthma risk, are important rationales for choosing to initiate treatment early in childhood and adolescence. In this context, those products for which the appropriate effects have been demonstrated should be considered.

#### 5. Indications and contraindications

##### 5.1. SCIT and SLIT

A number of variables influences the success of AIT and should therefore be considered when planning therapy (Tab. 5).

Tab. 6 contains an overview of the indications for specific immunotherapy using inhalant allergens. Fig. 3 outlines the clinical algorithm of the diagnostic work-up for the indication of AIT with seasonal allergens.

Tab. 7 outlines the possible advantages of a molecular allergy based diagnostic work-up to estab-



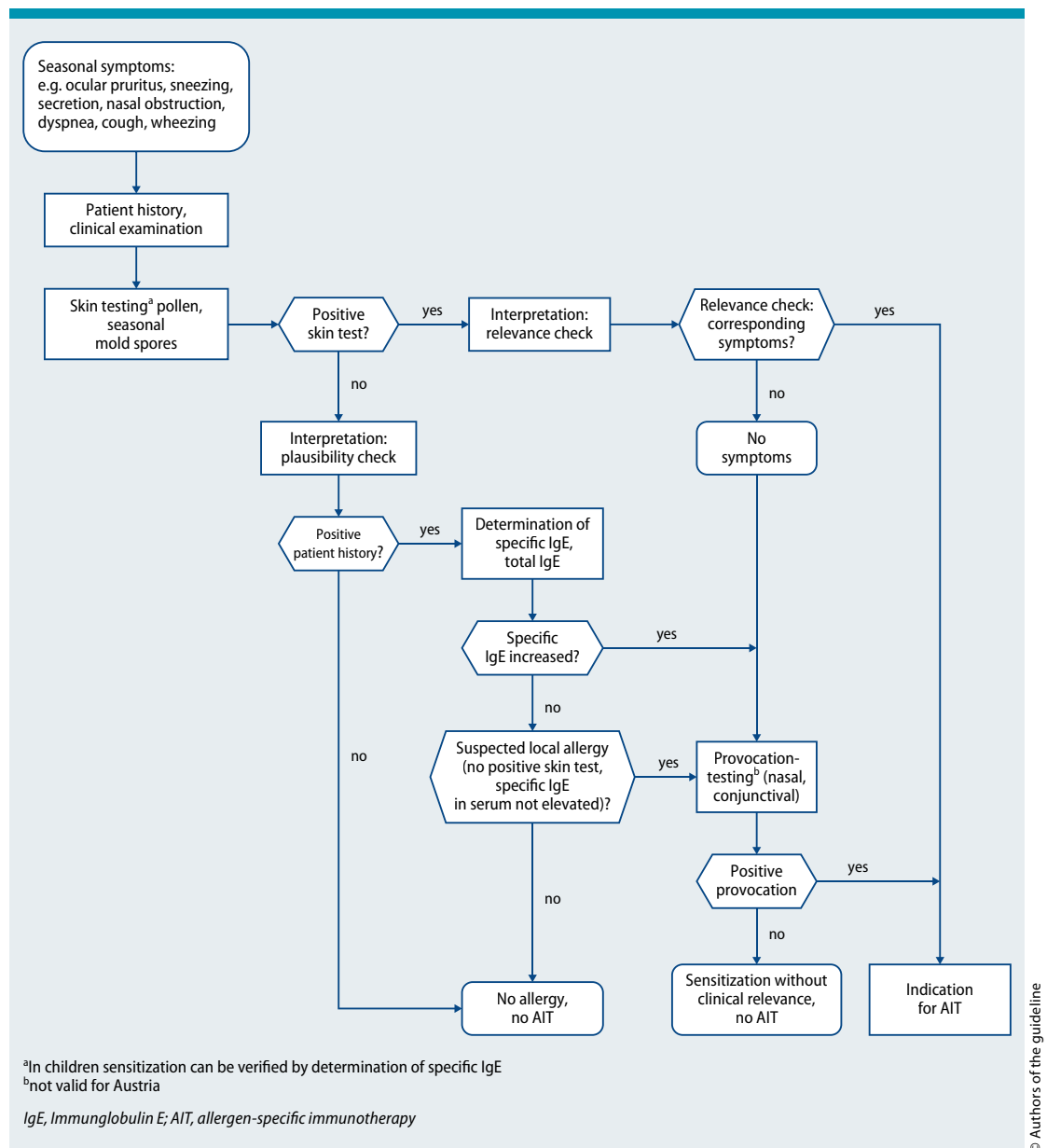
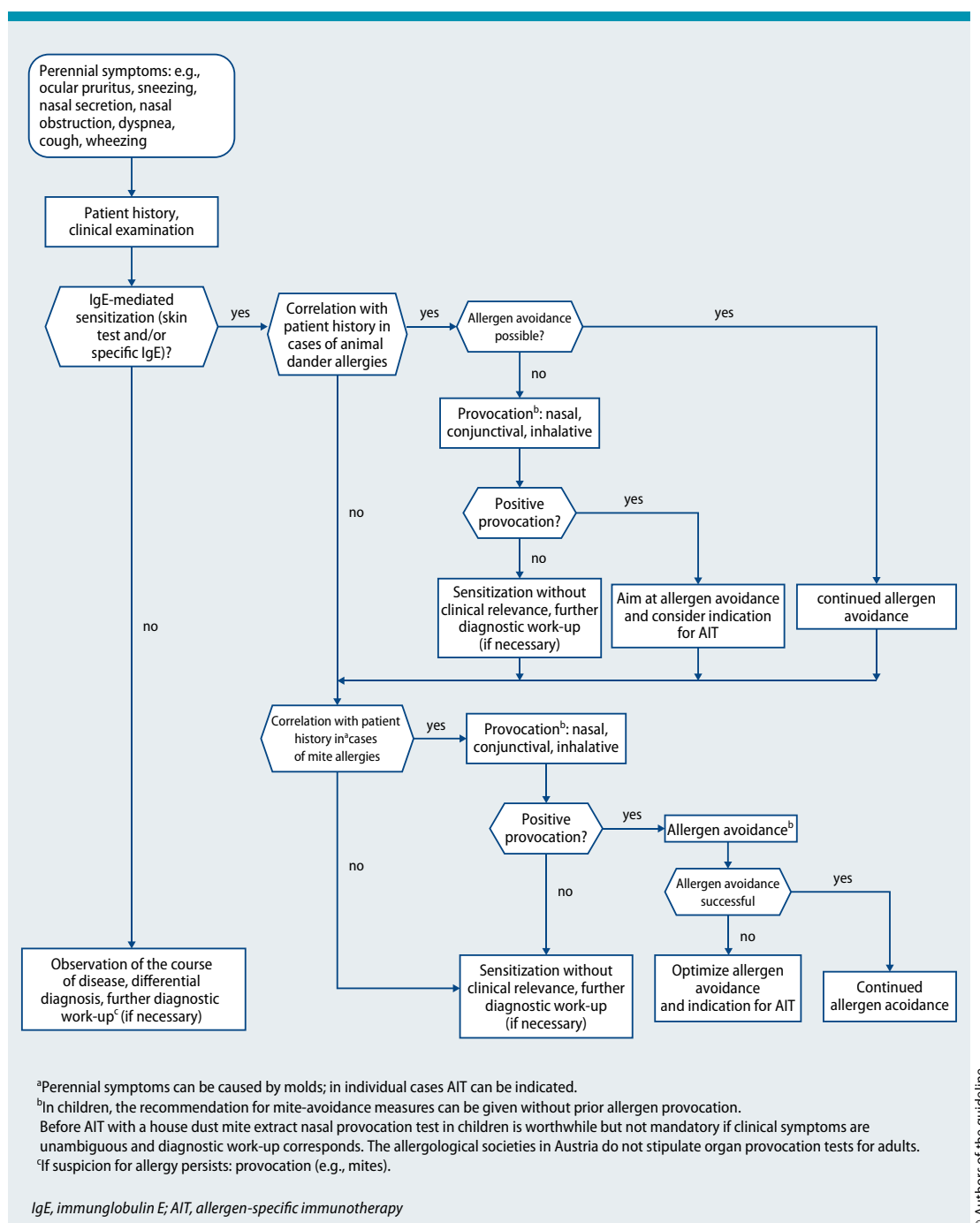


Fig. 3: Diagnostic work-up for AIT with seasonal allergens (clinical algorithm)

lish the indication for AIT. In some situations (polysensitized patients), the use of in vitro component-based IgE diagnostics can increase the likelihood of AIT being successful as early on as at the time of making the indication. Patients without sensitization to major allergens may receive less therapeutic benefit from AIT [147]; although detailed prospective studies on this topic are not currently available. Sensitizations solely to pollen-panallergens do not constitute indications for AIT.

