

Comparison of allergy immunotherapy medication persistence with a sublingual immunotherapy tablet versus subcutaneous immunotherapy in Germany



To the Editor:

Medication persistence and adherence in allergy immunotherapy (AIT) has been reported to be lower in real life than in clinical studies,¹ with manufacturers' sales figures often indicating poorer adherence and persistence than postmarketing studies.^{2,3} This might result from patients tending to be more compliant when their behavior is being recorded, which is commonly known as the Hawthorne effect.

The low risk of anaphylaxis and serious adverse reactions with sublingual immunotherapy (SLIT)^{4,5} has resulted in orodispersible SLIT-tablets being approved in Europe and the United States for self-administration provided that the first dose is tolerated under medical supervision. For many patients, self-administration of SLIT-tablets is an advantage over injection during subcutaneous immunotherapy (SCIT). However, dosing regimen and frequency of physician's office visits differ considerably between the 2 administration routes, and efficacy and safety profiles of individual products administered through each route vary widely. Because these factors have been reported to affect persistence and adherence,⁶ we compared medication persistence and adherence with a SLIT-tablet versus SCIT products in patients with grass pollen allergy over a 3-year period from treatment initiation.

This retrospective cohort study used prescription renewal rates for a 75,000 standardized quality units tablet (SQ-T), 2,800 BAU grass pollen SLIT-tablet, and 100 to 100,000 SQ-U/mL or 600 to 30,000 SQ+/mL suspension for subcutaneous injection from the German IMS Health Disease Analyzer database for the period of January 2006 to August 2014 to obtain an accurate picture of persistence and adherence in real life. More information about the products and database can be found in the [Methods](#) section in this article's Online Repository at www.jacionline.org. The primary end point was proportion of persistent patients (≥ 1 prescription in both the second and third years) in the SLIT-tablet and SCIT subcohorts over the 3-year follow-up period. Other end points included adherence, which was expressed as the medication possession ratio (MPR; ie, number of days from index date to end of last prescription/number of expected days of therapy [1095 days; ie, 3 years] expressed as a percentage for persistent patients).

Of 6954 patient profiles obtained from the database, 2429 in the SLIT-tablet and 2109 in the SCIT subcohorts met the inclusion criteria (see [Fig E1](#) in this article's Online Repository at www.jacionline.org). More than 60% were adults, with a mean age of around 27 years; 12% to 14% of patients had comorbid sinusitis, and less than 10% in each subcohort had a recorded diagnosis of asthma, although around one third were receiving medication for symptomatic asthma (see [Tables E1-E3](#) in this article's Online Repository at www.jacionline.org).

A similar proportion of patients in the SLIT-tablet and SCIT subcohorts had data available for years 2 and 3 after the index visit

(75% vs 72% and 61% vs 60%, respectively; [Fig 1, A](#)). The primary outcome showed that the overall proportion of persistent patients having prescriptions in year 3 was similar in the SLIT-tablet and SCIT subcohorts (30% vs 31%, respectively; $P = .51$). A higher proportion of patients receiving SCIT had a record of at least 1 prescription in year 2 (54%) versus patients receiving SLIT-tablets (41%, $P < .0001$), indicating that patients discontinued the SLIT-tablet slightly earlier. Among those who continuing treatment at year 2, proportionally fewer patients receiving the SLIT-tablet discontinued treatment in the third year ([Fig 1, B](#)).

The proportion of persistent patients in each age group was comparable between SLIT-tablets and SCIT within one age group, with the highest persistence in the 5- to 14-year-old age group and the lowest persistence in the 15- to 17-year-old age group ([Fig 1, C](#)). This might be related to parents caring for younger children while adolescents start to become more independent. Persistence also varied by prescribing physician's specialty ([Fig 1, D](#)). Adherence among persistent patients was comparable for the SLIT-tablet and SCIT products (MPR, 81% vs 83%) when each SCIT injection was assumed to cover a period of 4 weeks and was similar irrespective of patient age group or the specialty of the prescribing physician ([Fig 2](#)).

These findings show that despite similar persistence over 3 years, discontinuations in the first year of treatment were more frequent among patients taking the SLIT-tablet. However, those continuing treatment after the first year were less likely to discontinue treatment during the third year compared with those receiving SCIT, leading to comparable 3-year persistence between both application forms.

