

Long-term real-world effectiveness of allergy immunotherapy in patients with allergic rhinitis and asthma: Results from the REACT study, a retrospective cohort study.

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Summary

Background Allergen immunotherapy (AIT) is the only causal treatment for respiratory allergy. Long-term real-life effectiveness of AIT remains to be demonstrated beyond the evidence from randomised controlled trials (RCTs).

Methods REACT (Real world effectiveness in allergy immunotherapy) is a retrospective cohort study using claims data between 2007 and 2017. Study eligibility was a confirmed diagnosis of allergic rhinitis (AR), with or without asthma, and AIT. To ensure comparable groups, AIT-treated subjects were propensity score matched 1:1 with control subjects, using characteristic and potential confounding variables. Outcomes were analysed as within (pre vs post AIT) and between (AIT vs control) group differences across 9 years of follow-up (ClinicalTrials.gov: NCT04125888).

Findings 46,024 AIT-treated subjects were matched with control subjects and 14,614 were included in the pre-existing asthma cohort. AIT-treated subjects were 29.5 (16.3) years and 53% were male. Compared to pre-index year, AIT was consistently associated with greater reductions compared to control subjects in AR and asthma prescriptions, including both asthma controller and reliever prescriptions. Additionally, the AIT group had significantly greater likelihood of stepping down asthma treatment ($P < 0.0001$). In addition to the reduction in asthma treatment in the AIT group, a greater reduction in severe asthma exacerbations was demonstrated ($P < 0.05$). Reductions in pneumonia with antibiotic prescriptions, hospitalisations, and duration of inpatients stays were all in favour of AIT.

Interpretation The study extends the existing RCT evidence for AIT by demonstrating longer-term and sustained effectiveness of AIT in the real world. Additionally, in patients with concurrent asthma, AIT was associated with reduced likelihood of asthma exacerbations and pneumonia.

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Key words: Allergic rhinitis; Allergy; Allergy immunotherapy; Asthma; Effectiveness; Real-world evidence; Retrospective cohort study

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Abbreviations: AIT, allergy immunotherapy; AR, allergic rhinitis; FU, follow-up; HDM, house dust mite; HRU, health care resource utilisation; ICS, inhaled corticosteroids; INCS, intranasal corticosteroids; LABA, long-acting beta2-agonists; PSM, propensity score matching; RCT, randomised clinical trial; RWE, real world evidence; Rx, prescription; SABA, short-acting beta2-agonists; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy

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Research in context

Evidence before this study

In recent years, randomised controlled trials (RCTs) have confirmed the efficacy and safety of allergy immunotherapy (AIT) in subjects with allergic rhinitis (AR) with or without asthma, but real-world effectiveness data remain scarce. We searched PubMed using the search string (allergen immunotherapy OR allergy immunotherapy OR specific immunotherapy OR AIT OR SIT) AND (allergic rhinitis OR AR OR allergy OR asthma) AND (retrospective studies OR retrospective OR real-world evidence OR RWE OR cohort studies OR cohort stud* OR Follow-Up Studies). The search was limited to publications during the last 10 years and yielded 229 publications. Upon review of the publications, 19 real-world effectiveness studies in allergy immunotherapy (AIT) were identified. However, the 19 studies were limited to either a specific allergen or route of administration, by a short follow-period or focused on the impact of compliance on effectiveness.

Added value of this study

Based on the literature search, we conclude that this pre-specified propensity score matched retrospective cohort study is the most comprehensive real-world effectiveness study within AIT to date, looking at effect of AIT in AR and asthma. Since AIT is the only causal treatment for allergy, demonstrating sustained, long-term effects of AIT-treatment beyond the limited follow-up period in RCTs is highly relevant. Being a causal treatment for allergy also infers potential benefits on multiple manifestations e.g. allergic rhinitis and comorbid asthma. The results of the current study complement the existing RCT evidence for AIT, by demonstrating long-term and sustained reductions in prescriptions for symptom-relieving AR medication across nine years of follow-up. Additionally, the study provides novel long-term data in patients with asthma. In the study, AIT was found to be consistently associated with sustained, long-term reductions across clinically relevant outcomes, e.g. prescriptions of reliever and controller asthma medication, asthma exacerbations, pneumonia, and hospitalisations.

Implications of all the available evidence

While the study methodology addresses an important knowledge gap by providing high-quality real-world evidence in AIT, the findings of the study also add new information on how AIT works both long-term and in real life. The novel findings from the study are complementary to the evidence from RCTs and can further support clinical decision-making on AIT for the treatment and sustained control of both allergic rhinitis and asthma.

heterogeneous disease causing allergic rhinitis (AR) and asthma.² 10–40% of patients with AR have allergic asthma and a large proportion (up to 60–80%) of asthmatic patients experience chronic symptoms of AR.^{3,4} AR is a well-known risk factor for poor asthma control,^{5,6} as patients with asthma and severe AR are up to 4–5 times more likely to have poor asthma control than those without AR.⁷ As AR is associated with a great disease burden,⁸ the frequent co-existence with asthma only increases the overall impact of the allergic disease.^{9,10} Consequently there is a need for treatment options that target the underlying allergy and benefit both diseases.

Allergy immunotherapy (AIT) is the only causal treatment for allergy. Increased tolerance towards a causal allergen is achieved by repeated allergen administrations, resulting in modulation of the immunological response.¹¹ AIT can be administered sublingually (SLIT) as tablets or drops or subcutaneously (SCIT) for a minimum treatment period of three years.¹² Long-term, randomised controlled trials (RCTs) for SQ grass SLIT-tablets and SCIT have confirmed that AIT can modify the allergic disease by demonstrating sustained reductions in symptoms and symptom-relieving medication use up to two years after treatment cessation in patients with allergic rhinitis.^{13,14} Despite AIT being the only causal treatment, long-term data are limited. Data on the efficacy of AIT in patients with comorbid asthma were demonstrated in house dust mite (HDM), grass, and tree pollen allergy.¹⁵ In RCTs, treatment with SQ HDM SLIT-tablets in subjects with asthma and AR provided reductions in inhaled corticosteroids (ICS) use and a 34% relative risk reduction in moderate-severe asthma exacerbations was demonstrated.^{16,17} However, whether AIT can prevent disease progression from mild to severe asthma needs to be further examined.

While the efficacy and safety of AIT administered as SLIT-tablets for the most common respiratory allergies, e.g. grass, tree, HDM, cedar, and ragweed have been demonstrated in RCTs,¹⁵ uncertainty around real-world effectiveness and across longer follow-up periods of AIT in the real world, in particular on asthma related outcomes, remains.¹⁸ There is a need for generating robust real world evidence (RWE) for AIT as treatment of respiratory allergies to provide complementary evidence for the existing RCTs.^{18,19} The aim of the REACT (Real world effectiveness in allergy immunotherapy) study was to assess the long-term effectiveness of AIT for the treatment of AR and asthma in the real world setting.

Methods

Study design and dataset

For this retrospective, observational, propensity score matched (PSM) cohort study, anonymised claims data

Introduction

Allergy is caused by an abnormal reaction of the immune system to otherwise harmless allergens and afflicts 10–40% of populations.¹ Respiratory allergy is a

during 2007 to 2017 from a German health insurance fund database (Betriebskrankenkasse (BKK)) were used. The BKK health insurance fund is a branch of the statutory health insurance and is the most representative of persons insured by the German statutory health insurance,²⁰ covering approximately 90% of the German population.²¹ The real-world data used in this study comprised insurance claims of 5.9 million insured persons per year and included data on e.g. prescriptions, confirmed diagnosis codes, hospitalisations, specialist visits, and sick leave benefits.

Insurance data from January 1, 2007, through December 31, 2017 (study period) were used. Subjects were included in the dataset if they had an AIT prescription between January 1, 2008, and December 31, 2016, to allow for at least one-year pre and post AIT data availability. The study complied with European and German data protection regulations. Approval from the BKK database for the use of anonymized data was obtained. No institutional review board or ethical committee approval was needed. The study was pre-registered on clinicaltrials.gov (NCT04125888).

The study population consisted of subjects with AR with or without asthma and treated with AIT (AIT group) and a control group not treated with AIT. A confirmed diagnosis of AR had to be recorded during the study period for both groups. AIT-treated subjects were matched 1:1 using propensity score matching (PSM) to a control group of subjects with AR with or without asthma not treated with AIT (control group). The objective of PSM was to obtain an unbiased estimate of treatment effect adjusted for the impact of given confounding factors. The eligibility criteria for the AIT group were two consecutive prescriptions of the same AIT (index AIT) during the identification period (except for venom AIT); the first AIT prescription constituted the index date. The exclusion criterion for both groups was an AIT prescription during the pre-index period.

To evaluate the impact of AIT on asthma, two subcohorts, i.e. no asthma and pre-existing asthma, were specified from the main cohort (Suppl. Key definitions) before the index AIT. Hence, the study consisted of three cohorts (a main cohort, a pre-existing asthma cohort, and a no asthma cohort), each including AIT-treated subjects and their matched control subjects.

Outcomes

The primary outcome was AR prescriptions in each FU-year. Secondary outcomes were asthma prescriptions, severe asthma exacerbations, and change in asthma treatment steps (Suppl. Key definitions, Protocol). In the no asthma cohort, new onset of asthma was assessed as an outcome (Suppl. Key definitions). Diagnosis codes for asthma and use of controller medications mimicking the GINA (Global Strategy for Asthma

Management) steps were used to assess changes in asthma treatments (Suppl. Protocol).³ Short-acting beta-agonists (SABA) were reported separately. Key exploratory outcomes included health care resource utilisation (HRU), costs, sick leave, and respiratory tract infections (Suppl. Protocol). Events of anaphylaxis in relation to AIT index-date were assessed (Suppl. Protocol).