In case of a confirmed house dust mite allergy, AIT is an option if measures for mite avoidance (mite allergen-proof mattress encasings, washable blankets and further measures to reduce house dust mite allergens) are insufficient (Fig. 4) and no improvement in symptoms is observed after 3 months of mite avoidance. A meta-analysis published in 2008 questioned the efficacy of mite control measures [148]. In only 17 of 54 included studies evaluated a significant reduction in the number of house dust mites could be documented. Overall,



**Fig. 4:** Diagnostic work-up to establish the indication for AIT with perennial allergens

the intervention measures applied in the investigated studies were very heterogeneous and no subgroup analysis was carried out for children. Due to the methodological deficiencies of this meta-analysis, the conclusion drawn by the authors is questionable. Therefore, in patients with a clinical-

ly relevant house dust mite allergy, the aforementioned intervention measures are primarily indicated [149, 150]. The German S3 guideline on allergy prevention also underscores the value of mite control measures for secondary and tertiary allergy prevention [150].

Contraindications <sup>a, d</sup> to AIT with allergens		Table 8
Subcutaneous administration (SCIT)	Sublingual administration (SLIT)	
Partially controlled or uncontrolled bronchial asthma (classification according to the GINA guidelines, 2007 or NVL, see <b>Tab. 9</b> )	Partially controlled or uncontrolled bronchial asthma (classification according to the GINA guidelines, 2007 or NVL, see <b>Tab. 9</b> )	
Diseases in which administration of epinephrine is contraindicated (except in the case of insect venom allergies)	no contraindication	
Treatment with $\beta$ -blockers (local or systemic application) <sup>b</sup>	preparation-specific differences, see product information leaflet	
severe autoimmune diseases <sup>c</sup> ; immune defects, immunodeficiencies, immunosuppression	severe autoimmune diseases <sup>c</sup> ; immune defects, immunodeficiencies, immunosuppression	
malignant neoplastic diseases with current disease relevance	malignant neoplastic diseases with current disease relevance	
serious systemic reactions to AIT in the past	serious systemic reactions to AIT in the past	
	acute, severe inflammatory disorder of the oral cavity	
insufficient compliance	insufficient compliance	
<sup>a</sup> In justified individual cases and on the basis of a risk-benefit analysis, AIT may also be possible even with existing contraindications.		
<sup>b</sup> In Germany, treatment with ACE inhibitors is also currently a contraindication to SCIT with insect venom.		
<sup>c</sup> Diseases not among those severe autoimmune diseases that represent a contraindication to AIT include: Hashimoto thyroiditis, rheumatoid arthritis, ulcerative colitis and Crohn's disease, type-1 diabetes mellitus; see also Sect. 5.2.		
<sup>d</sup> When evaluating contraindications, the product information leaflet corresponding to the particular product must be consulted.		
GINA, global initiative for Asthma; NVL, Nationale Versorgungsleitlinie, National disease management guideline; AIT, specific immunotherapy		

Allergen avoidance is the treatment of choice for animal dander allergies. If allergen avoidance cannot be ensured, SCIT with animal allergen extracts can be considered in individual cases (in particular in the case of a cat allergy; **Fig. 4**).

In the case of mold allergy, total allergen avoidance is only possible in exceptional cases. SCIT using mold allergens can be considered in the case of seasonal mold allergy with a corresponding indication and a well-characterized therapeutic allergen preparation (*Alternaria*, *Cladosporium*) [50, 90, 91].

The efficacy of AIT depends on the optimal therapeutic dose of each clinically relevant allergen. Current knowledge on the clinical efficacy and immunological effects of AIT is based primarily on studies in which monotherapy with a single allergen extract was administered. Therefore, no different (non-homologous) allergen groups should be mixed in an allergen preparation used for therapy, if the use of the particular combination is not supported by data from clinical trials. A current SCIT DBPC study with a chemically modified mixture of tree pollen and grass pollen allergens found significant (albeit moderate) clinical efficacy throughout the entire tree and grass pollen season in the second year of treatment [151].

In general, seasonal and perennial allergens are not combined in one extract. One reason for this is to avoid an unnecessary reduction in the perennial allergen fraction during the pollen season. Similarly, due to enzymatic degradation reactions [152], mite and animal dander allergens, mite and mold allergens and extracts containing pollen and mold allergens should never be combined in one preparation.

Before one opts for SCIT, several contraindications need to be considered (**Tab. 8**). For safety reasons, partially controlled or uncontrolled bronchial asthma (**Tab. 9**) (classification according to NVL-Asthma [153] or the GINA guidelines, 2007 [56]) represents a contraindication to AIT in adults. In the German NVL, "partially controlled asthma" is defined more restrictively for the pediatric age group than for adults; therefore AIT may be performed in children in case of partially controlled asthma (NVL definition [153]) – provided they rarely experience asthma symptoms.

In addition to guideline recommendations, practitioners should also be aware of the product information leaflet issued by the product manufacturer. This information has been approved by the PEI and is binding with respect to product-specific contraindications.

Although pregnancy is considered to be a contraindication to initiating AIT, continuation of SCIT in the case of life-threatening allergies to insect venom (bee/wasp venom) is advisable as well in the case of allergies to inhalant allergens, AIT is permissible, if the treatment is well tolerated by the patient (and in case it is in accordance with the product information leaflet) [154, 155]. Only in isolated cases (e. g., life-threatening insect venom allergy), can SCIT be initiated during pregnancy.

Medication with  $\beta$ -blockers (also in topical preparations, such as eye drops) is listed as a contraindication to SCIT in the specialist information. An increased risk of adverse airway reactions (bronchial constriction) and the risk that potentially required emergency treatment with epinephrine might be less effective [156] are discussed. The decision as to whether it is, under the circumstances, necessary to continue therapy with  $\beta$ -blockers has to be made on an individual basis, together with the prescribing physician. Although specific data are lacking, it is logical to assume that treatment with immunosuppressants or (immunomodulatory) biologicals may reduce the efficacy of AIT [156].

Indications and contraindications also need to be considered with the sublingual application of AIT (see **Tab. 6** and **Tab. 8**). Systemic adverse events are observed less frequently with SLIT than with SCIT. Patients with chronic disease of the oral mucosa are not suitable for SLIT. Furthermore, similar contra-

indications to those for SCIT (**Tab. 8**) also apply, although the product manufacturer's information leaflet must be consulted.

## 5.2. AIT despite contraindications

In selected cases, immunotherapy can also be initiated despite the existence of relative contraindications. A typical example of burnt-out autoimmune disease that can be well compensated by drug-based treatment is Hashimoto's thyroiditis. If controlled by drug-based treatment, this disease need not contraindicate AIT. In the case of other autoimmune diseases, such as multiple sclerosis, myasthenia gravis, lupus erythematosus, rheumatoid arthritis and Crohn's disease, for example, initiating AIT may be judged possible on an individual basis considering activity and course of the disease.

An exception among the contraindications listed in **Tab. 8** under immunodeficiency is represented by acquired immunodeficiency in stable, well-controlled HIV (human immunodeficiency virus) infection under highly active antiretroviral therapy (HAART), with negative HIV replication and normal CD4 counts. A case report and one small series of three patients have been described in the literature to date [157, 158]. Although SCIT during HAART is safe and does not negatively influence the disease course, there are currently no data to support the clinical efficacy of SCIT in HIV-positive patients. In the case of a clear indication, SCIT may be initiated in individual HIV-positive patients with stable disease who are undergoing HAART.

Because advanced age no longer represents a contraindication to AIT and the incidence of cancer increases with increasing age, there is a growing population of allergic rhinitis/asthma patients with a past history of neoplastic disease. Even relatively recent, but currently stable, malignant disease need not necessarily represent a contraindication. In a case study of four patients with melanoma and an insect venom allergy and one patient with breast cancer and seasonal allergic rhinitis, it was possible to complete AIT. Moreover, in most of these patients, no reactivation of malignant disease was observed even after more than 5 years of cancer follow-up [159].

A Swiss case series of 25 patients (with a clear and strictly defined indication for SCIT due to a history of severe anaphylactic reactions to insect venom) with cardiac disease who were taking  $\beta$ -blockers observed no increase in the instance of severe adverse events during SCIT [160].

Evidence for the triggering of autoimmune diseases by AIT is based on case studies (15 articles reporting 22 cases, of which 12 cases were vasculitis) [161].