Reasons underlying treatment discontinuation and nonadherence with AIT are varied; studies of clinical trials and real life cite medication costs, inconvenience, fear of injections, patient impressions of poor efficacy, and adverse events as factors.⁶ Adverse events were shown to account for at least a quarter of all dropouts in clinical trials, with the rate likely to be even higher in clinic practice.⁵

The majority of adverse reactions with SLIT-tablets are local oral reactions that occur early in treatment and often disappear during the first days or weeks without any medical intervention as the immune system develops tolerance; however, in some patients these can be bothersome enough to cause treatment discontinuation.⁴ These early adverse effects could be responsible for the higher rates of discontinuation we observed in the first year of treatment with the SLIT-tablet; however, because such data are not recorded in the database, based on current data, this hypothesis cannot be confirmed. The lower discontinuation rates in the second and third years suggest that patients who stick to treatment until adverse effects have disappeared, which is a sign that the immune system has developed tolerance to the allergen, have a greater treatment motivation and therefore better persistence in the second and third years of treatment compared with SCIT. If this is indeed the reason for the high frequency of early discontinuations with the SLIT-tablet, programs to educate patients, general practitioners, and specialists on early local adverse reactions to SLIT-tablets, their management, and the decrease in the first weeks of treatment can help more patients continue treatment.