Subgroup analyses across different populations and treatment modalities were included and a sensitivity analysis was pre-specified for the assessment of asthma treatment steps. In the main analysis one prescription within a FU-year was sufficient to qualify for a treatment step. As asthma treatment may fluctuate, the asthma treatment steps were evaluated in a sensitivity analysis that required a confirmatory prescription (within the same drug class). A validation analysis was pre-specified to detect profound bias, i.e. reductions in AR medication previously demonstrated in multiple RCTs for SLIT-tablets^{22–25} should be demonstrated for the SLIT-tablet subgroup to show consistency with the existing evidence base.^{22–25}

Statistical analysis

To mitigate the risk of confounding due to differences in subjects treated with AIT and control subjects, PSM was used to balance the groups with respect to known confounders. In PSM, the likelihood of being treated with AIT (i.e. the propensity score) is calculated based on a range of variables for both treated and untreated subjects. Treated subjects are then matched with untreated subjects with a very similar propensity score. In this study, a range of variables was used to estimate the propensity scores for each individual subject (Suppl. Protocol). Treated subjects were matched 1:1 with control subjects using the fitted value on the logit scale and matching using the nearest neighbour approach without replacement with a calliper of 0.01. For successful matching, all standardised mean differences for variables included in the matching had to be <10% for the main cohort. All modifications to the PSM to achieve all standardised mean differences <10% took place prior to cohort lock and outcomes analyses (Suppl. Protocol). In addition to successful matching of the main cohort, the pre-existing asthma cohort, the no asthma cohort, and the age subgroup (age: <18 years and ≥18 years) were matched using the same PSM. Per protocol, all cohorts were locked prior to initiating any analyses of outcome. An index event (index AIT prescription) could only be observed in the AIT group; therefore control subjects were assigned the same index date as the subjects in the AIT group to whom they were matched. (Suppl. Protocol). Since a control could receive AIT at a later time-point, the matched control subjects were censored when they were prescribed AIT alongside the matched subject in the AIT group.

Outcomes were analysed as within group changes from pre-index year and between group differences i.e. AIT vs. control subjects. Continuous variables were reported as mean, absolute mean difference, relative mean difference, 95% confidence interval (CI) and p-value. For continuous variables, a paired *t*-test was used and for between groups differences an unpaired *t*-test was used as independent samples were assumed. Categorical variables were reported as odds ratio, 95% CI and p-value. For categorical variables, the Fisher's exact test was used to test for statistically significant differences. For variables with multiple categories, the Monte Carlo Simulation was used. Time-to-first analyses were summarised using Kaplan Meier (KM) curves. The median time to event was reported with 95% CI. The Cox Constant Proportional Hazards method was used to estimate the ratio of treatment effects and 95% CI. The proportional hazard assumption was tested using the Kolmogorov-type supremum test. For the time-to-any analysis including recurrent events, Cox proportional regression, i.e. the "The Prentice, Williams, and Peterson Total Time Model" (PWP total time model) was applied. (Suppl. Protocol, Statistical Analysis Plan).²⁶

Role of the funding source: As employees at ALK A/S, SB, LE, MR, and JRL designed the study in collaboration with BF, CB, MC, and NF. Data retrieval, PSM, cohort lock, outcome analyses, and statistical reporting were provided by a third-party vendor. SB, LE, MR, and JRL assessed and interpreted the findings in collaboration with BF, CB, MC, and NF. All authors had full access to the results, contributed to the preparation of the manuscript and concurred to its submission for publication.

Results

From 2007 to 2017, a total of 115,098 subjects had at least one AIT prescription out of the 5,983,511 available subjects in the database. 47,440 subjects with an AIT prescription were eligible for the study and included in the PSM alongside 1,003,332 control subjects who had at least one AR diagnosis and no AIT prescription 12 months prior to index date (Suppl. Figure S1). Before the matching, AIT-treated subjects were younger, more had asthma, and the rate of AR related comorbidities was higher than untreated patients (Suppl. Table S1). The PSM resulted in well balanced cohorts meeting the pre-specified criterion of standardised mean differences <10% for all variables (Suppl., Table S1, Figure S2). The final AIT cohort included 46,024 subjects matched 1:1 with a control subject, resulting in a main cohort of 92,048 subjects. The pre-existing and no asthma cohort were matched separately, after the main cohort was matched. Subjects, for which no good match was found were lost. In the pre-existing asthma cohort, 4635 subjects could not be matched and therefore lost. Similarly,

in the no asthma cohort 3911 subjects were not matched and therefore not included in the asthma subcohorts (AIT and control subjects). Hence, from the main cohort, 29,228 subjects were included in a pre-existing asthma cohort and 54,274 in a no asthma cohort (Suppl. Figure S3). Subgroups by route of administration comprised *N* = 36,927; *N* = 4816, and *N* = 3754 for SCIT, SLIT-drops, and SLIT-tablets, respectively. Subgroups by allergen comprised *N* = 11,713 on grass AIT, *N* = 7774 on HDM AIT, *N* = 11,897 on tree AIT, and *N* = 9726 on other allergens. In the main cohort, the AIT group had a mean age of 29.5 (16.3) years, 53% were males, and had a high prevalence of comorbidities. AIT-treated subjects were exposed to AIT treatment for a mean of 549 (284) days and had 1.084 (1.705) AR prescriptions. The demographics were overall similar across the main, pre-existing, and no asthma cohorts (Table 1, Suppl. Tables S2-S4).

In the pre-existing asthma cohort, the AIT group had on average 2.465 (3.022) asthma prescriptions. Subjects with pre-existing asthma were mainly on asthma treatment step 1–3 (Table 1). Furthermore, 16% had at least one severe asthma exacerbation. The sample size declined gradually over time. At 9 years of follow-up (FU) the study populations consisted of 3692 subjects (main cohort) and 1142 subjects (pre-existing asthma cohort) (Suppl. Figure S4).

In the main cohort, both the AIT and control group had reductions in AR prescriptions per subject across the FU-years compared to the pre-index year, with effect sizes ranging from –0.140 to –0.646 and –0.155 to –0.522 for AIT-treated subjects and control subjects, respectively (Suppl. Table S6). AIT was associated with greater reductions over time compared to the control group, which was sustained for 9 years (Fig. 1, Table 2). The AIT group was also found to have fewer AR prescriptions compared to the controls, when analysed cross-sectionally year by year (Suppl. Table S6). The overall reductions were consistent across drug classes, but slightly greater for antihistamine compared to intranasal corticosteroids (INCS) (Table 2 and Suppl. Table S5-S6, Figure S6). Greater reductions in AR prescriptions per subject were seen in AIT-treated subjects, while a larger proportion of AIT-treated subjects received at least one AR prescription during year 1–4 (Table S5) and in the same period also had more ambulatory care visits (including specialist visits) compared to control subjects (Suppl. Figure S5).

Similarly, in the pre-existing asthma cohort, both the AIT and the control group had reductions in asthma prescriptions per subject, with effect sizes ranging from –0.363 to –1.110 and –0.253 to –1.063 for AIT-treated subjects and control subjects, respectively (Suppl. Table S7). AIT was associated with greater reductions in asthma prescriptions over time compared to the control group, which was sustained for 9 years (Table 2, Suppl. Table S5). The AIT group was also found to have fewer

	Main				Pre-existing asthma			
	AIT N=46024		Control N=46024		AIT N=14614		Control N=14614	
Age* (years)	29.5	16.3	29.5	17.4	28.3	16.9	29.5	17.7
Sex# (males)	24410	53%	24134	52%	7919	54%	7766	53%
Key comorbidities#								
Conjunctivitis	10001	22%	10126	22%	3869	26%	3898	27%
Eczema	11909	26%	12868	28%	4418	30%	4830	33%
Health care utilisation*								
Ambulatory care visits (visits)	15.6	12.3	17.9	16.6	18.1	13.3	20.7	17.0
Hospitalisations (days)	0.2	0.6	0.2	0.7	0.2	0.7	0.2	0.7
Sick leave (days)	0.7	1.4	0.8	1.5	0.7	1.4	0.8	1.6
Treatment with AIT* (days)								
Duration until first discontinuation	216	118	..	..	218	120	..	..
Total duration on index-AIT	549	284	..	..	559	289	..	..
AR prescriptions*	1.084	1.705	1.034	1.878	1.415	1.985	1.416	2.258
Antihistamine	0.452	1.063	0.404	1.101	0.628	1.283	0.587	1.390
INCS	0.464	0.925	0.445	1.090	0.552	1.054	0.602	1.292
Asthma prescriptions*	0.996	2.199	0.986	2.367	2.465	3.022	2.495	3.308
SABA	0.398	1.033	0.393	1.169	0.964	1.489	0.980	1.715
ICS	0.221	0.724	0.209	0.767	0.565	1.095	0.540	1.166
ICS/LABA	0.261	0.901	0.267	0.980	0.650	1.359	0.679	1.462
At least one severe asthma exacerbations in pre-index year*	2756	6%	2368	5%	2329	16%	2088	14%
Asthma treatment steps#								
Treatment step 1	..	..	..	..	5499	38%	6074	42%
Treatment step 2	..	..	..	..	3289	23%	2888	20%
Treatment step 3	..	..	..	..	4600	31%	4434	30%
Treatment step 4	..	..	..	..	531	4%	524	4%

Table 1: Key demographics for main and pre-existing asthma cohort

* Continuous variables are reported as mean $\pm$ SD; # Categorical variables are reported as n (%); Prescriptions (Rx) are reported as Rx/ subject; Pre-existing asthma: At least one asthma diagnosis or two prescriptions of SABA/ICS within the pre-index year; Asthma treatment step [cross sectional]: Predefined categories based on asthma diagnoses codes and asthma medication prescriptions within pre-index year - Treatment step 1: Asthma diagnosis in the absence of controller asthma medication; Treatment step 2: Monotherapy with either low dose ICS or LTRA; Treatment step 3: Dual therapy or therapy with medium-high ICS, LABA, or methylxanthine; Treatment step 4: Triple therapy or therapy with anti-IgE or anti-IL-5; AIT: allergen immunotherapy; AR: allergic rhinitis; Rx: prescription; IL: interleukin; ICS: inhaled corticosteroids; LABA: long-acting beta-agonists; SABA: short-acting beta2-agonists; LTRA: leukotriene receptor antagonists; INCS: intranasal corticosteroids.

asthma prescriptions compared to the controls, when analysed cross-sectionally (Suppl. Table S7). The between group differences in asthma prescriptions were mainly driven by SABA and ICS/long-acting beta2 agonists (LABA) prescriptions (Table 2, Suppl. Table S7, Figure S7). The greater reduction in both reliever and controller prescriptions for AIT-treated subjects, resulted in significantly greater odds of stepping down asthma treatment across all FU-years (Fig. 2, Table 3).