In contrast, a registry-based observational study conducted in Denmark showed that SCIT was asso-

Table 9			
Level of asthma control (translated by the authors, © of the German version ÄZQ, BÄK, KBV and AWMF 2013, NVL [153], modified according to GINA 2007 [56], www.ginasthma.org)			
Criterion	controlled asthma (all criteria fulfilled)	partially controlled asthma (one or two criteria fulfilled within 1 week)	uncontrolled asthma
Daytime symptoms	≤ 2x per week no	> 2x per week yes	three or more criteria of "partially controlled asthma" fulfilled within 1 week
Restrictions in activities of daily living	no	yes	
Nighttime symp- toms/awakening	no	yes	
Use of reliever medication/ emergency treatment	≤ 2x per week no	> 2x per week yes	
Lung function (PEF or FEV <sub>1</sub> )	normal	< 80 % of the predicted value (FEV <sub>1</sub> ) or personal best value (PEF)	
Exacerbation <sup>1</sup>	no	one or more per year	one per week

Information relates to any one week within the preceding 4 weeks.  
green = applies only to adults, red = applies only to children and adolescents, blue = general recommendations  
<sup>1</sup>Any exacerbation in 1 week signifies by definition "uncontrolled asthma". Definition of exacerbation: an episode involving increased dyspnea, coughing, wheezing and/or chest tightness, associated with a deterioration in PEF or FEV<sub>1</sub>.  
FEV<sub>1</sub>, forced expiratory volume in 1 second; NVL, nationale Versorgungsleitlinie, National disease management guideline; PEF, peak expiratory flow

ciated with reduced mortality [hazard ratio (HR) 0.71; 95 % CI 0.62–0.81], as well as with a lower incidence of myocardial infarction (HR 0.70; 95 % CI 0.52–0.93) and autoimmune diseases (HR 0.86; 95 % CI 0.74–0.99) over a 10-year observation period (1997 to 2006) [162].

Although the risk of SCIT causing an autoimmune disease is probably very low, this risk should be considered, particularly in light of the fact that the therapy lasts several years. Where relevant suspicions are raised, AIT should be interrupted until any possible relation has been ruled out.

**Conclusion:** SCIT or SLIT with pollen or mite allergens can be performed in patients with allergic rhinoconjunctivitis using allergen extracts that have been proven to be effective in at least one double-blind placebo-controlled (DBPC) study. At present, clinical trials are underway for the indication in asthma due to house dust mite allergy, some of the results of which have already been published, whilst others are still awaited (see the DGAKI table "Approved/potentially completed studies" via [www.dgaki.de/Leitlinien/s2k-Leitlinie-sit](http://www.dgaki.de/Leitlinien/s2k-Leitlinie-sit) (according to [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu))).



Practice/stamp:	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td colspan="3" style="padding: 2px;">Health insurance or payer</td> </tr> <tr> <td colspan="3" style="padding: 2px;">Surname and forename of the insured</td> </tr> <tr> <td colspan="3" style="padding: 2px;">Date of birth</td> </tr> <tr> <td style="padding: 2px;">Health insurance number</td> <td style="padding: 2px;">Number of the insured</td> <td style="padding: 2px;">Status</td> </tr> <tr> <td style="padding: 2px;">Residence number</td> <td style="padding: 2px;">Physician number</td> <td style="padding: 2px;">Phone</td> </tr> </table>	Health insurance or payer			Surname and forename of the insured			Date of birth			Health insurance number	Number of the insured	Status	Residence number	Physician number	Phone
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**TREATMENT INFORMATION SHEET: SCIT**

**Patient information on subcutaneous specific immunotherapy (Desensitization)**

Dear patient,

In many cases, the cause of an allergy can be treated by means of repeated injections of the relevant allergens – for example, pollen, house dust mite, wasp or bee venom – responsible for your/your child's disease. This treatment is recommended when adequate allergen avoidance is not possible and drug treatment has proved unsatisfactory. The allergen is injected under the skin of the upper arm at increasing concentrations and volumes until the maximum dose is reached. This type of therapy also has a positive effect on mucosal (like your nasal cavity) hypersensitivity and susceptibility to mucosal infections. Alternatively, the mode of allergen administration can be varied (instead of an injection under the skin of the upper arm, the allergen can be administered under the tongue, i.e. in tablet form), provided a suitable preparation is available and there are no contraindications to this form of administration in your particular case. The potential success of this particular type of therapy generally requires a significant level of commitment. Your cooperation is crucial to the success and safety of the treatment!

- Please provide information on any medications that you/your child use regularly, occasionally or have just begun. This also applies to one time medications that you have used around the time of your immunotherapy injection. A small number of medications can have an unfavorable effect on the therapy.
- Please attend the appointments arranged for you at your doctor's practice regularly; children under the age of 12 years should be accompanied by a responsible adult (mother, father, etc.). If children aged 12 years or older are to attend desensitization appointments unaccompanied, please provide your written and signed permission as parents for them to do so.
- Please answer the following questions prior to each new hyposensitization injection:
  - How well did you/your child tolerate the last injection? Did you experience, for example, swelling of the skin or mucosa, cold symptoms, sneezing, skin rash, itching, dizziness, circulation problems, nausea, coughing or shortness of breath?
  - Are you or your child currently suffering from an infection, shortness of breath, a cough or cold symptoms?
  - Have you made any changes to your/your child's medication? It is essential that you inform your doctor about the use of new/ additional medications, in particular antihypertensive agents (β-blockers and ACE inhibitors).
  - Have you/your child received any recent vaccinations or do you plan to do so?
  - Have you/your child experienced the onset of a new, previously undiagnosed disease?
  - Have you/your child become pregnant?
- It is important that you remain in the room designated by your doctor for 30 min following treatments as mentioned above, children aged under 12 years should be accompanied by an adult. The following side effects may occur: swelling, redness and itching at the injection site occur most commonly; cold symptoms, sneezing, skin rash, shortness of breath as well as circulatory and gastrointestinal symptoms are rare; an allergic shock reaction is extremely rare. If you should experience any of the symptoms mentioned above, or any other unexpected symptoms, please inform a member of staff immediately. These could be treatment side effects requiring immediate medical attention.

- Although side effects very rarely occur more than 30 min after desensitization, this cannot be completely ruled out. Should you experience severe symptoms, such as shortness of breath, skin rash, dizziness, circulatory symptoms, palpitations or nausea/vomiting after you have left the office, contact your doctor immediately or seek medical advice immediately from the nearest doctor or hospital. Side effects of this kind are often triggered by taking a sauna or hot shower, strenuous physical activity and alcoholic beverages. You may occasionally experience severe fatigue, which could impair your fitness to drive.
- Avoid contact with the substances causing your allergy during the entire period of hyposensitization, in particular immediately before and after your injections! Your doctor will emphasize this.
- Avoid strenuous physical activity shortly before and for the remainder of the day following injection.
- Treatment success is likely only if appointments are attended regularly as arranged with your doctor. For this reason, it is important for you to attend appointments as scheduled or to inform your doctor in advance if you are unable to attend an appointment.
- Please pay careful attention to these instructions to help your treatment be successful and with minimal side effects! The information provided above is not intended as a substitute to reading the product information leaflet and serves only as additional information. Your doctor can provide you with further important information during the patient information and informed consent consultation prior to the start of treatment.

Additional medical notes (e.g., individual risks):

**Patient consent to subcutaneous specific immunotherapy**

I have read and understood the information on my allergic disease and on the possible treatment options. My doctor has explained the planned subcutaneous immunotherapy as well as alternatives to me and, having had a suitable period of time to consider the options, I consent to undergo this form of treatment using the preparations selected. My questions relating to this treatment have been answered. My doctor has informed me of the possibility of side effects and I am aware that it is not possible to predict treatment success with certainty. Should side effects occur, I will contact my doctor. For further information, I can refer to the product information leaflet. In addition, my doctor continues to remain available to me as my person of contact.

I confirm that I have no further questions.

DATE	SIGNATURE (patient or legal guardian)*
DATE	SIGNATURE (doctor)

\*In cases where parents have joint custody but only one parent signs, he/she confirms with his/her signature that the other parent gives their consent, or that they, the signatory, have sole custody.

**Fig. 5:** Treatment information sheet for subcutaneous specific immunotherapy (SCIT), available at [www.dgaki.de/Leitlinien/s2k-Leitlinie-sit](http://www.dgaki.de/Leitlinien/s2k-Leitlinie-sit)

When establishing the indication for AIT, factors that favour clinical efficacy should be taken into consideration (**Tab. 5**). Differences between SCIT and SLIT are to be considered primarily in terms of contraindications. In individual cases, AIT may be justifiably indicated despite the presence of contraindications.