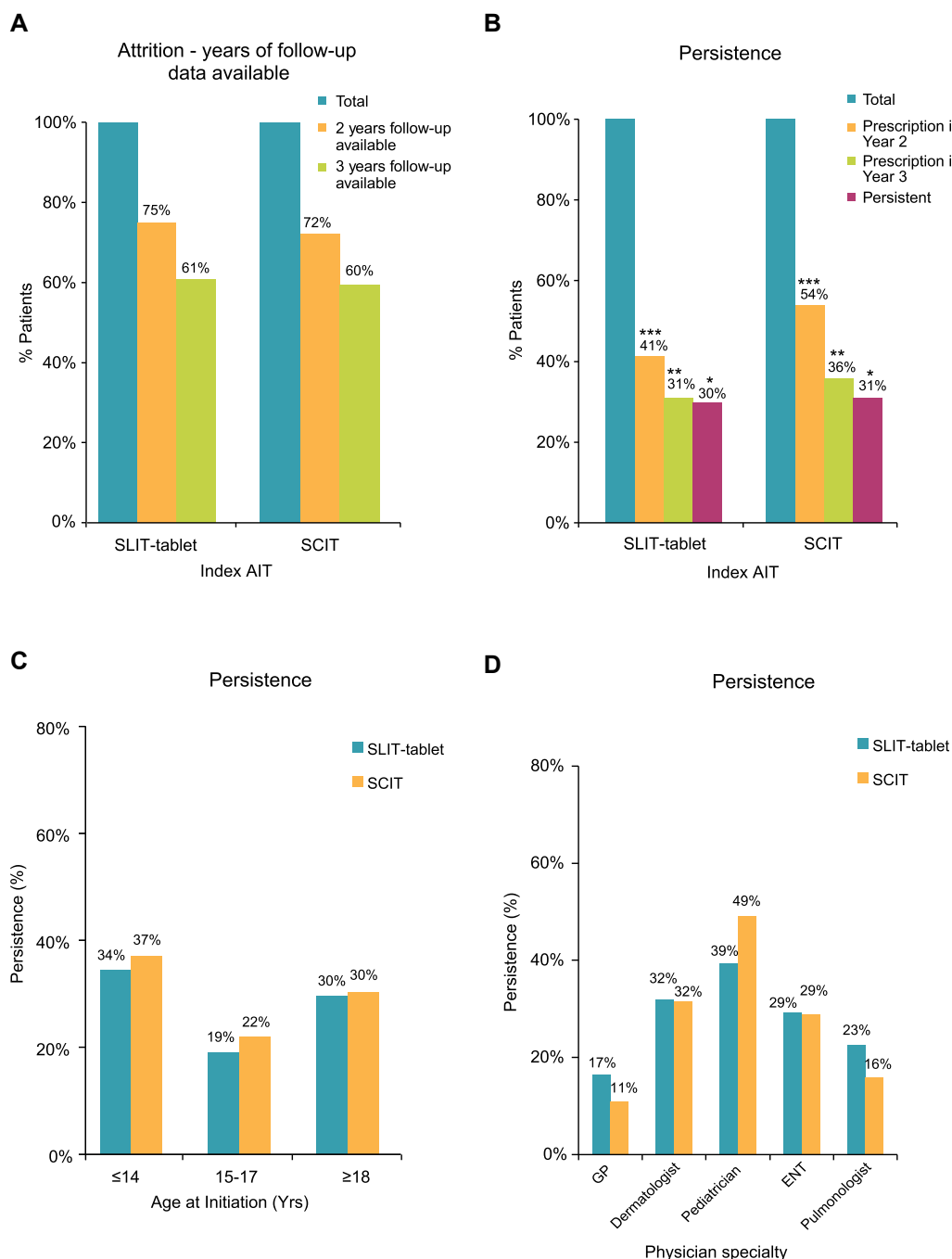


FIG 1. Patient attrition and persistence. **A**, Proportion of patients with follow-up data available in years 2 and 3. Patients were included if they had a prescription between January 2006 and August 2014. Patients with their index prescription between September 1, 2012, and August 31, 2014, do not have 2 years of follow-up available; likewise, index prescriptions between September 1, 2011, and August 31, 2012, do not have 3 years of follow-up available. **B**, Proportion of persistent patients. * $P = .5104$, ** $P = .0071$, and *** $P < .0001$ for comparison of SLIT-tablet versus SCIT (2-sided test). **C**, Proportion of persistent patients by age at index (SLIT-tablet vs SCIT: ≤14 years [$P = .5709$], 15-18 years [$P = .7031$], and ≥18 years [$P = .8365$, 2-sided test]). **D**, Proportion of persistent patients by prescribing physician's specialty (SLIT-tablet vs SCIT: general practitioner, $P = .5255$; dermatologist, $P = .9547$; pediatrician, $P = .1968$; ear, nose, and throat physician, $P = .9312$; and pulmonologist, $P = .5389$ [2-sided test]).

In contrary to the (after first intake) at-home administered SLIT tablets, the SCIT products evaluated in this study involve frequent physician's office visits during the up dosing phase, which could also play a part in the lower rate of early discontinuations

observed. Published data show an association between more frequent physician's office visits and better persistence; a 2-year follow-up survey in children treated with SLIT showed that the discontinuation rate decreased with increasing numbers of