This was supported by time-to-first and time-to-any stepping down of asthma treatment, both demonstrating a greater likelihood of stepping down asthma treatment in the AIT group ($p < 0.0001$ for both) (Suppl. Table S8-S9, Figure S8). There was no increased risk of stepping up asthma treatment in the AIT group as the odds were similar between the AIT and the control group across most FU years (Table 3), and time-to-first stepping up of treatment showed a significantly lower risk of stepping

up for the AIT group ($P < 0.0001$) and time-to-any a similar risk ($P = 0.42$) (Suppl. Tables S10-S11, Figure S9).

Subjects treated with AIT had concurrent lower odds of experiencing a severe asthma exacerbation across the FU years (Fig. 2A) with significantly fewer events in years 2–7 (Suppl. Table S14). These findings were supported by time-to-first and time-to-any asthma exacerbation in the pre-existing asthma cohort, demonstrating a significantly reduced hazard ratio (HR) of 0.94 (95% CI: 0.90–0.98); $p < 0.05$ and 0.92 (95% CI: 0.90–0.95); $p < 0.0001$, respectively (Suppl. Tables S12-S13, Figure S9). Time-to-first and time-to-any asthma exacerbation were similar in the main cohort (Suppl. Table S10). In the no asthma cohort, the number of asthma prescriptions over time was low, however, while asthma prescriptions remained stable for the AIT group across the 9 FU years, prescriptions tended to increase in the control group (Suppl. Figure S12A). Opposing results

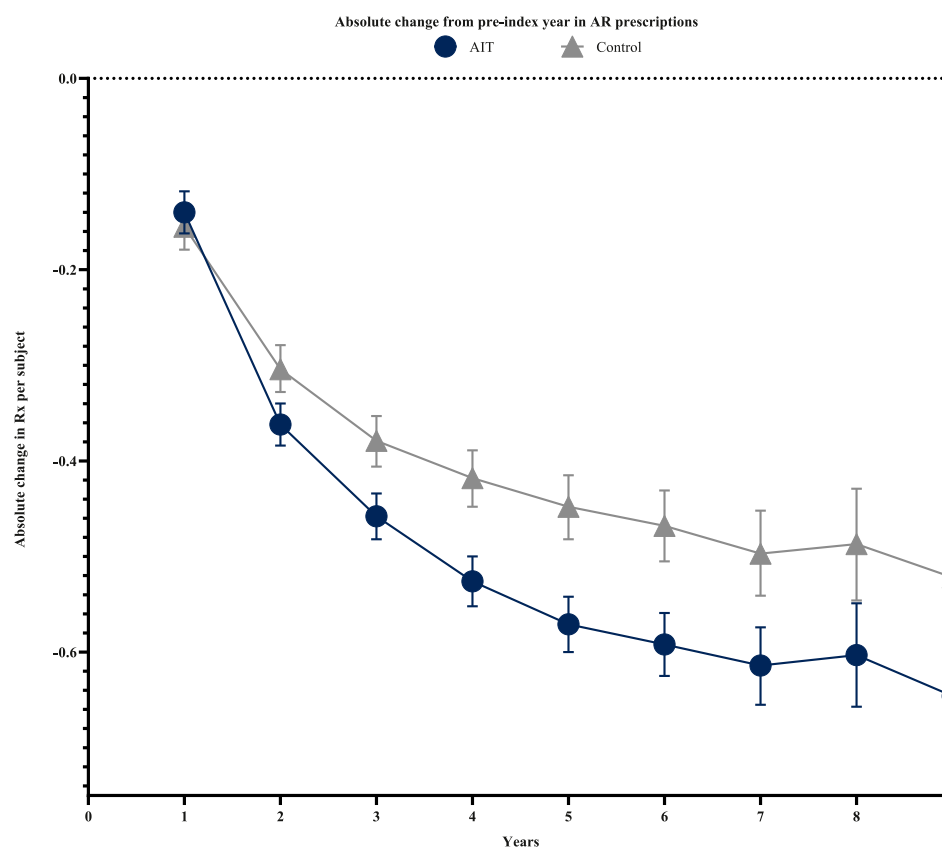


Fig. 1. Change from pre-index year in average Rx/subjects per follow-up year. AR prescriptions includes symptom-relieving allergic rhinitis medication, e.g. antihistamine and INCS.

were found in time-to-first onset of asthma, with an increased risk for the AIT group (HR: 1.22 (1.12–1.32); $p < .0001$) (Suppl. Table S15 and Figure S11) and no significant difference was found for the 3-point composite of time-to-worsening of asthma (Suppl. Tables S10–S11 and Figure S9). For the remaining survival analyses, the proportional hazard assumption was violated and only KM-curves and p-values were reported (Suppl. Figures S8–S10).

Key exploratory outcomes supported the secondary asthma outcomes (Table 3, Fig. 3). Compared to the control group, respiratory tract infections with antibiotic use, HRU with fewer hospital visits, hospital stays, and costs of inpatient hospitalisations were in favour of AIT (Table 3 for pre-existing asthma cohort, Suppl. Tables S16–S17 for main cohort). Similar to ambulatory care visits, increases in total health care costs were higher after 3 FU-years in the AIT group, while at 5-years of FU and 9-years of FU total health care costs increased more in the control group (Suppl. Table S18). Diagnosis codes for key comorbidities related to asthma such as bronchitis and chronic cough were also reduced for the AIT group (Suppl. Table S19).

The number of anaphylaxis cases around index date were low (Suppl. Definitions). amongst AIT-treated

subjects in total 33 cases were recorded; 30 of 36,927 subjects treated with SCIT; 2 of 4816 subjects treated with SLIT-drops; and 1 of 3754 subjects treated with SLIT-tablets.

The primary outcome, AR prescriptions, was consistently associated with greater reductions across all subgroups (Suppl. Table S20). The sensitivity analyses for asthma treatment steps were less robust, however, the likelihood of stepping down treatment remained significant in favour of AIT in FU-years 4–6 (Suppl. Table S21) and the validation analysis confirmed greater reduction in AR prescriptions for the SLIT-tablet subgroup (Suppl. Figure S13).

Discussion

This is the largest and most comprehensive AIT effectiveness study in the real world to date to our knowledge, demonstrating sustained, long-term reductions in both AR and asthma medication use, improved asthma control, prevention of asthma exacerbations, and respiratory tract infections.

The disease modifying effects of AIT were previously confirmed by sustained reductions in symptoms and symptom-relieving medication use two years post-

MAIN COHORT									
	Rx/subject	SD	Change from pre-index	95% CI	Rx/subject	SD	Change from pre-index	95% CI	P-value
Year 3	AIT (N= 32112)				Control (N= 32112)				AIT vs. Control
AR Rx*	0.609	1.344	-0.458	-0.482;-0.434	0.629	1.544	-0.379	-0.406;-0.353	0.081
Antihistamine	0.240	0.788	-0.217	-0.232;-0.203	0.250	0.895	-0.150	-0.165;-0.134	0.14
INCS	0.292	0.843	-0.155	-0.168;-0.141	0.291	0.970	-0.143	-0.159;-0.128	0.86
Year 5	AIT (N= 19783)				Control (N= 19783)				AIT vs. Control
AR Rx*	0.471	1.191	-0.571	-0.600;-0.542	0.533	1.504	-0.448	-0.482;-0.415	<0.0001
Antihistamine	0.179	0.695	-0.282	-0.300;-0.264	0.202	0.807	-0.194	-0.213;-0.175	0.0021
INCS	0.247	0.789	-0.178	-0.195;-0.162	0.278	1.034	-0.143	-0.164;-0.122	0.0008
Year 9	AIT (N= 1846)				Control (N= 1846)				AIT vs. Control
AR Rx*	0.393	1.142	-0.646	-0.741;-0.551	0.384	1.156	-0.522	-0.617;-0.427	0.81
Antihistamine	0.175	0.787	-0.333	-0.397;-0.269	0.138	0.659	-0.250	-0.305;-0.194	0.12
INCS	0.200	0.733	-0.183	-0.235;-0.131	0.225	0.842	-0.154	-0.214;-0.095	0.34