## 6. Performing specific immunotherapy

AIT is carried out by physicians with a (sub)specialty in allergy or adequate relevant treatment experience. Furthermore, the treating physician must be capable of dealing with adverse events (including anaphylactic shock and severe asthma attacks) [163, 164]. Since January 1<sup>st</sup> 1996, product information leaflets for desensitization solutions used in Germany are required to include the following warning: "Desensitization injections may be prescribed and administered only by physicians with specialized allergological training or physicians experienced in allergy." (PEI, communication dated April 5<sup>th</sup> 1995). In Austria, solutions for AIT may be prescribed and administered by physicians specialized or experienced in allergy. The continuation of AIT can then be delegated to a general practitioner. In Switzerland, AIT can also be performed by primary care physicians, provided an allergological work-up with a specialist has been undertaken before commencing treatment.

Before initiating AIT, patients must be informed about the following: the practical procedure, type and duration of treatment; expected effects; as well as possible risks of and alternatives to treatment [165]. The process of providing patients with this information must be documented (Patients' Rights Act of the German Civil Code [Patientenrechtsgesetz des BGB]; §630f BGB: Documentation of Treatment [Dokumentation der Behandlung]; available at [www.patientenrechte-gesetz.de/bgb-sgbv/dokumentation.html](http://www.patientenrechte-gesetz.de/bgb-sgbv/dokumentation.html)).

Printed information (see "Treatment information sheet", available as a handout at [www.dgaki.de/Leitlinien/s2k-Leitlinie-sit](http://www.dgaki.de/Leitlinien/s2k-Leitlinie-sit); **Fig. 5** and **Fig 6**) on how AIT is carried out and how to deal with possible adverse events should be made available to patients. Adequate documentation of patient counseling is obligatory and written informed consent from the patient (or the patient's parent or legal guardian, as appropriate) is advisable.

In cases where AIT is to be administered or continued by a different physician other than the one who initially established the indication, close cooperation is required in order to ensure that treatment is implemented consistently and at low risk. If necessary, the patient should be referred back to the physician who originally made the indication.

If the treatment shows no signs of success after 1 to a maximum of 2 years, it should be critically re-

assessed – if possible by the physician who made the indication. Where indicated a change of preparation or a change from preseasonal to perennial treatment can be considered. Discontinuation of treatment is also an option. In general, it is recommended that SCIT and SLIT should only be performed using preparations for which adequate clinical trial data are available (see Sect. 4.).

## 6.1. SCIT with inhalant allergens

Prior to injection, the patient is interviewed regarding current allergic, or other relevant symptoms: pyrexia or other signs of infection; the tolerability of the last injection; any current or recent illnesses; or new or altered medications or vaccinations. The time interval since the last injection should be checked [165]. Confusion can be avoided by, for example, reading the names of the allergen preparation and of the patient out loud in the patient's presence.

For AIT injection – which represents a medical task and should thus be performed by the physician – a 1 ml syringe with fine graduation down to 0.01 ml with an injection needle (size 14–18, short bevel, sufficient length) is used. First, the area of skin where the injection is to be administered is disinfected. The injection is made strictly subcutaneously: following prior or, depending on the injection volume, repeated aspiration, injections are made into a lifted skin fold a hand's width above the olecranon on the extensor side of the upper arms. Details of the injection site and dose are documented. The patient must remain under medical observation for at least 30 min after injection [165]. During this period, the patient must report any symptoms that may indicate an allergic reaction to the medical staff. Once the waiting time has elapsed, the injection site should be examined. If a strong local reaction develops, the diameter should be documented, since a dose adjustment according to the product information leaflet of the administered SCIT preparation may be required (see Sect 8.1).

After a 3-year transitional period, the national policy for the prevention of injury from sharp/pointed instruments in hospitals and the health sector came into force in Germany on May 11<sup>th</sup> 2013, within the context of the Biological Agents Act (Biostoffverordnung) BGR 250/TRBA 250 (rules of the employers' liability insurance association (BG)/technical rules for biological materials; overview in [166]). This policy regulates the use of, e.g., hypodermic needles such as those used for subcutaneous allergen-specific immunotherapy (SCIT) according to state regulations covering occupational safety and accident prevention. Since the introduction of these regulations, the use of injection systems less likely to cause injury (including SCIT syringes with

Practice/stamp:		Health insurance or payer	
		Surname and forename of the insured	
		Date of birth	
Health insurance number	Number of the insured	Status	
Practice number	Physician number	Date	

TREATMENT INFORMATION SHEET: SLIT

**Patient information on sublingual specific immunotherapy**

Dear patient,

Often, specific immunotherapy involving the continuous administration of the allergy trigger can help your body to develop a natural tolerance. If treatment is successful, your body becomes tolerant – and therefore less sensitive – to the allergy trigger over the course of treatment – the cause of the allergy is treated! This type of therapy often also has a positive effect on mucosal (such as your nasal cavity) hypersensitivity and susceptibility to mucosal infections. In the case of sublingual immunotherapy („under the tongue“), treatment is administered in the form of a tablet or liquid solution. This treatment is recommended when adequate allergen avoidance is not possible and drug therapy has proved unsatisfactory. It does not cause new allergies.

Alternatively, the mode of allergen administration can be varied (allergen administration via injection under the skin of the upper arm at regular intervals at a medical practice instead of sublingual allergen administration, often in tablet form), provided a suitable preparation is available and there are no contraindications to this form of administration in your particular case.

In order to ensure the success of your or your child's treatment, please observe the following points:

1. Treatment success depends on your compliance (daily administration!). Since the treatment is recommended for a period of 3 years, this requires a high level of cooperation from you. We would ask you to participate in treatment only if you are confident that you intend and are able to perform the treatment reliably (fulfilling these criteria increases the chances of benefitting from treatment).
2. Please attend the follow-up appointments arranged for you at your doctor's practice regularly and obtain follow-up prescriptions in a timely manner. To achieve optimal and long-lasting treatment results (even after treatment is concluded), a full 3 year course is recommended.
3. The first allergen administration should be performed at your doctor's practice under his/her supervision. This is to ensure that the tablet or drops are taken in the appropriate manner. Sublingual immunotherapy is very well tolerated. Local symptoms, such as itching in the mouth or throat (rarely also swelling of the tissue in this area, but generally only transiently in the initial treatment phase) sometimes occur. Gastrointestinal symptoms are rare. Major allergic reactions are extremely rare and have only been seen to date in patients with uncontrolled asthma. Discuss these possible side effects with your doctor.
4. Inform your doctor promptly if you need to undergo tooth extraction or if any other form of surgery in the oral cavity is planned; have an infection in the oral cavity; taking new medication; or if you become pregnant. Please also read the carefully the instructions for use in the medication package.
5. It is important for you to attend appointments as scheduled or to inform your doctor sufficiently in advance if you are unable to attend an appointment.

6. Please talk to your doctor about how to proceed in the event of side effects or if you are suffering from other disorders (e.g., flu, asthma aggravation); also, remember your regular follow-up appointments with your doctor, as well as appointments to collect prescriptions.

7. Please pay careful attention to these instructions to ensure that your treatment can be carried out successfully, hopefully, without (troublesome side effects). The information provided above is not intended as a substitute to reading the product information leaflet and serves only as additional information. Your doctor can provide you with further important information during the consultation and will ask for your informed consent prior to the start of treatment.

Additional medical notes (e.g., individual risks):

\_\_\_\_\_

**Patient consent to sublingual specific immunotherapy**

I have read and understood the information on my allergic disease and on the possible treatment options. My doctor has explained to me the planned sublingual immunotherapy as well as alternatives and, having had a suitable period of time to consider the options, I consent to undergo this form of treatment using the preparations selected. My questions relating to this treatment have been answered. My doctor has informed me of the possibility of side effects and I am aware that it is not possible to predict treatment success with certainty. Should side effects occur, I will contact my doctor. For further information, I can refer to the product information leaflet. In addition, my doctor continues to remain available to me as my person of contact.

I confirm that I have no further questions.

DATE \_\_\_\_\_ SIGNATURE (patient or legal guardian) \_\_\_\_\_

DATE \_\_\_\_\_ SIGNATURE (doctor) \_\_\_\_\_

\*In cases where parents have joint custody but only one parent signs, he/she confirms by signing that the other parent gives their consent, or that they, the signatory, have sole custody

**Fig. 6:** Treatment information sheet for sublingual specific immunotherapy (SLIT), available at [www.dgaki.de/Leitlinien/s2k-Leitlinie-sit](http://www.dgaki.de/Leitlinien/s2k-Leitlinie-sit)

retraction systems, needle shields etc.) is obligatory for employees active in the field of allergy. As an employer, the allergist is not only specifically obliged to exercise due care personally, but also has a special obligation to ensure that his employees also exercise due care. It can be assumed that official checks on the implementation of the Biological Agents Act in allergy practices will be heightened in the future.