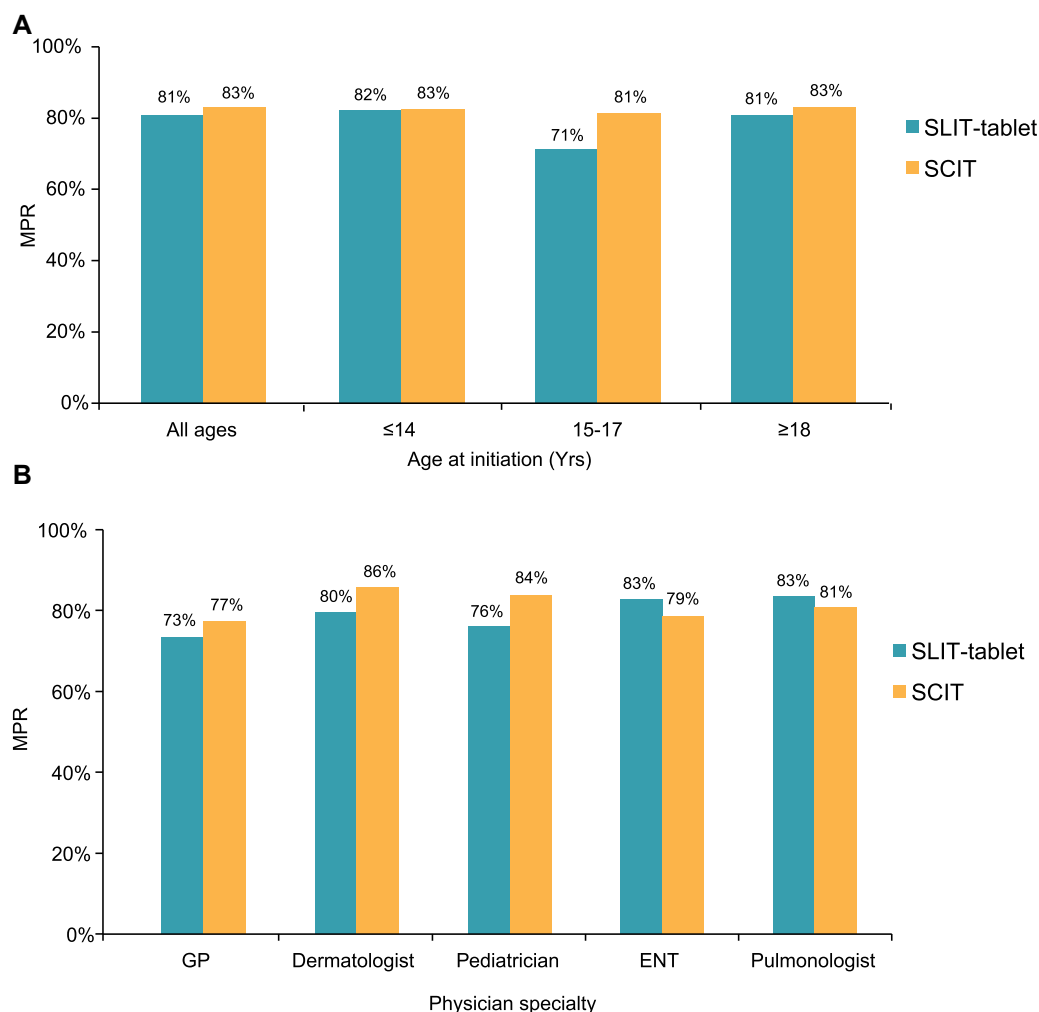


FIG 2. Adherence, expressed as the MPR (ie, number of days from index date to end of last prescription/number of expected days of therapy [1095 days; ie, 3 years] expressed as a percentage for persistent patients). **A**, Adherence with the SLIT-tablet and SCIT over the 3-year study period and by age at initiation. **B**, Adherence with the SLIT-tablet and SCIT over the 3-year study period by prescribing physician's specialty.

physician's office visits per year, with adequate adherence seen only in patients with 4 or more visits per year.⁷

The literature points to a clear need to improve persistence and adherence in real life because the effect size of SLIT is dependent on it. Treatment initiation in AIT differs in some aspects from other medications because treatment is initiated usually outside the allergen season and the patient does not see an immediate treatment effect. Initiation of SLIT leads to mostly local oral discomfort. We propose that better informing patients on early local adverse effects and their improvement with continued treatment as a first sign of increasing tolerance and treatment efficacy, even outside the pollen season, could increase treatment motivation and therefore also persistence. The 30-minute waiting time at first intake could be used to provide patients with this information. Because of the retrospective nature of the present study, it was not possible to test this hypothesis. We also propose monitoring programs with periodic controls. Both could encourage more patients to continue SLIT-tablet treatment during the first year, which might improve persistence over the whole treatment period; however, both proposals need to be tested in clinical studies.

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Isotype-specific agglutination-PCR (ISAP): A sensitive and multiplex method for measuring allergen-specific IgE



To the Editor:

Component-resolved diagnostics (CRD) is a rapidly growing class of *in vitro* tests for evaluating individuals thought to have allergic diseases. In contrast to using whole-allergen extracts,

CRD uses individual, molecularly pure allergen components to measure allergen-specific IgE (sIgE), thereby helping to assess the risk of allergy to such allergens with improved accuracy.¹ For example, the presence of sIgE against certain peanut components (eg, Ara h 1, Ara h 2, and Ara h 3) indicates a higher risk for anaphylaxis than does anti-Ara h 8 sIgE (which can reflect cross-reactivity with birch pollen).¹ Although ELISA-based CRD tests may lack analytical sensitivity, the alternative more sensitive assays currently used clinically (eg, ImmunoCAP) are not multiplexable and may omit certain critical allergens.² These problems can be mitigated by collecting more blood for additional tests. However, this approach can be problematic when studying small animals or testing young children.