PRE-EXISTING ASTHMA COHORT									
	Rx/subject	SD	Change from pre-index	95% CI	Rx/subject	SD	Change from pre-index	95% CI	P-value
Year 3	AIT (N=10370)				Control (N=10370)				AIT vs. Control
Asthma Rx*	1.666	2.713	-0.825	-0.904;-0.746	1.880	3.308	-0.630	-0.718;-0.542	<0.0001
SABA	0.618	1.289	-0.361	-0.400;-0.322	0.725	1.579	-0.264	-0.310;-0.219	<0.0001
ICS	0.308	0.863	-0.274	-0.301;-0.247	0.316	0.920	-0.250	-0.279;-0.221	0.49
ICS/LABA	0.554	1.338	-0.076	-0.112;-0.039	0.613	1.387	-0.031	-0.070;0.007	0.0019
Year 5	AIT (N=6545)				Control (N=6545)				AIT vs. Control
Asthma Rx*	1.445	2.490	-1.022	-1.119;-0.926	1.740	2.964	-0.763	-0.872;-0.653	<0.0001
SABA	0.530	1.168	-0.429	-0.476;-0.382	0.657	1.517	-0.320	-0.377;-0.263	<0.0001
ICS	0.249	0.789	-0.347	-0.381;-0.313	0.263	0.841	-0.315	-0.351;-0.278	0.33
ICS/LABA	0.502	1.227	-0.095	-0.139;-0.051	0.610	1.382	-0.015	-0.063;0.033	<0.0001
Year 9	AIT (N=571)				Control (N=571)				AIT vs. Control
Asthma Rx*	1.331	2.651	-1.030	-1.361;-0.699	1.511	2.735	-1.063	-1.433;-0.693	0.26
SABA	0.443	1.131	-0.464	-0.613;-0.316	0.532	1.340	-0.501	-0.684;-0.318	0.22
ICS	0.172	0.620	-0.343	-0.437;-0.247	0.198	0.782	-0.452	-0.577;-0.327	0.53
ICS/LABA	0.553	1.271	-0.056	-0.210;0.098	0.601	1.298	0.096	-0.059;0.252	0.53

Table 2: AR and asthma prescriptions in key follow-up years

* Continuous variables are reported as mean +/- SD. Changes from pre-index year are presented as the within group absolute change and 95% confidence intervals CI; P-values are between group comparison of AIT vs. control subjects; Rx prescriptions are reported as Rx/subject; Only selected years are presented: Year 3 = expected end of treatment; Year 5 = duration of long-term RCTs investigating disease-modification; Year 9 = last year of observation. Outcomes across all nine follow-up years are presented in Suppl. Table S6-S7. AIT: allergy immunotherapy; AR: allergic rhinitis; INCS: intranasal corticosteroids; SABA: short-acting betaz-agonists; ICS: inhaled corticosteroids; LABA: long-acting betaz-agonists.

treatment in RCTs, following three-years of treatment with once-daily SQ grass SLIT tablets.¹³ In this study the real world effectiveness of AIT was confirmed by greater reductions in AR medications in the AIT group across 9 years of FU, demonstrating long-term and sustained effects substantially beyond the observation period from RCTs.¹³ Since AIT is considered a causal therapy, long-term follow-up data are of fundamental importance.

To date, two large RCTs with SQ HDM SLIT-tablets have confirmed the efficacy of AIT for treatment of asthma. One study found significant reductions in daily ICS dose compared to placebo while another RCT

demonstrated a significant risk reduction in moderate-severe asthma exacerbation.^{16,17} In the current study, AIT-treated subjects with AR and pre-existing asthma had significant reductions in both controller and reliever medication, suggesting improved asthma control. Concurrently to being more likely to step down asthma treatment, AIT reduced the odds of experiencing asthma exacerbations. As the findings were sustained across the nine years of FU, the study suggests prevention of asthma progression. Interestingly, the beneficial effects of AIT on asthma were found in a less severe asthmatic population, as only 4% were at treatment step 4, supporting the hypothesis that AIT may be

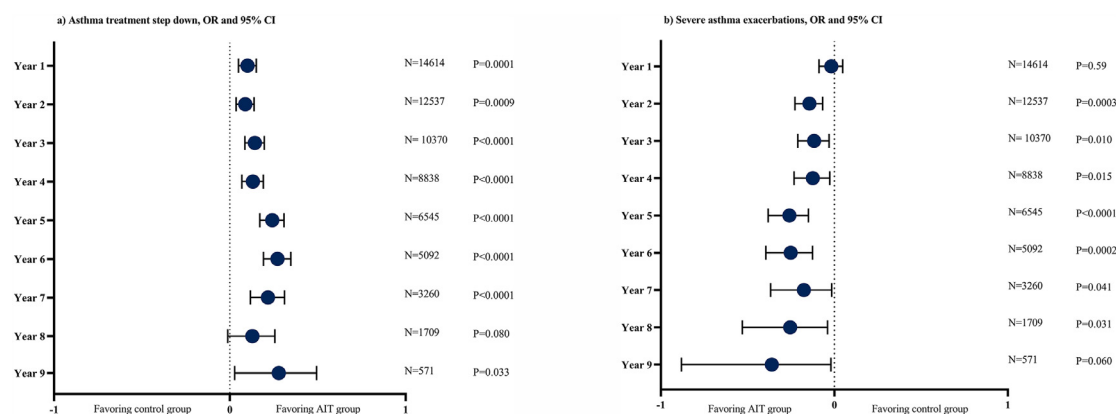


Fig. 2. a and b): Odds ratio for stepping down asthma treatment (a) and severe asthma exacerbations (b) in pre-existing asthma cohort. Panel a): Odds ratio and 95%CI of stepping down in asthma treatment step compared to pre-index year per follow-up year. Panel b): Odds ratio and 95%CI of severe asthma exacerbation per follow-up year. Asthma treatment step [change]: The definition of improvement or worsening in asthma treatment step was met, if subjects with pre-existing asthma changed asthma treatment step compared to the pre-index year. The asthma treatment steps were pre-defined categories based on asthma diagnoses codes and asthma medication prescriptions during pre-index and post-index years. Treatment step 1: Asthma diagnosis in the absence of controller asthma medication; Treatment step 2: Monotherapy with either low dose ICS or LTRA; Treatment step 3: Dual therapy or therapy with medium-high ICS, LABA or methylxanthine; Treatment step 4: Triple therapy or therapy with anti-IgE or anti-IL-5; Severe asthma exacerbation: 3-point composite of either new systemic corticosteroid prescription, status asthmaticus recorded in ambulatory care or hospitalisation for asthma. AIT: allergen immunotherapy; CI: confidence interval; OR: odds ratio; IL: interleukin; SABA: short-acting beta2-agonists, ICS: inhaled corticosteroids; LABA: long-acting beta2-agonists; LTRA: leukotriene receptor antagonists.

able to prevent progression from mild to more severe asthma and should be considered earlier in the treatment of allergic patients with asthma.²⁷ AIT-treated subjects were less likely to experience respiratory tract infections requiring antibiotics. Respiratory tract infections and allergy are known risk factors for asthma exacerbations, and the findings are further supported by another study that found AIT to be associated with a reduced risk of respiratory tract infections.²⁸ The clinical benefits of AIT seen in AR and asthma outcomes were supported by reductions in hospitalisations, length of stays and related costs. Ambulatory care visits and related costs, as well as specialist visits were increased, possibly due to subjects on SCIT having more HCP visits for AIT treatment. A low frequency of anaphylaxis cases was recorded.

RCTs have shown a beneficial effect of AIT on prevention of asthma.²⁹ A few RWE studies have also assessed onset of asthma with conflicting results.^{30–32} Due to different methodologies and definitions used, and due to risk of bias in these studies, it is difficult to draw general conclusions. The finding herein may be explained by confounding. AIT-treated subjects were mainly treated with SCIT which is also administered in clinics, and consequently, the AIT group had more ambulatory, and specialists care visits, particularly during the expected 3-year AIT treatment period. As new onset of asthma required a confirmed asthma diagnosis, the higher frequency of specialist visits may have

resulted in more asthma diagnoses being coded in the AIT group, despite asthma prescriptions remaining lower in the AIT group compared to the control subjects.

The study was pre-registered, and all outcomes and statistical analyses were pre-specified in the protocol. Further strengths include strong matching, documented locking of cohorts before outcome analyses, pre-defined validation step, large sample size, long-term follow-up, and robustness of results across FU years, outcomes, and subgroups.

In RCTs for AIT, patients are included based on diagnostic allergy testing, and symptoms and medication intake are recorded on a daily basis both to inform severity at baseline and efficacy of the treatment. In claims databases, such as the one used for this study, subjects' symptoms are not captured, and neither are results from diagnostic allergy testing captured to inform inclusion of subjects. Filled prescriptions, diagnosis codes and health care resource utilisation are used as proxies instead. This approach can cause some limitations. 1) When assessing the effectiveness of AIT using filled prescriptions, information on the subjects' symptom control is lacking. The less granularity of the available data makes it difficult to compare the effect size with RCTs. Instead, filled prescriptions are used as a proxy for symptom and medication scores, and a range of clinically relevant outcomes like confirmed diagnosis codes for known comorbidities and pneumonia, asthma exacerbations, hospitalisations, the number of

PRE-EXISTING ASTHMA COHORT							
	N	%	N	%	OR	95% CI	p-value
Year 3							
	AIT N=10370		Control N=10370		AIT vs. Control		
Asthma treatment step[#]							
≥1 step improvement	4582	44%	4225	41%	1.15	1.09;1.22	<0.0001
≥1 step worsening	1449	14%	1425	14%	1.02	0.94;1.10	0.64
Severe asthma exacerbations	1001	10%	1114	11%	0.89	0.81;0.97	0.010
Respiratory tract infection[#]							
Pneumonia diagnosis	147	1.4%	204	2.0%	0.72	0.58;0.89	0.0025
Pneumonia with Rx antibiotic	67	0.6%	105	1.0%	0.64	0.47;0.87	0.0045
Hospitalisations[#]	1792	17%	1915	18%	0.92	0.86;0.99	0.027
Inpatient stay	1091	11%	1345	13%	0.79	0.73;0.86	<0.0001
Outpatient stay	911	9%	851	8%	1.08	0.98;1.19	0.14
Ambulatory visits[#]	10232	99%	10096	97%	2.01	1.64;2.47	<0.0001
Year 5							
	AIT N=6545		Control N=6545		AIT vs. Control		
Asthma treatment step							
≥1 step improvement	3391	52%	3000	46%	1.27	1.19;1.36	<0.0001
≥1 step worsening	918	14%	947	14%	0.96	0.87;1.06	0.48
Severe asthma exacerbations	571	9%	724	11%	0.77	0.69;0.86	<0.0001
Respiratory tract infection							
Pneumonia diagnosis	81	1.2%	117	1.8%	0.69	0.52;0.92	0.012
Pneumonia with Rx antibiotic	40	0.6%	69	1.1%	0.58	0.39;0.85	0.0068
Hospitalisations	1171	18%	1256	19%	0.92	0.84;1.00	0.059
Inpatient stay	739	11%	867	13%	0.83	0.75;0.93	0.0007
Outpatient stay	578	9%	565	9%	1.03	0.91;1.16	0.71
Ambulatory visits	6341	97%	6343	97%	0.99	0.81;1.21	0.96
Year 9							
	AIT N=571		Control N=571		AIT vs. Control		
Asthma treatment step							
≥1 step improvement	320	56%	283	50%	1.30	1.03;1.64	0.032
≥1 step worsening	79	14%	108	19%	0.69	0.50;0.94	0.025
Severe asthma exacerbations	41	7%	60	11%	0.66	0.44;1.00	0.060
Respiratory tract infection							
Pneumonia diagnosis	9	1.6%	12	2.1%	0.75	0.31;1.78	0.66
Pneumonia with Rx antibiotic	4	0.7%	9	1.6%	0.44	0.14;1.44	0.26
Hospitalisations	93	16%	121	21%	0.72	0.54;0.98	0.040
Inpatient stay	61	11%	88	15%	0.66	0.46;0.93	0.022
Outpatient stay	42	7%	49	9%	0.85	0.55;1.30	0.51
Ambulatory visits	546	96%	549	96%	0.88	0.49;1.57	0.77