Shortly before and for the remainder of the day of injection, factors augmenting allergic reactions (e.g., physical exertion, whirlpool or sauna, alcohol) should be avoided. The time interval between a SCIT injection and a planned vaccination should be at least 1 week [165]. Vaccinations should, therefore, be carried out during the SCIT maintenance phase and administered between two SCIT injections performed at a 4-week interval. Emergency vaccinations (e.g., tetanus due to injury) can of course be administered at any time. Thereafter, SCIT is continued either according to the product information leaflet, or 2 weeks after the vaccination using the previously administered dose (overview in [167]).

Treatment is usually carried out on an outpatient basis. In the case of rush desensitization protocols (see below) or high-risk patients (pronounced systemic reactions, relative contraindications), it may be appropriate to initiate SCIT in an inpatient setting.

Allergen extracts for SCIT are mainly applied as depot solutions. During the dose escalation period (frequently doubling of the previous dose; see product information leaflet), treatment intervals are between 3 and 7 days for aqueous solutions and between 1 and 2 weeks for depot solutions. If cluster or rush titration protocols are applied, several injections are administered on each day of treatment (reviewed in [168, 169]). Once the maximum tolerated dose has been reached, the injection intervals can be increased to 4 to 8 weeks, according to the corresponding product information leaflet. In the case of seasonal aeroallergens, treatment escalation to the maximum dose is initiated outside of the allergen season and continued for at least 3 additional years [165]. The general implementation of purely intra-seasonal dose escalation has recently been investigated. This study employed a single preparation for which good tolerability to this type of approach could be demonstrated [170]. Scientific data on the efficacy of such a strategy are currently not available in published form; therefore, no general recommendations for intra-seasonal initiation of SCIT in pollen allergic patients can be made at present. Co-seasonally performed SCIT (continuation during the allergy season) without dose reduction is possible where this is in line with the preparation's product information leaflet and there are no

allergic symptoms at the time of injection. Precise clinical documentation is necessary.

Due to potential differences in biological activity and where stated in the product information leaflet, a reduction in the intended dose may be necessary at the beginning of a new batch during treatment continuation. However, preparations which no longer require this are now available from various manufacturers.

If the injection interval is exceeded, the dose is reduced according to the product information leaflet. The greater the discrepancy between the intended and actual intervals, the more the dose needs to be reduced [165]. In the case of airway allergies, the duration of SCIT should be at least 3 years. Although no controlled studies on parallel immunotherapy with two different allergen extracts administered during the same sitting exist, safety considerations mandate a time interval of at least 30 min between injections/sublingual administrations for safety reasons. After the final injection, the usual observation period of 30 min must be adhered to.

In patients with allergic bronchial asthma it is recommended that a peak flow protocol be run during treatment and that lung function tests are performed at regular intervals.

## 6.2. SLIT with inhalant allergens

SLIT is performed on an outpatient basis according to the manufacturer's product information leaflet. Recommendations for practical use can be found in [120, 165].

Depending on the preparation and the manufacturer, the initial dose should be administered (and followed-up) under the supervision of a physician experienced in allergy [120, intended as an update of 171]. With some SLIT preparations, and in accordance with their product information leaflets, SLIT can be initiated during the pollen season (intra-seasonal start).

In cases of viral infections of the respiratory tract, it may be possible to continue administration based on a physician's recommendation or it may be necessary to interrupt treatment (see product information leaflet). According to the product information leaflet of the particular preparation, administrations can then once again be increased to the maximal dose. No SLIT allergen extracts should be administered in cases of acute inflammation or injury to the oral or pharyngeal mucosa, significant surgical interventions (tooth extraction) in the oral cavity, acute gastroenteritis or uncontrolled asthma (consult corresponding product information leaflet).

Co-seasonally performed SLIT (continuation during the allergy season) without dose reduction is possible where this is in line with the preparation's product information leaflet and there are no,

or only minor, allergic symptoms at the time of administration. Precise clinical documentation is necessary. Following an unintended break in administrations of several days, the dose should be reduced according to the product information leaflet. The greater the lapsed interval, the more the dose needs to be reduced.

Based on experience with SCIT, the duration of SLIT should also be at least 3 years. If the treatment is continued in another practice, close cooperation with the physician who made the initial indication should be maintained, particularly in the event of questions relating to efficacy and safety.

**Conclusion:** SCIT injections and the initiation of SLIT are performed by a physician experienced in this type of treatment and who is able to administer emergency treatment in the case of an allergic reaction. Patients must be fully informed about the procedure and risks of possible adverse events, and the details of this process must be documented (see “Treatment information sheet”, **Fig. 5** and **Fig. 6**; available as a handout via [www.dgaki.de/Leitlinien/s2k-Leitlinie-sit](http://www.dgaki.de/Leitlinien/s2k-Leitlinie-sit)). Treatment should be performed according to the manufacturer's product information leaflet. In cases where AIT is to be performed or continued by a different physician to the one who established the indication, close cooperation is required in order to ensure that treatment is implemented consistently and at low risk.

In general, it is recommended that SCIT and SLIT should only be performed using preparations for which adequate proof of efficacy is available from clinical trials.

### 6.3. Compliance and adherence

The term compliance describes a patient's passive observance of the physician's instructions, whereby the patient is primarily responsible for the success or failure of therapy [172, 173]. The modern concept of adherence, however, describes the extent of agreement between physician and patient on jointly made treatment decisions and therapeutic goals, as well as the extent to which patients take medications as prescribed by their physician on the basis of these decisions [173, 174].

Since the success of AIT depends on the duration of appropriately performed treatment, it is particularly important that AIT is carried out in accordance with prescriber's recommendations. Analogous to other types of treatment, the likelihood of treatment success and adherence to therapy is improved by thoroughly informing the patient about the way in which AIT works [165, 175, 176].

As SCIT is administered by a physician, it would initially seem that adherence is easier to monitor for SCIT than for SLIT. However, exactly how much bet-

ter this renders adherence to SCIT than to SLIT is currently controversial. There is a general lack of suitable independent studies addressing the important issue of compliance/adherence under real-life conditions.

In a review by Senna, data from clinical studies on SCIT and SLIT were pooled together [177]. This review reports adherence rates of approximately 70 % for SCIT and 75 % for SLIT. However, these results have only limited significance, since data from studies from the US and Europe – with differing treatment regimens, indications and patient groups – were pooled together.

In a randomized controlled trial, 271 patients (age 15 to 65 years) with allergic rhinitis with/without accompanying asthma were to receive SLIT over a course of three years [145]. The authors found in 72 % of the patients treated over the whole course of three years an adherence-rate of more than 80 % and in 18 % of the patients an adherence-rate between 60 % and 80 %.

No differences in compliance rates between SCIT and SLIT were reported in a comprehensive review of Incorvaia et al. [30], independently of the form of administration compliance rates in recent trials varied between 75 % and 90 %. However, these data are from clinical trials and are not likely to predict treatment adherence in a real-world setting [120].

Low treatment adherence obviously jeopardizes therapeutic success. This conclusion was confirmed by an analysis of real German statutory healthcare insurance SCIT prescription data conducted by Claes et al. [178]. This study demonstrated persistence rates (consecutive average prescription rates) that dropped off over the years: in only 24 % of patients treated with established SCIT products was SCIT continued into the third year. Similarly negative results from Germany and Italy for SLIT over 3 years have also been published as posters or letters (13,2 % to 22,7 %) [179, 180, 181]. Another analysis of real German statutory healthcare insurance prescription data investigated persistence rates among 1,409 patients treated with market-leading SCIT and SLIT products [182]. This analysis found unsatisfactory persistence rates in the third year of therapy in 34 % to 51 % of patients. An evaluation of German statutory healthcare insurance prescription data from 562 children and adolescents aged between 4 and 18 years demonstrated a persistence rate of 44.1 % in the third year [183].

Following therapy, a study by Sondermann et al. questioned SCIT and SLIT patients on what they perceived as disadvantageous aspects of the treatment in order to explain the unsatisfactory adherence to therapy [173]. The heavy time demands of the treatment were considered a problem by 69.5 % of patients, while 62.5 % reported adverse effects of the therapy as a problem. Furthermore, 60.7 % of



Table 10

**Reasons for non-compliance in AIT  
(modified from [173])****Patient information**

- Patient inadequately informed/motivated
- no understanding of primary and secondary preventative effects of AIT (allergic march, new sensitization)

**Therapeutic procedure**

- Adverse events
- no reduction in symptoms or self-medication use
- incorrect patient selection

**Clinic/Practice Management**

- heavy time demands on patients (particularly for SCIT)
- treatment insufficiently integrated into daily life
- no recall system or patient counselling, possibly due to lack of financial resources

patients experienced no relief of symptoms and 53.7 % had not received adequate information about the therapy.