Here, we report isotype-specific agglutination-PCR (ISAP), a highly sensitive and multiplexable approach for measuring allergen-specific immunoglobulins in 1 μ L of sample (Fig 1, A). ISAP uses chemically synthesized allergen-DNA and secondary antibody-DNA conjugates (see Fig E1 in this article's Online Repository at www.jacionline.org). Each DNA conjugate bears either the 5' or the 3' portion of a split DNA barcode (Fig 1, A). Upon binding to the target immunoglobulin in the sample, the allergen-DNA and secondary antibody-DNA conjugates are agglutinated into close proximity. The addition of a short complementary bridge oligo and DNA ligase reunites the 2 halves of the barcode to create a full-length DNA amplicon, which can then be quantified by quantitative PCR (qPCR). The amount of the amplicon directly reflects the quantity of analyte

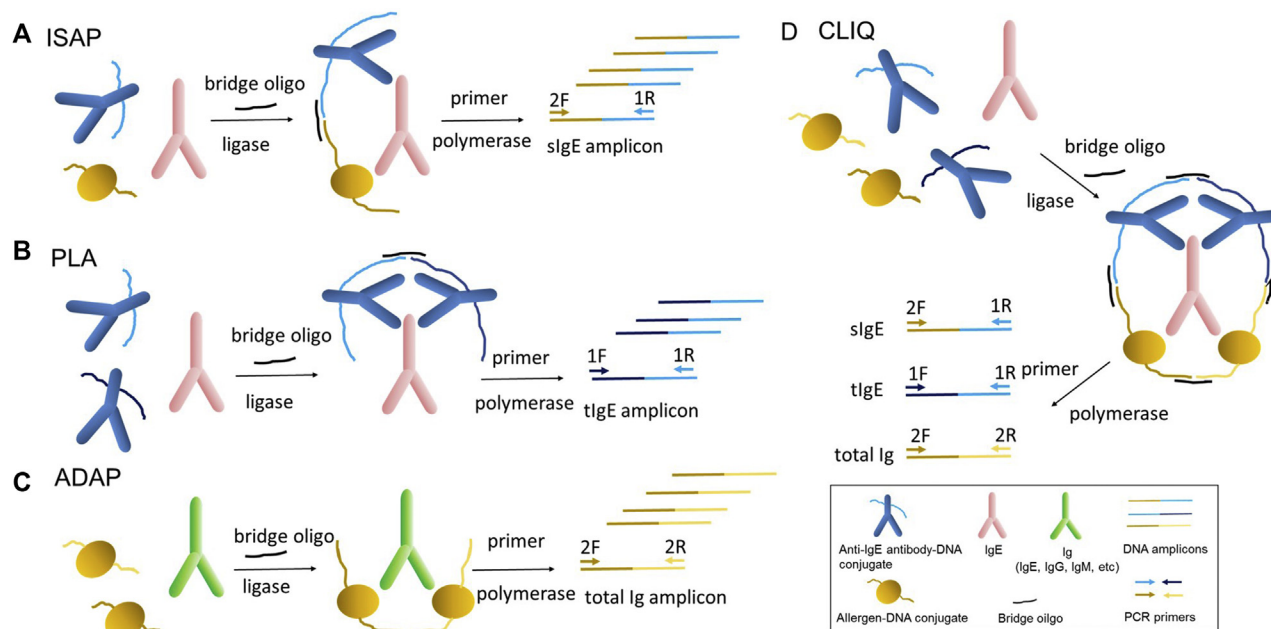


FIG 1. Principle scheme of PCR-based antibody quantification methods. **A**, ISAP for quantification of sIgE. Samples containing sIgE are first incubated with allergen-DNA and antibody-DNA (in this case, anti-IgE antibody-DNA) conjugates. Upon formation of immune complexes consisting of sIgE, allergen-DNA, and anti-IgE-DNA, the DNA components of the conjugates are brought into close proximity, and the addition of a short bridge oligo and DNA ligase joins the 2 halves of DNA into a full-length amplicon. Real-time qPCR is then used to quantify the abundance of the ligated DNA amplicons, which reflects the level of sIgE in the sample. **B**, PLA for quantification of tIgE. Samples are incubated with 2 anti-IgE-DNA conjugates that each bear half of a full-length DNA amplicon. **C**, ADAP for quantification of all anti-allergen immunoglobulins (IgE, IgG, IgM, etc). This procedure is performed as before, but with 2 allergen-DNA conjugates. **D**, Integration of ISAP, PLA, and ADAP into a single assay, termed CLIQ. The sample is incubated with 2 allergen-DNA and 2 anti-IgE-DNA conjugates followed by ligation. The reconstituted DNA amplicons can be interrogated independently by dedicated primer pairs in the different wells of a 96- or 384-well plate. *Ig*, Immunoglobulin.