Table 3: Supportive secondary and explorative outcomes across key follow-up years in subjects with pre-existing asthma

[#] Categorical variables are reported as n % and changes as odds ratio (OR) and 95% confidence interval (CI) from pre-index year; P-values are between group comparison of AIT vs. control subjects; Asthma treatment step [change]: The definition of improvement or worsening in asthma treatment step was met, if subjects with pre-existing asthma changed asthma treatment step compared to the pre-index year. The asthma treatment steps were pre-defined categories based on asthma diagnoses codes and asthma medication prescriptions during pre-index and post-index years. Treatment step 1: Asthma diagnosis in the absence of controller asthma medication; Treatment step 2: Monotherapy with either low dose ICS or LTRA; Treatment step 3: Dual therapy or therapy with medium-high ICS, LABA or methylxanthine; Treatment step 4: Triple therapy or therapy with anti-IgE or anti-IL-5; Severe asthma exacerbation: 3-point composite of either new systemic corticosteroid prescription, status asthmaticus recorded in ambulatory care or hospitalisation for asthma. Only selected years are presented: Year 3 = expected end of treatment; Year 5 = duration of long-term RCTs investigating disease-modification, Year 9 = last year of observation. Rx: prescriptions; AIT: allergen immunotherapy; ICS: inhaled corticosteroids; LABA: long-acting beta2-agonists; LTRA: leukotriene receptor antagonists; IL: interleukin

ambulatory visits, and overall drug burden were used as markers of severity and included to further substantiate the clinical relevance of the findings. 2) Many AR medications are also available as over the counter medicines and are therefore not captured in a claims database unless they were prescribed by a physician. 3)

Prescriptions do not necessarily translate into utilisation of medication. 4) PSM is restricted to variables which are observed in the database, which causes some limitations to matching subjects in terms of AR disease severity and allergic sensitisation. However, the PSM in this study has included a range of variables as proxy for

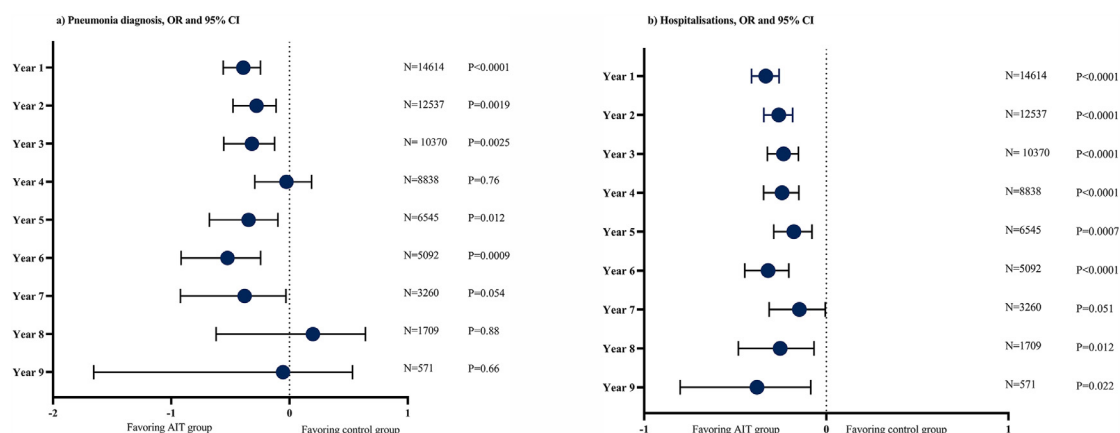


Fig. 3. a) and b): Odds ratios for pneumonia diagnosis (a) and inpatient hospitalisations (b) in pre-existing asthma cohort. Panel a) Odds ratio and 95%CI of pneumonia diagnosis per follow-up year. Panel b) Odds ratio and 95%CI of inpatient hospitalisations per follow-up year. AIT: allergen immunotherapy; CI: confidence interval; OR: odds ratio.

disease severity. Still, socio-economic status and smoking may be confounding factors for asthma exacerbations as the PSM did not directly account for this beyond age, gender, insurance status, and regional distribution.

Despite all the efforts done with matching the cohorts, some small differences in the pre-index year may remain, which may affect outcomes reported as change from pre-index year (i.e. change in AR or asthma prescriptions). Although, the effect sizes of changes in prescriptions from pre-index year appear small, the differences were larger than the differences between prescriptions per subject seen in the pre-index year, inferring a true decline in prescriptions per subject over time amongst AIT-treated subjects. The results for AR and asthma prescriptions were consistent regardless of data being presented as a change from pre-index year or cross-sectional between group differences.

Subjects on AIT were seen more frequently by specialists, likely due to SCIT being an injection given repeatedly under medical supervision. The increased number of specialist visits may disfavour the AIT group and bias the results, leading to a higher proportion of AIT subjects having prescriptions in the first years of FU compared to control subjects. Although AIT-treated subjects were more likely to get AR prescriptions than control subjects they showed a larger reduction in AR prescriptions per subject.

The control group also experienced reductions in AR prescriptions per subject compared to the pre-index year with a progressive trend mimicking the AIT group, and likely explained by regression towards the mean, a statistical phenomenon that can make natural variation in repeated data look like real change. Of this large cohort, 3692 in the main and 1142 subjects in the pre-existing asthma cohort had the full 9 years of FU data available. However, despite these limitations, a larger sustained effect across all years for the majority of

outcomes was found in the AIT group compared to control subjects.

With rigorous methodology, a large sample size, and long-term follow up the REACT study further substantiated the existing evidence from RCTs and added new information about the effects of AIT beyond the limited follow-up in RCTs. The effectiveness of AIT in real life was confirmed with sustained reductions in AR and asthma prescriptions, prevention of asthma exacerbations, and improved and sustained long-term asthma control. The findings emphasised AIT as a safe and effective treatment option for patients with respiratory allergies.

Contributors

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Data availability statement

Data are owned by the BKK sickness fund, which provides access to anonymised data derived from routinely collected administrative claims data. These data can only be accessed by a permitted 3rd party (Team Gesundheit, Gesellschaft für Gesundheitsmanagement GmbH, Essen, Germany) for research purposes.

Declaration of interests

Dr. Fritzsche reports personal fees (pertaining travelling to study meeting) from ALK during the conduct of the study; and speaker honorarium from Novartis and from Merck Sharp & Dohme, outside the submitted work. Dr. Contoli reports personal fees from Alk-Abello, during the conduct of the study; grants, personal fees and non-financial support from Chiesi, personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from Boehringer Ingelheim, grants, personal fees and non-financial support from GlaxoSmithKline, personal fees and non-financial support from Novartis, personal fees and non-financial support from Zambon, grants from University of Ferrara - Italy, outside the submitted work. Dr. Porsbjerg reports grants from ALK, grants and personal fees from Astra Zeneca, grants and personal fees from GSK, grants and personal fees from Novartis, grants, and personal fees from Chiesi, grants and personal fees from Sanofi, grants and personal fees from TEVA, outside the submitted work. Sarah Buchs reports to be employed at ALK-Abello. Dr. Rask Larsen reports being an employee at ALK. Dr. Elliott has nothing to disclose. Ms. Romano Rodriguez reports she is an ALK employee. Dr. Freemantle reports personal fees from Astrazeneca, personal fees from Ipsen, personal fees from Sanofi Aventis, personal fees from Grifols, personal fees from Novartis, personal fees from Aimmune, personal fees from Vertex, personal fees from MSD, personal fees from Allergan, outside the submitted work.