According to these data, reasons for early discontinuation of therapy may be based on inadequate patient information, on the way in which treatment is carried out and on practice management (see **Tab. 10**). Patient compliance rates should be increased by better organization in the medical office and an attempt to better educate the patient. In order to ensure adequate therapeutic adherence and compliance, recall systems are necessary for both SLIT and SCIT. Improvements in AIT adherence represent one of the most important goals for the future, in order to ensure success of the therapy. Additional motivation and support measures for physicians (e. g., the “Bavarian Selective Contract”) are desirable.

**Conclusion:** Treatment adherence among AIT patients is lower than assumed by physicians, irrespective of the form of administration. Clearly, adherence is of vital importance for treatment success. Improving AIT adherence is one of the most important future goals, in order to ensure efficacy of the therapy.

## 7. Subcutaneous immunotherapy with insect venom allergens

A systemic allergic reaction with symptoms of an immediate-type allergy (anaphylaxis) occurs in about 3.5 % of the population following a hymenoptera sting (e. g., bee, wasp) [184].

Reactions can occur with various degrees of severity, which should be considered when making the indication for AIT. The success rate of guideline-oriented AIT performed with the standard maintenance dose lies between 75 % and 85 % for bee-ven-

om allergic patients and between 90 % and 95 % in wasp-venom allergic patients. In non-responders an increased maintenance dose results in a therapeutic success in almost all the cases [184].

For information on indications, contraindications, performing treatment, possibilities for monitoring treatment as well as treatment duration, the reader is referred to the current guideline on “Diagnosis and treatment of bee and wasp venom allergy” (S2-AWMF-LL registry number 061-020 [184]).

## 8. Safety, risk factors and adverse events

### 8.1. SCIT

When administered correctly to properly selected patients, in a medical office/hospital with experience in this type of treatment, allergen-specific immunotherapy with SCIT preparations is safe and well tolerated [165, 185, 186].

Local reactions including redness, swelling or itching at the injection site occur very frequently, but can be treated using local measures (e. g., cooling or topical glucocorticoids) or systemic antihistamines.

When increased local reactions (redness and/or swelling >10 cm in diameter) occur at the injection site, the specific information contained in the manufacturer's product information leaflet for the corresponding SCIT preparation should be consulted for the dosage of the subsequent injection. However, in a retrospective evaluation of their own patient data, an American group was able to show that increased local reactions do not predict an increased individual risk of a systemic reaction [187].

In the case of  $\text{Al}(\text{OH})_3$ -containing SCIT products, rarely and particularly with incorrect intradermal administration, but also as a result of  $\text{Al}(\text{OH})_3$ -contact allergy, protein contact dermatitis, or a vasculitic inflammatory reaction, granulomas may result from a foreign body reaction [188, 189, 190]. In such cases, it is recommended that treatment continues with an allergen extract that does not contain  $\text{Al}(\text{OH})_3$ . The possible systemic risks from adjuvant aluminum have been the topic of critical discussion for some time. In response to the increasing number of requests, the PEI published a safety evaluation of aluminum in therapeutic allergens on its website in 2014 ([www.pei.de/DE/arzneimittelsicherheit-vigilanz/archiv-sicherheitsinformationen/2014/ablage2014/2014-01-21-sicherheitsbewertung-von-aluminium-in-therapieallergenen.html](http://www.pei.de/DE/arzneimittelsicherheit-vigilanz/archiv-sicherheitsinformationen/2014/ablage2014/2014-01-21-sicherheitsbewertung-von-aluminium-in-therapieallergenen.html)). The statement addresses not only local tolerability, but also sensitization potential, toxicity and German pharmacovigilance data. According to this publication, the overall sensitization potential of aluminum is to be considered low; only isolated cases of sensitization in SCIT patients have been reported [189, 190, 191]. Toxic effects depend on the quantity of aluminum absorbed [191].

The contribution of SCIT to the lifelong accumulation of aluminum in the human body is low compared with other sources. The specific evaluation of all reports of treatment-related AEs between 1986 and 2013 also raised no alarms regarding the safety of these preparations.

The PEI concludes that the currently available scientific data do not suggest that children or adults are put at risk by undergoing SCIT with aluminum adjuvanted allergens and that, on the basis of current knowledge, there is no reason to reconsider the use of licensed therapy allergens containing aluminum adjuvants.

Systemic allergic reactions to SCIT can take the form of mild to severe reactions of the skin, gastrointestinal tract, airways or cardiovascular system. In a retrospective analysis of a large patient population (2,206 patients) and a large total number of injections (192,505 injections) over a 10-year observation period, a total of 115 systemic reactions (5.2 % of patients or 0.06 % of all injections) were observed, almost all of which occurred within the 30 min post-injection observation phase (no fatalities) ([192], reviewed in [186]). A more recent analysis conducted between 2008 and 2011 by the American Academy of Allergy, Asthma and Immunology (AAAAI), based on an average of 6.3 million injection visits per year, found systemic reactions in approximately 0.1 % of all injection visits. Once again, no fatal reactions were observed [193, 194]. Fatal reactions with clear causal relation to SCIT were estimated in a survey of American allergists for the period of 1990 to 2001 to have a frequency of 1 in 2.5 million injections [195].

According to PEI data (1991 to 2000), the incidence of severe reactions is calculated to be 0.002 % to 0.0076 % (in terms of injections) for non-modified ("native") allergen extracts and 0.0005 % to 0.01 % for chemically modified allergen extracts (allergoids) [196]. If risk factors are considered, severe reactions are sometimes predictable and can usually be avoided with appropriate care and prophylactic measures [165, 186, 197].

**Tab. 11** provides an overview of possible risk factors that may be related to the occurrence of systemic reactions during AIT.

In 2010, the WAO has published a new standardized five-grade classification of systemic adverse events in SCIT (**Tab. 12** [198]).

In the case of recurrent severe reactions or insufficient compliance (e.g., the patient does not stay in the medical office long enough, intervals between injections are too long, inappropriate physical exertion or avoidable contact with allergens around the time of injection), the decision on whether to continue or discontinue therapy should be made by an allergist. When making this decision, the allergist

Table 11

#### Risk factors for systemic reactions during AIT (modified from [165, 186, 197, 202])

Current allergy symptoms and potential allergen exposure
Current infections
Mast cell disease
Hyperthyroidism
Unstable or insufficiently treated asthma
A high degree of sensitization
Inadequate dose escalation during initiation
Pharmaceutical use (β-blockers)
Inadequate circulatory stress, excessive alcohol consumption, high-intensity physical exercise, sauna (shortly before and for the rest of the day of injection, augmenting factors should be avoided)
Poor technique of injection
Allergen extract overdose
Manufacturer's recommendation for dose reduction upon changing to a new production batch was overlooked

should weigh the risks associated with continuing treatment against the urgency of the indication and possible treatment alternatives (see also Sect. 6.).

In order to aid decision-making, the patient should be referred back to the physician who established the original indication for SCIT where required. The risk factors described above should be investigated and avoided in relation to SCIT. In cases where treatment is continued, it is recommended that the dose be reduced in accordance with the individual preparation's product information leaflet.

Where adverse effects occur, it is possible to pre-medicate with an antihistamine in order to reduce the frequency and severity of possible systemic reactions; however, premedication does not eliminate the possibility of systemic reactions [156, 168, 169, 199, 200].

The management of severe adverse events is described in detail in Sect. 9. ("Emergency treatment").

**Conclusion:** Severe, potentially life-threatening systemic reactions during SCIT are possible, but – providing all safety measures are adhered to – these events are very rare. Most adverse events are mild to moderate and can be treated well.

#### 8.2. SLIT

When administered correctly to patients selected based on the given indications, allergen-specific immunotherapy with SLIT preparations is safe and well tolerated [110, 120].

Adverse events during SLIT are dose-dependent and, depending on the preparation, manifest in 40 % to 75 % of the cases as temporary local mucosal reactions (pruritus or dysesthesia in the oral

Table 12

**Grading system of systemic adverse events for subcutaneous immunotherapy (SCIT) according to the World Allergy Organization (WAO) 2010 [198] and for sublingual immunotherapy (SLIT) according to WAO 2013 [205]**

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
<b>Symptom(s)/sign(s) of one organ system present</b>  <u>Cutaneous</u> Generalized pruritus, urticaria, flushing, or sensation of heat or warmth <sup>a</sup> or Angioedema (not laryngeal, tongue or uvular) or <u>Upper respiratory</u> Rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) or Throat-clearing (itchy throat) or Cough perceived to originate in the upper airway, not the lung, larynx, or trachea or <u>Conjunctival</u> Erythema, pruritus or tearing or <u>other</u> Nausea, metallic taste, or headache	<b>Symptom(s)/sign(s) of more than one organ system present</b> or <u>Lower respiratory</u> Asthma: cough, wheezing, shortness of breath (e.g., less than 40 % PEF or FEV <sub>1</sub> drop, responding to an inhaled bronchodilator) or <u>Gastrointestinal</u> Abdominal cramps, vomiting, or diarrhea or <u>other</u> Uterine cramps	<u>Lower respiratory</u> Asthma (e.g., 40 % PEF or FEV <sub>1</sub> drop not responding to an inhaled bronchodilator) or <u>Upper respiratory</u> Laryngeal, uvula, or tongue edema with or without stridor	<u>Lower or upper respiratory</u> Respiratory failure with or without loss of consciousness or <u>Cardiovascular</u> Hypotension with or without loss of consciousness	Death

Patients may also have a feeling of impending doom, especially in grades 2, 3, or 4.