METHODS

Study description

The study used prescription data from the German IMS Health Disease Analyzer database for the period from January 1, 2006, to August 31, 2014. Medication persistence to a SLIT-tablet and an SCIT preparation were calculated and compared over 3 years from AIT initiation. Grazax/Grastek *Phleum pratense* 75,000 SQ-T/2,800 BAU and Avanz 600 or 30,000 SQ+/mL or Alutard SQ 100 to 100,000 SQ-U/mL grass pollen (ALK-Abelló, Hørsholm, Denmark) were chosen as representatives of SLIT-tablets and SCIT, respectively. The study period covered the last grass pollen season before the launch of Grazax in Germany in November 2006.

IMS Disease Analyzer database

The IMS Disease Analyzer database is derived from electronic medical records from a panel of German General Practitioners and other office-based, specialist physicians.^{E1} It contains information on diagnosis (International Classification of Diseases–Tenth Revision), disease history, prescription medications (including pack size and strength), routine laboratory tests, and referrals. Data are anonymous and truncated to ensure confidentiality, and demographic information is limited to year of birth, sex, height, body weight, and insurance status.

IMS Disease Analyzer coverage in the last 3 moving annual totals up to May 2014 comprised 13.4 million patients with 81.9 million recorded medication prescriptions. The database contains records from 2.9% of physicians in Germany; coverage is 2.5% of general practitioners, 4.6% of pulmonologists, 3.5% of pediatricians, 4.2% of dermatologists, and 4.6% of ear, nose, and throat specialists.

AIT products

Grazax is a SLIT-tablet containing 75,000 SQ-T allergen extract of grass pollen (*P pratense*). In Europe Grazax is approved as a disease-modifying treatment for pollen-induced rhinitis and conjunctivitis in adults and children aged 5 years and more with clinically relevant symptoms and a positive skin prick and/or specific IgE test response to grass pollen.^{E2}

Avanz is a suspension for subcutaneous injection containing 600 SQ+/mL or 30,000 SQ+/mL of *P pratense* or grass mix and rye allergens adsorbed on aluminum hydroxide and is indicated for the treatment of allergic rhinoconjunctivitis in patients with grass pollen allergy with or without mild-to-moderate asthma.^{E3}

Alutard SQ is a suspension for subcutaneous injection containing 100, 1,000, 10,000, or 100,000 SQ-U/mL grass mix, rye, or grass mix and rye allergens adsorbed on aluminum hydroxide. It is approved in Germany for causal treatment of immediate-type allergy caused by the respective pollens, such as hay fever, allergic conjunctivitis, and allergic bronchial asthma, as well as allergic nettle rash in special cases, and prevention of allergic bronchial asthma.^{E4}

Patient selection

Patients who fulfilled all of the following criteria were eligible for inclusion in the study:

- record of Anatomical Therapeutic Chemical code V01AA02 for grass pollen–induced allergies at any point in the medical history;
- current prescription for Grazax, Avanz, or Alutard SQ;
- treatment-naïve status for AIT at the index visit (during all available patient history); and
- at least 6 months of medical history available before the index visit.

The index date was defined as the date of the first AIT prescription. Patients prescribed multiple AIT products at the index visit were excluded from the study.

Data analysis

Entire prescription and diagnosis records for eligible patients were imported and analyzed in SAS software (Version 9.3; SAS Institute, Cary, NC). Patient attrition, demographics, and relevant comorbid conditions at the index visit were tabulated (see Table E1 for relevant International Classification of Diseases–Tenth Revision codes).

Adherence was expressed as the MPR for persistent patients who had at least 1 prescription in each year of follow-up. MPR was calculated for the whole 3-year study period and for each of the 3 follow-up years. MPR for the 3-year study period was stratified by prescribing physician's specialty and age at index.