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Supplementary materials

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References

- 1 GW. Pawankar RC, Holgate ST, Lockey RF, et al. WAO white book on allergy 2013 update. Milwaukee: Wisconsin World Allergy Organization; 2013.
- 2 Bousquet J, Hellings PW, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) Phase 4 (2018): change management in allergic rhinitis and asthma multimorbidity using mobile technology. *J Allergy Clin Immunol* 2019;143(3):864–79.
- 3 GINA. *Global Strategy for Asthma Management and Prevention* 2021.
- 4 Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108(5):S147–334. Suppl.
- 5 Braido F, Baiardini I, Brandi S, Porcu A, Canonica GW. Allergic rhinitis and asthma ad hoc survey: clinical and psychological perspectives. *Clin Exp Allergy* 2007;37(5):788–93.
- 6 Vandenplas O, Dramaix M, Joos G, et al. The impact of concomitant rhinitis on asthma-related quality of life and asthma control. *Allergy* 2010;65(10):1290–7.
- 7 Clatworthy J, Price D, Ryan D, Haughney J, Horne R. The value of self-report assessment of adherence, rhinitis and smoking in relation to asthma control. *Prim Care Respir J* 2009;18(4):300–5.
- 8 Linneberg A, Dam Petersen K, Hahn-Pedersen J, Hammerby E, Serup-Hansen N, Boxall N. Burden of allergic respiratory disease: a systematic review. *Clin Mol Allergy* 2016;14:12.
- 9 Linneberg A, Henrik Nielsen N, Frolund L, et al. The link between allergic rhinitis and allergic asthma: a prospective population-based study. The Copenhagen Allergy Study. *Allergy* 2002;57(11):1048–52.
- 10 Ozdoganoglu T, Songu M. The burden of allergic rhinitis and asthma. *Ther Adv Respir Dis* 2012;6(1):11–23.
- 11 Larsen JN, Broge L, Jacobi H. Allergy immunotherapy: the future of allergy treatment. *Drug Discov Today* 2016;21(1):26–37.
- 12 Roberts G, Pfaar O, Akdis CA, et al. EAACI Guidelines on Allergen Immunotherapy: allergic rhinoconjunctivitis. *Allergy* 2018;73(4):765–98.
- 13 Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012;129(3):717–25. e5.
- 14 Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;341(7):468–75.
- 15 Nolte H, Maloney J. The global development and clinical efficacy of sublingual tablet immunotherapy for allergic diseases. *Allergol Int* 2018;67(3):301–8.
- 16 Mosbech H, Deckelmann R, de Blay F, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2014;134(3):568–75. e7.
- 17 Virchow JC, Backer V, Kuna P, et al. Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma: a Randomized Clinical Trial. *JAMA* 2016;315(16):1715–25.
- 18 Paoletti G, DiBona D, Chu DK, et al. Allergen immunotherapy: the growing role of observational and randomised trial "Real-World Evidence". *Allergy* 2021.
- 19 Roche N, Reddel HK, Agusti A, et al. Integrating real-life studies in the global therapeutic research framework. *Lancet Respir Med* 2013;1(10):e29–30.
- 20 Pilny A, Wubker A, Ziebarth NR. Introducing risk adjustment and free health plan choice in employer-based health insurance: evidence from Germany. *J Health Econ* 2017;56:330–51.
- 21 Busse R, Blumel M, Knieps F, Barnighausen T. Statutory health insurance in Germany: a health system shaped by 135 years of solidarity, self-governance, and competition. *Lancet* 2017;390(10097):882–97.
- 22 Biedermann T, Kuna P, Panzner P, et al. The SQ tree SLIT-tablet is highly effective and well tolerated: results from a randomized, double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol* 2019;143(3):1058–66. e6.
- 23 Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of Grass Pollen Allergen Sublingual Immunotherapy Tablets for Seasonal Allergic Rhinoconjunctivitis: a Systematic Review and Meta-analysis. *JAMA Intern Med* 2015;175(8):1301–9.
- 24 Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2010(12):Cd002893.
- 25 Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: allergic Rhinitis. *Int Forum Allergy Rhinol* 2018;8(2):108–352.

- 26 PRENTICE RL, WILLIAMS BJ, PETERSON AV. On the regression analysis of multivariate failure time data. *Biometrika* 1981;**68**(2):373–9.
- 27 Schmitt J, Wustenberg E, Kuster D, Mucke V, Serup-Hansen N, Tesch F. The moderating role of allergy immunotherapy in asthma progression: results of a population-based cohort study. *Allergy* 2020;**75**(3):596–602.
- 28 Woehlk C, von Bulow A, Kriegbaum M, Backer V, Porsbjerg C. Allergic asthma is associated with increased risk of infections requiring antibiotics. *Ann Allergy Asthma Immunol* 2018;**120**(2):169–76. [e1](#).
- 29 Halken S, Larenas-Linnemann D, Roberts G, et al. EAACI guidelines on allergen immunotherapy: prevention of allergy. *Pediatr Allergy Immunol* 2017;**28**(8):728–45.
- 30 Zielen S, Devillier P, Heinrich J, Richter H, Wahn U. Sublingual immunotherapy provides long-term relief in allergic rhinitis and reduces the risk of asthma: a retrospective, real-world database analysis. *Allergy* 2018;**73**(1):165–77.
- 31 Schmitt J, Schwarz K, Stadler E, Wustenberg EG. Allergy immunotherapy for allergic rhinitis effectively prevents asthma: results from a large retrospective cohort study. *J Allergy Clin Immunol* 2015;**136**(6):1511–6.
- 32 Wahn U, Bachert C, Heinrich J, Richter H, Zielen S. Real-world benefits of allergen immunotherapy for birch pollen-associated allergic rhinitis and asthma. *Allergy* 2019;**74**(3):594–604.

Supplementary material

Long-term real-world effectiveness of allergy immunotherapy in patients with allergic rhinitis and asthma: results from the REACT study by Benedikt Fritzsche, Marco Contoli, Celeste Porsbjerg, Sarah Buchs, Julie Rask Larsen, Lisa Elliott, Mercedes Romano, and Nick Freemantle

Protocol.....	3
Key definitions referred to in the manuscript.....	3
Figure S1 Flow chart for identification of main cohort	5
Table S1 Demographics for the main cohort in the pre-index year before and after matching	6
Figure S2 Distribution of logits of propensity scores before and after matching	8
Figure S3 Flow chart for identification of subcohorts and subgroups	9
Table S2 Demographics in the no asthma subcohort	10
Table S3 Additional demographics /comorbidities.....	11
Table S4 AIT medication use.....	12
Figure S4 Subject disposition over time in the main cohort.....	13
Table S5 Subjects with AR and asthma prescriptions in follow-up year 1-9	14
Figure S5 The number of ambulatory care visits per subject per year in the main cohort in follow-up year 1-9	15
Table S6 AR prescriptions by drug class in follow-up years 1-9 in main cohort.....	16
Figure S6 A, B and C: Relative change in total AR prescriptions (A), antihistamine prescriptions (B) and INCS prescriptions (C) in main cohort.....	17
Table S7 Asthma prescriptions by drug class in follow-up years 1-9 in pre-existing asthma cohort.....	18
Figure S7 A, B, C and D: Relative change in total asthma prescriptions (A), SABA prescriptions (B), ICS prescriptions (C) and ICS/LABA prescriptions (D) in asthma cohort	20
Table S8 Time-to-first improvement of asthma in the pre-existing asthma cohort	21
Figure S8 Kaplan Meier curve; Time-to-first improvement of asthma in the pre-existing asthma cohort.....	22
Table S9 Time-to-any improvement of asthma in the pre-existing asthma cohort	23
Table S10 Time-to-first worsening of asthma defined by a 3-point composite endpoint.....	24
Figure S9 Kaplan Meier curve; Time-to-first worsening of asthma in the pre-existing asthma cohort.....	25
Table S11 Time-to-any worsening of asthma defined by a 3-point composite endpoint.....	26
Table S12 Time-to-first severe asthma exacerbation in the pre-existing asthma cohort	27
Figure S10 Kaplan Meier curve; Time-to-first severe asthma exacerbation in the pre-existing asthma cohort.....	28

Table S13 Time-to-any severe asthma exacerbation in the pre-existing asthma cohort.....	29
Table S14 Severe asthma exacerbations by components in follow-up years 1-9 in pre-existing asthma cohort.....	30
Table S15 Time-to-first onset of asthma in the no asthma cohort	32
Figure S11 Kaplan Meier curve; Time-to-first onset of asthma in the no asthma cohort	33
Figure S12 A and B: Ambulatory care visits (A) and change in asthma medication (B) in the no asthma cohort.....	34
Table S16: Subjects with events of health care resource utilisation, sick leave, and biologic prescriptions in main cohort in year 3, 5, and 9	35
Table S17 Events of health care utilisation, sick leave, biologics prescriptions in main cohort in year 3, 5, and 9	37
Table S18 Change from pre-index year in health care costs for the main cohort in year 3, 5, and 9.....	39
Table S19 Change from pre-index year in comorbidities[§] for main cohort in year 3, 5 and 9.....	40
Table S20 Subgroup analyses: Change from pre-index year to year 3 in AR prescriptions	41
Table S21 Sensitivity analysis with different definition of asthma treatment steps	42
Figure S13 Validation analysis; Change from pre-index year in AR prescriptions in SLIT-tablet subgroup.....	43

Protocol



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Key definitions referred to in the manuscript

Definitions

- **Asthma** is defined based on asthma diagnoses (J45 Asthma; J45.0 Predominantly allergic asthma; J45.8 Mixed asthma; J45.9 Asthma, unspecified; J46 Status asthmaticus and/or two at least two prescriptions of SABA/ICS within an index-year.
- **Severe asthma exacerbations** will be defined by any of the following:
 - Ambulatory care: ICD-10-GM code J46 Status asthmaticus
 - Hospitalization with ICD-10-GM asthma code (see Table 1 as the main diagnosis)
 - New prescription of oral, intravenous, or subcutaneous corticosteroid with any ICD-10-GM asthma code. A prescription is defined as “new” when more than 7 days have passed since the last prescription.