*Note:* Children with anaphylaxis seldom convey a sense of impending doom and their behavior changes may be a sign of anaphylaxis; eg, becoming very quiet or irritable and cranky. Scoring (grade 1-4) includes a suffix (a–d or z) that denotes if and when epinephrine is or is not administered in relationship to onset of symptom(s)/sign(s) of the SR: a, ≤ 5 minutes; b, >5 minutes-to ≤ 10 minutes; c, > 10 to 20 minutes; d, > 20 minutes; z, epinephrine not administered. (further details in [198])

The final grade of the reaction will not be determined until the event is over, regardless of the medication administered. The final report should include the first symptom(s)/sign(s) and the time of onset after the subcutaneous allergen immunotherapy injection<sup>b</sup> and a suffix reflecting if and when epinephrine was or was not administered, e.g., Grade 2a; rhinitis: 10 minutes

Final Report: Grade a–d, or z \_\_\_\_\_, First symptom(s)/sign(s) \_\_\_\_\_ Time of onset of first symptom \_\_\_\_\_  
 Comments (on reaction and treatment): \_\_\_\_\_

<sup>a</sup>This constellation of symptoms may rapidly progress to a more severe reaction.

<sup>b</sup>Symptoms occurring within the first minutes after the injection may be a sign of severe anaphylaxis. Mild symptoms may progress rapidly to severe anaphylaxis and death.

cavity, swelling of the oral mucosa, throat irritation) [120, 201, 202, 203]. These reactions usually occur during the initiation of SLIT, are mostly mild and generally subside 1 to 3 weeks after the start of treatment [120]. However, particularly in the early treatment phase, these reactions can lead to self-discontinuation of therapy. It is thus particularly important that the patient is thoroughly informed at the start of treatment (see also “treatment information sheet for SLIT”, Fig. 6; available as a handout at [www.dgaki.de/Leitlinien/s2k-Leitlinie-sit](http://www.dgaki.de/Leitlinien/s2k-Leitlinie-sit)). Gastrointestinal symptoms during SLIT are described as occurring at a frequency of 14 % [110].

Premedication with antihistamines may also be suitable for SLIT in order to reduce the extent of local reactions. A lack of compliance, newly arising

contraindications, persisting unacceptable local adverse events, severe reactions after administration and a lack of clinical response after two years of SLIT are indications for early discontinuation of therapy [165].

In regards to the safety profile of SLIT, it is important to note that most adverse events occur at home, where there is no possibility of immediate medical intervention in the (very rare) case of a systemic reaction. It is therefore important to inform patients – and, when applicable, their parents – thoroughly on how to react if adverse events occur or if administration of the SLIT preparation is forgotten, as well as about situations in which SLIT should be temporarily interrupted. Examples of the latter include elective maxillofacial surgery, as well as the existence of oropharyngeal in-

Table 13

### Grading system for local adverse events in sublingual immunotherapy (SLIT) according to the WAO (modified from [205])

Symptom/sign	Grade 1: mild	Grade 2: moderate	Grade 3: severe	unknown severity
Pruritus/swelling of mouth, tongue, or lip; throat irritation*, nausea, abdominal pain, vomiting, diarrhea, heartburn, or uvular edema	not troublesome <i>and</i> no symptomatic treatment required <i>and</i> no discontinuation of SLIT because of local side effects	troublesome <i>oder</i> requires symptomatic treatment <i>and</i> no discontinuation of SLIT because of local side effects	Grade 2 <i>and</i> SLIT discontinued because of local side effects	Treatment is discontinued, but there is no subjective, objective, or both description of severity from the patient/physician.

*Each local adverse events can be early (< 30 minutes) or delayed, \*for example, itchy palate, burning or swelling of the throat (added by guideline authors)*

fections and lesions (ulcers, gingivitis, periodontitis), gastroenteritis and asthma exacerbations [120].

Although the risk of severe systemic adverse reactions is lower with SLIT compared with SCIT [120, 196], 11 incidences—in some cases with severe anaphylaxis—are described in the literature following sublingual administration of allergens in droplet or tablet form (reviewed in [202]). However, treatment in these cases was not administered according to the standards that apply today (non-standardized extracts, rush protocols, excessive allergen dose, patients in whom SCIT had previously been interrupted due to severe reactions) [202]. An important risk factor for severe systemic adverse events during SLIT – as is also the case for SCIT – is insufficiently controlled asthma [202].

The recommendation of one expert team that patients with severe adverse events during SCIT should switch to SLIT [176] cannot be supported: a history of severe systemic reactions after subcutaneous application of allergens also constitutes a risk factor for possible severe systemic reactions during SLIT [204].

The WAO recommends the adoption of the grading system for systemic reactions on SCIT also for SLIT and, moreover, proposes a new, standardized classification of local reactions during SLIT (Tab. 13) [120, 205]. The aim of both classification systems is to provide a worldwide standardized reporting system that should enable the frequency and severity of adverse events of AIT (SLIT and SCIT) to be more precisely defined.

**Conclusion:** Dose-dependent adverse local reactions occur frequently in the mouth and throat in SLIT. Systemic reactions have been described in SLIT, but are seen far less often than with SCIT. In terms of anaphylaxis and other severe systemic reactions, SLIT has a better safety profile than SCIT.

### 8.3. Reporting adverse events from AIT in Germany, Austria and Switzerland

In Germany, in accordance with §63c (2) of the German AMG ([www.gesetze-im-internet.de/amg\\_1976/\\_63c.html](http://www.gesetze-im-internet.de/amg_1976/_63c.html)), the marketing authorization holder of a particular drug is legally obliged to report within 15 days every suspected serious adverse event (SAE) of which he gains knowledge to the competent higher federal authority and additionally, in the case of a SAE occurring in third countries, to the European EudraVigilance database. Moreover, it is planned that suspected non-serious adverse events are to be reported to the European database by the marketing authorization holder within 90 days.

Reporting suspected AEs occurring in daily practice is of great importance for collecting as much data as possible pertaining to the safety of a drug, as well as for allowing continued monitoring of its risk–benefit ratio. Physicians, pharmacists and other healthcare professionals, as well as patients, parents, legal guardians and other relatives should report every suspected AE via the national reporting system (in Germany, for allergen preparations located at the PEI; in accordance with AMG §11a Sect. 1). Patients in Germany can report an AE via <https://verbraucher-uaw.pei.de/fmi/iwp/cgi?-db=Verbraucher-UAW&-loadframes>.

In Austria, the Institute of Pharmacovigilance of the Austrian Medicines and Medical Devices Agency (BASG/AGES Medizinmarktaufsicht) is responsible for operational tasks. According to the Austrian Medicinal Products Act and Pharmacovigilance Regulations, 2006 (AMG §75j; [www.basg.gv.at/ueber-uns/gesetzliche-grundlagen/arzneimittel](http://www.basg.gv.at/ueber-uns/gesetzliche-grundlagen/arzneimittel)), members of the following professions are legally obliged to report AEs to the Institute of Pharmacovigilance of the Austrian Medicines and Medical Devices Agency: physicians, dentists, veterinarians, midwives, pharmacists and druggists, as well as tradespersons who are



Table 14

**Emergency equipment for the treatment of anaphylactic reactions (S2-AWMF-LL registry number 061–025, 2014 [207])**

Stethoscope, blood pressure monitor
Tourniquet, syringes, indwelling venous catheters, infusion set
Oxygen with face mask/nasal cannula
Guedel-tube, bag valve mask, suction unit, intubation set
Adrenaline for injection
H1-antihistamines for intravenous injection
infusion solutions (0.9% NaCl solutions, balances electrolytes/colloids)
Glucocorticoids for intravenous injection
Bronchodilator (rapidly acting $\beta_2$ adrenoreceptor agonist for inhalation or intravenous injection)
Automated external defibrillator (optional)
Pulse oximeter (optional)
<i>NaCl, Sodium chloride</i>

authorized for the manufacture or wholesale of drugs in accordance with the Austrian Commercial Code of 1994 and the marketing authorization holders of proprietary medicinal products. As in Germany, marketing authorization holders are legally obliged to report all information on suspected serious AEs arising within the European Economic Area and third countries electronically to the European Eudra-Vigilance database within 15 days after gaining knowledge. Information on all suspected non-serious AEs occurring within the European Economic Area must be reported electronically by the marketing authorization holder to the EudraVigilance Database (AMG §75j Sect. 3) within 90 days after gaining knowledge. Patients in Austria also have the option to report AEs electronically via [www.basg.gv.at/pharmakovigilanz/elektronische-meldung/registrierung/patientangoeriger](http://www.basg.gv.at/pharmakovigilanz/elektronische-meldung/registrierung/patientangoeriger).