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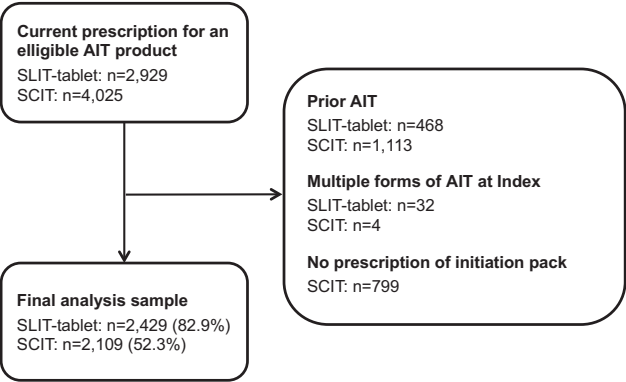


FIG E1. Attrition of patient profiles and selection of final analysis sample.

TABLE E1. Demographic characteristics of the study sample

Characteristic	SLIT-tablet (n = 2429)	SCIT (n = 2109)
Mean age (y [SD])	28.8 (14.8)	26.6 (13.4)
Median age (y)	27.0	25.0
Mean age ≥ 18 y (y [SD])	35.1 (12.3)	33.1 (11.1)
Median age ≥ 18 (y)	33.0	31.0
Age <18 y, no. (%)	661 (27.2)	659 (31.2)
Age ≥ 18 y, no. (%)	1768 (72.8)	1450 (68.8)
Female sex, no. (%)	1182 (48.7)	998 (47.3)
Male sex, no. (%)	1247 (51.3)	1111 (52.7)
Prescribing specialist		
Dermatologist, no. (%)	759 (31.2)	833 (39.5)
Ear, nose, and throat specialist, no. (%)	1111 (45.7)	871 (41.3)
General practitioner, no. (%)	170 (7.0)	113 (5.4)
Pediatrician, no. (%)	227 (9.3)	185 (8.8)
Pulmonologist, no. (%)	162 (6.7)	107 (5.1)

TABLE E2. Comorbidities

Comorbidity*/comedication	SLIT (n = 2429), no. (%)	SCIT (n = 2109), no. (%)
Asthma	189 (7.8)	150 (7.1)
Eczema	166 (6.8)	136 (6.4)
Hives	28 (1.2)	17 (0.8)
Eosinophilic esophagitis	0 (0)	0 (0)
Sinusitis	346 (14.2)	264 (12.5)
Symptomatic asthma medication	791 (32.6)	635 (30.1)

*Comorbidities determined by using International Classification of Diseases–Tenth Revision diagnosis codes.

TABLE E3. Symptomatic asthma medications

Inhaled medications
Short-acting inhaled β -agonists
Maxair Autohaler (pirbuterol)
Ventolin, Proventil, Proair (albuterol HFA)
Xopenex (levalbuterol)
Other, specify name on form
Long-acting inhaled β -agonists
Foradil Aerolizer (formoterol)
Serevent Diskus (salmeterol)
Other, specify name on form
Inhaled corticosteroids
Aerobid (flunisolide)
Asmanex Twisthaler (mometasone)
Azmecort (triamcinolone)
Flovent, Flovent Diskus (fluticasone)
Pulmicort (budesonide)
QVAR (beclomethasone HFA)
Other, specify name on form
Combination inhaled corticosteroids, long-acting inhaled β -agonist
Advair (fluticasone-salmeterol)
Dulera (mometasone furoate and formoterol fumarate dihydrate)
Symbicort (budesonide-formoterol)
Other, specify name on form
Other, including anticholinergics
Atrovent (ipratropium)
Combivent (ipratropium with albuterol)
Spiriva (tiotropium bromide)
Other, specify name on form
Mast cell stabilizers
Intal (cromolyn)
Other, specify name on form
Oral medications
Leukotriene modifiers
Accolate (zafirlukast)
Singulair (montelukast)
Zyflo, Zyflo CR (zileuton)
Other, specify name on form
Systemic corticosteroids
Dexamethasone
Methylprednisolone
Prednisolone
Prednisone
Other, specify name on form
Methylxanthines
Theophylline
Other, specify name on form
Medications injected under the skin
Antibody neutralizers
Xolair (omalizumab)
Other, specify name on form

HFA, Hydrofluoroalkane.