• Asthma treatment steps

Asthma treatment step 1: No asthma controller medication

- asthma diagnosis in the absence of criteria for treatment step 2-4

Asthma treatment step 2: Monotherapy

- Monotherapy:
 - Low dose ICS or
 - LTRA

Asthma treatment step 3: Dual therapy and specific monotherapy

- Monotherapy:
 - Medium or high dose ICS or
 - LABA or
 - Methylxanthine
- Dual therapy – combination of:
 - Medium or high dose ICS
 - LTRA
 - LABA
 - Methylxanthine

Asthma treatment step 4: Triple therapy or specific monotherapy

- Monotherapy
 - anti-IgE or
 - anti-IL-5
- Triple therapy – combination of:

- Low, medium, or high dose ICS
- LTRA
- LABA
- Methylxanthine
- LAMA

Abbreviations: ICS inhaled corticosteroids; LTRA: leukotriene receptor antagonists; LABA: long-acting beta2-agonists; SABA: short-acting beta2-agonists; LAMA: long-acting muscarinic antagonists

- **Anaphylaxis** related to allergy immunotherapy (AIT) initiation is defined as diagnosis code for anaphylactic shock (see Annex 2 of protocol) ≤ 2 days of the first AIT prescription being filled (index date. Due to quarterly information on outpatient diagnosis an anaphylaxis will count when relevant diagnosis code for anaphylactic shock appears in index quarter.
- **Time to first and time to any worsening**, of asthma (days), defined as a 3-point composite:
 - No asthma subcohort: New onset of asthma (see section 4.2.1 of protocol) or
 - Pre-existing asthma subcohort: Increased asthma treatment step (see section 4.2.2 of protocol) or
 - Severe asthma exacerbations (see section 4.2.3 of protocol)

Figure S1 Flow chart for identification of main cohort

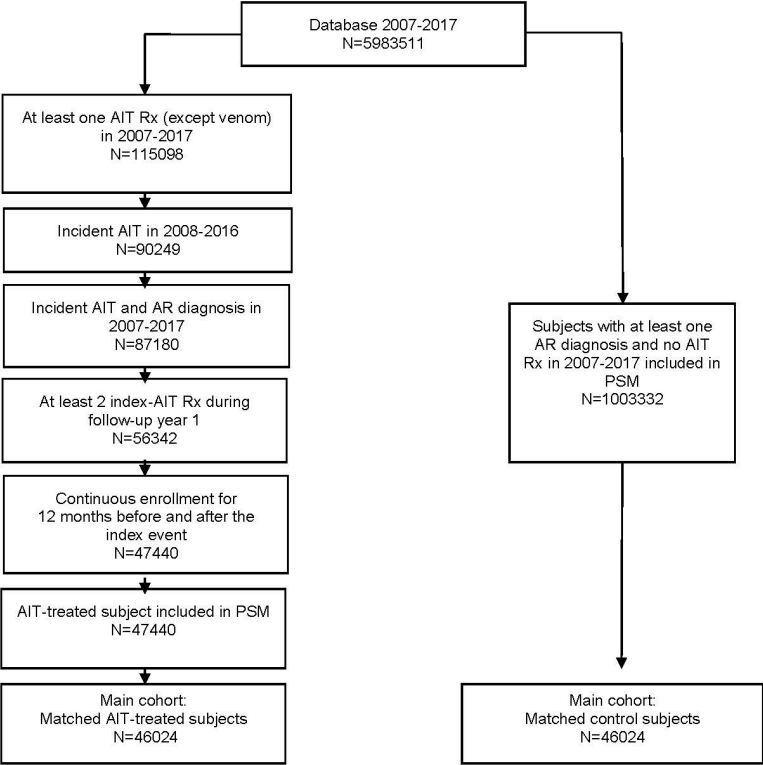


Figure S1 Flow chart for identification of the main cohort. AIT: allergy immunotherapy; AR: allergic rhinitis; Rx: prescription, PSM: propensity score matching

Table S1 Demographics for the main cohort in the pre-index year before and after matching

	Before matching			After matching		
	AIT N= 46069	Control N=6487556	Std Diff	AIT N= 46024	Control N= 46024	Std Diff
	Mean	Mean		Mean	Mean	
Age* (years)	29·5	38·7	-0·50	29·5	29·5	0·00
Age categories[#]						
Children <11 years	0·17	0·09	0·22	0·17	0·16	0·02
Adolescents 12-17 years	0·15	0·08	0·23	0·15	0·15	0·00
Adults >18 years	0·68	0·83	-0·34	0·68	0·69	-0·01
Gender[#] (males)	1·47	1·52	-0·10	1·47	1·48	-0·01
Geographical location[#]						
East	0·17	0·17	0·01	0·17	0·18	-0·01
North	0·12	0·13	-0·02	0·12	0·12	0·00
South	0·32	0·32	-0·02	0·32	0·32	-0·01
West	0·39	0·38	0·02	0·39	0·39	0·01
AR diagnosis code[#]						
Vasomotor rhinitis (J30.0)	0·84	0·36	1·11	0·84	0·86	-0·04
AR due to pollen (J30.1)	0·62	0·25	0·82	0·62	0·63	-0·02
Other seasonal AR (J30.2)	0·03	0·01	0·19	0·03	0·03	0·02
Other AR (J30.3)	0·27	0·07	0·56	0·27	0·27	0·01
AR unspecified (J30.4)	0·32	0·10	0·58	0·32	0·32	0·01
Asthma diagnosis codes[#]						
Non-allergic-asthma (J45)	0·02	0·03	0·07	0·02	0·02	0·00
Predominantly allergic asthma (J45.0)	0·23	0·08	0·42	0·23	0·22	0·01
Mixed asthma (J45.8)	0·05	0·02	0·14	0·05	0·04	0·01
Asthma, unspecified (J45.99)	0·21	0·11	0·26	0·21	0·20	0·01
AR prescriptions* (Rx/subject)	1·101	0·353	0·520	1·094	1·095	0·000
Asthma prescriptions* (Rx/subject)	1·021	0·532	0·236	1·018	1·019	0·001
Pre-existing asthma[#]	0·37	0·18	0·43	0·37	0·37	0·00
SABA only	0·00	0·01	0·02	0·01	0·01	0·01
Treatment step 1	0·15	0·08	0·20	0·15	0·15	-0·01
Treatment step 2	0·08	0·03	0·24	0·08	0·08	0·01
Treatment step 3	0·12	0·06	0·22	0·12	0·12	0·01
Treatment step 4	0·01	0·01	0·07	0·01	0·01	0·01
AR related comorbidities[#]						
Atopic dermatitis (L20 - L20.9)	0·13	0·08	0·19	0·13	0·13	0·01
Urticaria (L50 - L50.9)	0·03	0·02	0·06	0·03	0·03	0·00
Conjunctivitis (H10 - H10.9)	0·25	0·10	0·40	0·25	0·24	0·01
Acute allergic conjunctivitis (H10.1)	0·11	0·03	0·33	0·11	0·11	0·00
Upper respiratory tract infections (J00-J39.9)	0·92	0·64	0·72	0·92	0·93	-0·02
Charlson Comorbidity Index*	0·57	0·72	-0·14	0·57	0·57	0·00
Healthcare Resource Utilization*						
Ambulatory care visits(visits)	17·63	15·39	0·16	17·62	18·43	-0·06
Hospitalizations (days)	0·20	0·26	-0·09	0·20	0·20	0·00
Surgical procedures (procedures)	0·03	0·01	0·07	0·03	0·03	0·00
Sick leaves (days)	0·72	0·73	-0·01	0·72	0·77	-0·04
Cost* (Euro)						
Ambulatory care visits	508·91	478·51	0·05	508·67	555·33	-0·07
Medication	573·07	344·33	0·09	561·46	443·64	0·04

Hospitalisations	266·51	555·56	-0·13	266·45	305·56	-0·02
Sick leaves	63·70	112·46	-0·04	63·77	64·15	0·00
The table lists all variables included in the propensity score matching (PSM) and shows the demographics for the main cohort in the pre-index year before and after matching. *Continuous variables; # Categorical variables; AIT: allergen immunotherapy; AR: allergic rhinitis; Rx: prescription; Pre-existing asthma: At least one asthma diagnosis or two prescriptions of SABA/ICS within the pre-index year; Asthma treatment step [cross sectional]: Predefined categories based on asthma diagnoses codes and asthma medication prescriptions within pre-index year - Treatment step 1: Asthma diagnosis in the absence of controller asthma medication; Treatment step 2: Monotherapy with either low dose ICS or LTRA; Treatment step 3: Dual therapy or therapy with medium-high ICS, LABA or methylxanthine; Treatment step 4: Triple therapy or therapy with anti-IgE or anti-IL-5; ICS: inhaled corticosteroids, LABA: long-acting beta-agonists; SABA: short-acting beta2-agonists, LTRA: leukotriene receptor antagonists						