Since the introduction of the new Medicinal Products Act (HMG) 2002, medical professionals in Switzerland are legally obliged to report particular AEs that are fatal or life-threatening, cause severe or permanent damage and those which are either not mentioned in or are inadequately addressed by drug information (drug compendium) [206]. Reports are made to regional pharmacovigilance centers by means of a special form. These centers take over the data entry and electronically forward the information (anonymously regarding patient and primary reporter) to Swissmedic. Swissmedic administers the central Swiss AE database and forwards information on severe and new AEs to the relevant pharmaceutical companies. Further to this, Swissmedic conveys all reports to the World Health Organization (WHO). Marketing authorization holders, manufacturers and distributors are also legally obliged to report AEs and quality complaints.

AEs covered by this legal obligation are serious or previously unknown AEs, accumulation of known or previously unknown AEs, quality complaints and unusual constraints on distribution. Manufacturers are required to send quarterly safety update reports on each of their approved drugs to the national competent authority.

## 9. Emergency treatment

Systemic reactions following AIT generally occur within the first 30 min following administration. Therefore, in the case of SCIT, it is essential that patients remain under medical observation for at least 30 min following injection and that they report immediately any symptoms that may arouse suspicion of an allergic reaction [165].

Systemic reactions require immediate treatment due to the risk of rapid exacerbation [207, 208].

The personnel involved need to be familiar with the obligatory medications and with the equipment used in an allergic emergency (see **Tab. 14**) [207]. Initial measures include: suitable positioning of the patient, i.m. epinephrine (150  $\mu$ g for patients weighing 15 to 30 kg, 300  $\mu$ g for patients weighing > 30 kg), infusion therapy via a large-lumen intravenous access as well as O<sub>2</sub> administration. Early use of i.m. epinephrine in the acute management of anaphylactic reactions helps guarantee rapid efficacy of medication (stabilization of the cardiovascular system) [208]. For practical reasons, having an epinephrine auto-injector available is recommended in order to ensure prompt therapeutic intervention. Regular training in immediate procedures for allergic systemic reactions is to be recommended [207].

Early signs of a severe reaction include: a burning sensation and pruritus of the palms and soles; perianal or perigenital pruritus; an urge to defecate and urinate; sneezing attacks and generalized pruritus. In addition, further respiratory and/or cardiovascular symptoms may occur rapidly.

Although treatment recommendations for the emergency management of anaphylaxis are based on only limited data from clinical studies, they are nonetheless consistent on an international, European [209] as well as national level [207] regarding the use of Adrenalin i.m., which is also valid in the acute management of emergencies in the AIT setting.

The described recommendations also apply in the case of anaphylactic reactions occurring in regard to SLIT.

**Conclusion:** The risk and effects of adverse systemic reactions in the setting of AIT can be effectively reduced by training of personnel, adhering to safety standards and prompt use of emergency measures, including early administration of i.m. epinephrine. Details on the acute management of anaphylactic

Table 15

### Requirements on future AIT trials (modified according to the "PRACTALL" consensus report (EAACI and AAAAI [193] as well as the current ARIA report [221])

Development and implementation of clinical studies	<ul style="list-style-type: none"> <li>– Standardization and validation of clinical endpoints (e.g., CSMS) in AIT studies to ensure future comparability of clinical documentation on differing preparations, including independently for children, adolescents and adults</li> <li>– Clear definition of the period during which data on clinical symptoms are recorded (standardized classification of the severity of measured pollen exposure)</li> <li>– Further validation and standardization of the use of allergen exposure chambers, in order that these can be used in AIT not only in phase-II AIT studies</li> <li>– More detailed investigation of underlying immunological mechanisms of AIT</li> </ul>
Specific questions	<ul style="list-style-type: none"> <li>– AIT in polysensitized patients</li> <li>– (Secondary) preventive effects, such as preventing allergic march and new sensitizations with which AIT preparations</li> <li>– Long-term effects of AIT (adults and children)</li> <li>– Recording and analyzing the safety of AIT in patients that receive AIT in the case of particular co-factors or (relative) contraindications</li> <li>– More data from non-interventional observational trials in order to better assess the efficacy of AIT under practical conditions</li> <li>– Direct comparison of different preparations [unmodified (native) versus chemically modified], treatment regimens and modes of administration in a direct head-to-head comparison</li> </ul>
Patient selection for clinical studies	<ul style="list-style-type: none"> <li>– Development of methods/biomarkers to select patients ideally suited for AIT on the basis of responder phenotypes</li> <li>– Phenotyping according to indication (allergic rhinitis, bronchial asthma and atopic dermatitis)</li> </ul>
Measurement of allergen content in various extracts	<ul style="list-style-type: none"> <li>– Standardization, validation and general acceptance of measuring methods to determine the (major) allergen content</li> </ul>
Biomarkers	<ul style="list-style-type: none"> <li>– Identification and validation of biomarkers as predictive factors for the success of AIT</li> </ul>
Efficacy and safety of AIT at different ages	<ul style="list-style-type: none"> <li>– More studies complying with up-to-date quality standards on clinical efficacy, immunological effects and safety stratified according to age (children, adults, &gt;65 years)</li> </ul>
New approaches in AIT	<ul style="list-style-type: none"> <li>– Investigation and confirmation of the efficacy and safety of AIT by using new adjuvants, synthetically produced peptides, recombinants or modified therapy allergens as well as by means of new modes of allergen administration, such as intralymphatic or epicutaneous immunotherapy</li> </ul>
Safety and tolerability of AIT	<ul style="list-style-type: none"> <li>– Clear international definition of contraindications in AIT</li> <li>– Central register to record systemic reactions to AIT in everyday practice</li> </ul>
Adherence	<ul style="list-style-type: none"> <li>– Development of further programs to improve patient compliance</li> </ul>
Socio-economics	<ul style="list-style-type: none"> <li>– Long-term (&gt;3 years) cost-effectiveness of AIT</li> </ul>

reactions can be found in the current S2 guideline on anaphylaxis issued by the AWMF (S2-AWMF-LL Registry Number 061-025 [207]).

## 10. Future perspectives for AIT

By using novel or optimized adjuvants, it is possible to achieve stronger stimulation of the immune system at otherwise unchanged doses or higher doses can be implemented without increased risk [210, 211]. With the aid of recombinant allergens, immunotherapeutics can be produced in precisely defined concentrations and quality in a highly standardized manner [212].

By modifying such allergens, novel preparations that also offer potential in terms to optimize effects/side effects profiles can be produced. The first products of this kind are currently being investigated in phase-II trials [213].

Furthermore, with recombinant allergens, attention can also be turned to new indications for AIT, e.g., food allergies.

By using allergens at other administration sites [epidermal immunotherapy (EPIT) or intralymphatic immunotherapy (ILIT)], it is possible to achieve similarly good immune responses compared with conventional AIT (with patch applications or only a few (3 to 6) injections) [214].

These approaches are also undergoing clinical investigation in phase-II and also in early phase-III trials with altogether promising results to date [215, 216, 217].

Combination therapy, using in particular the humanized anti-IgE antibody omalizumab, makes AIT possible in patients with moderate to severe bronchial asthma or hymenoptera venom allergy to whom AIT was previously inaccessible due to allergic side effects [218, 219].

**Conclusion:** AIT is undergoing some innovative developments in many areas (e.g., allergen characterization, new administration routes, adjuvants, faster and safer dose escalation protocols), some of

which are already being investigated in clinical trials.

### 11. Requirements on future AIT trials

Despite the fact that AIT has been used for the disease-modifying treatment of type-I allergic diseases (such as allergic rhinitis and allergic asthma) for over a century [220], a number of important questions remain to be answered with large multicenter trials (see **Tab. 15**, modified according to [193] and [221]).

### Final

10th October 2014 (ed: Pfaar), following a consensus process and approval by the guideline authors on 18-07-2014 and by board members of the scientific medical societies involved and professional associations by 01-10-2014

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