Figure S2 Distribution of logits of propensity scores before and after matching

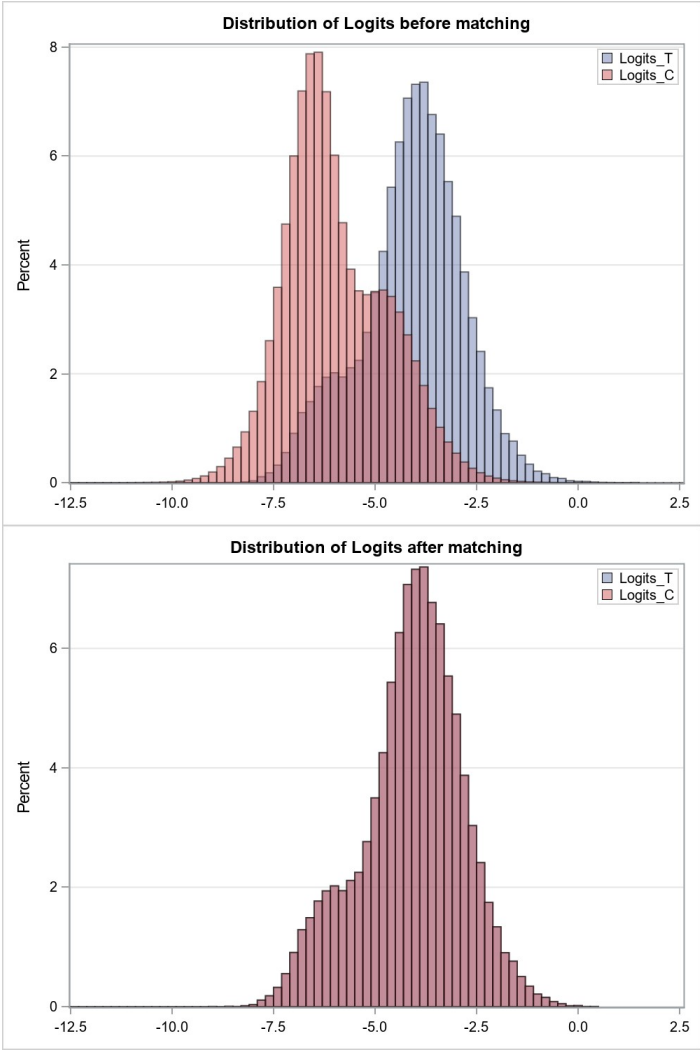


Figure S3 Flow chart for identification of subcohorts and subgroups

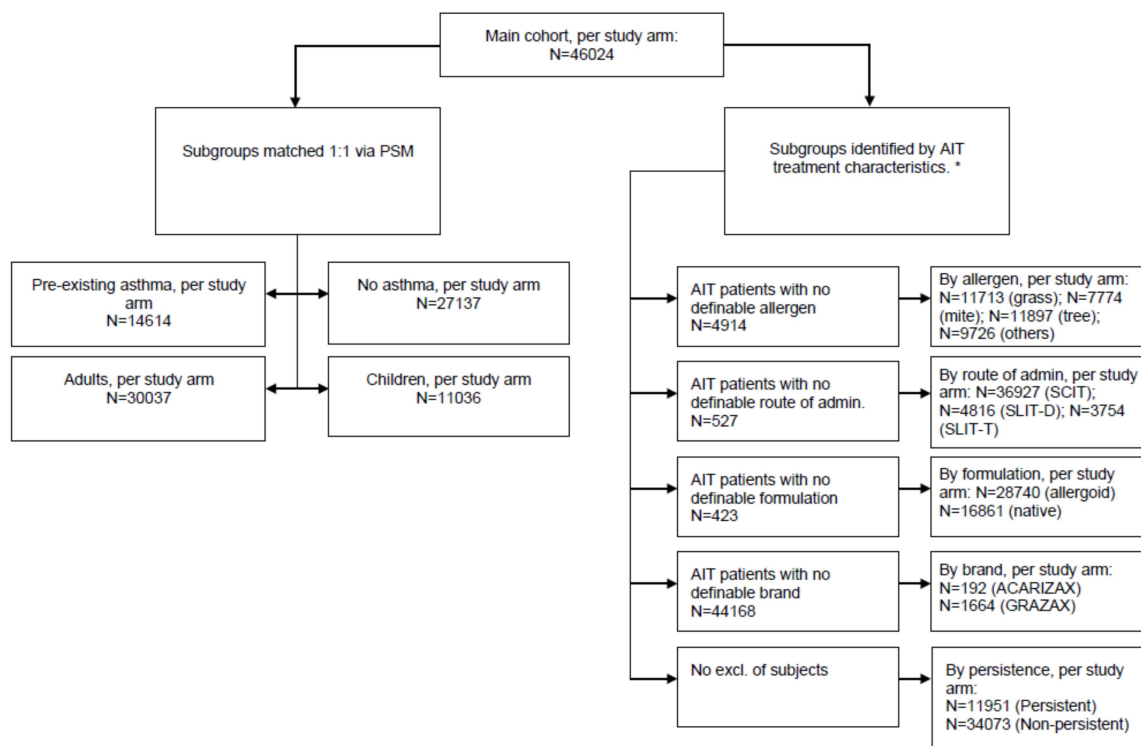


Figure S3 Flow chart for identification of the subcohorts and subgroups showing the numbers for the AIT group; parallel to these groups there is an identical number of control subjects due to the matching of subjects in pairs. In the pre-existing asthma cohort, 4635 subjects could not be matched and were therefore lost from both the AIT-group and controls. Similarly, in the no asthma cohort 3911 subjects, 6091 children, and 3183 adults were not matched and therefore lost. *No PSM; treated patients were separated based on the treatment characteristic; the corresponding matched controls are not shown here. Pre-existing asthma: At least one asthma diagnosis or two prescriptions of SABA/ICS within the pre-index year. Children <18 years. Persistence: $\geq$ two index-AIT prescriptions in two consecutive follow up (FU-years). AIT: allergen immunotherapy; SCIT: subcutaneous immunotherapy; SLIT-D /SLIT-T: sublingual immunotherapy drops /tablets; ICS: inhaled corticosteroids, SABA: short-acting beta2-agonists; PSM: propensity score matching.

Table S2 Demographics in the no asthma subcohort

	No asthma			
	AIT N=27137		Control N=27137	
Age* (years)	30·1	15·8	29·4	17·1
Sex[#] (males)	14145	52%	14085	52%
Key comorbidities[#]				
Asthma	487	1·8%	415	1·5%
Conjunctivitis	5171	19%	5162	19%
Eczema	6382	24%	6781	25%
Health care utilisation*				
Ambulatory care visits	14·1	11·4	16·3	16·2
Hospitalisation's days	0·2	0·6	0·2	0·6
Sick leave days	0·7	1·4	0·7	1·5
Treatment with AIT* (days)				
Duration until first Discontinuation	215	116	..	..
Total duration on index-AIT	543	282	..	..
AR and asthma prescriptions* (Rx/subject)				
AR prescriptions	0·866	1·417	0·803	1·540
Asthma prescriptions	0·134	0·470	0·101	0·449

*Continuous variables are presented as means ± standard deviations (SD); # Categorical variables are presented as n (%)
AIT: allergen immunotherapy; AR: allergic rhinitis; Rx: prescriptions

Table S3 Additional demographics /comorbidities

	Main				Pre-existing asthma				No asthma			
	AIT N=46024		Control N=46024		AIT N=14614		Control N=14614		AIT N=27137		Control N=27137	
AR prescriptions by class*	1·084	1·705	1·034	1·878	1·415	1·985	1·416	2·258	0·866	1·417	0·803	1·540
Antihistamines	0·452	1·063	0·404	1·101	0·628	1·283	0·587	1·390	0·337	0·862	0·293	0·879
INCS	0·464	0·925	0·445	1·090	0·552	1·054	0·602	1·292	0·405	0·820	0·353	0·930
Fixed-dose combination	0·017	0·168	0·16	0·211	0·020	0·187	0·020	0·223	0·014	0·145	0·011	0·167
Asthma prescriptions by class*	0·996	2·199	0·986	2·367	2·456	3·022	2·495	3·308	0·134	0·470	0·101	0·449
SABA	0·398	1·033	0·393	1·169	0·964	1·489	0·980	1·715	0·066	0·265	0·047	0·225
ICS	0·221	0·724	0·209	0·767	0·565	1·095	0·540	1·166	0·024	0·166	0·016	0·136
ICS/LABA	0·261	0·901	0·267	0·980	0·650	1·359	0·679	1·462	0·031	0·237	0·026	0·250
LABA	0·031	0·310	0·032	0·372	0·070	0·476	0·088	0·629	0·003	0·082	0·002	0·088
LTRA	0·066	0·474	0·061	0·481	0·168	0·749	0·152	0·748	0·008	0·125	0·007	0·127
Methylxanthine	0·000	0·000	0·000	0·000	0·000	0·000	0·000	0·000	0·000	0·000	0·000	0·000
Anticholinergics	0·005	0·140	0·004	0·116	0·009	0·187	0·009	0·181	0·000	0·025	0·000	0·037
Biologic	0·001	0·066	0·001	0·077	0·002	0·118	0·002	0·113	0·000	0·000	0·000	0·000
LAMA/LABA	0·000	0·037	0·000	0·017	0·000	0·000	0·000	0·014	0·000	0·006	0·000	0·037
ICS/LAMA/LABA	0·000	0·000	0·000	0·000	0·000	0·000	0·000	0·000	0·000	0·000	0·000	0·000
Comorbidities^{#§}												
Upper respiratory tract infection (J00 – J39)	38572	84%	40569	88%	13253	91%	13803	94%	21925	81%	23110	85%
Asthma (J45 – J46)	14868	32%	15213	33 %	12317	84%	12874	88%	487	1·8%	415	1·5%
Eczema (L20 – L54)	11909	26%	12868	28%	4418	30%	4830	33%	6382	24%	6781	25%
Bronchitis (J20 – J44)	10610	23 %	11633	25 %	4931	34%	5555	38%	4570	17%	4901	18%
Conjunctivitis (H10)	10001	22%	10126	22 %	3869	26%	3898	27%	5171	19%	5162	19%
Headache (R51, G44)	4094	9 %	5331	12 %	1382	9%	1831	13%	2321	9%	3077	11%
Chronic cough (R05)	3532	8%	3709	8%	1556	11%	1548	11%	1629	6%	1790	7%
Otitis media (H65 – H67)	3203	7%	3820	8%	1241	8%	1318	9%	1650	6%	2137	8%
Depression (F32 – F33)	3081	7 %	4563	10%	1115	8%	1632	11%	1679	6%	2423	9%
Migraine (G43)	2110	5%	2876	6%	707	5%	1037	7%	1215	4%	1600	6%
*Continuous variables are presented as means ± standard deviations (SD); # Categorical variables are presented as n %; § The ten most frequently reported comorbidities in the AIT group in the main cohort (and with ICD-10 codes); AIT: allergen immunotherapy; AR: allergic rhinitis; INCS intranasal corticosteroids; SABA short-acting beta2-agonists, ICS: inhaled corticosteroids; LABA: long-acting beta2-agonists; LTRA: leukotriene receptor antagonists; LAMA: long-acting muscarinic antagonists.												

Table S4 AIT medication use

	Main N=46024		Pre-existing asthma N=14614		No asthma N=27137	
Duration of treatment with any AIT* days						
Duration until first discontinuation	216	118	218	120	215	116
Total duration of days on any-AIT	826	473	851	479	812	470
Treatment patterns[#]						
Monotherapy	44450	97%	14094	96%	26225	97%
Co-administration	337	0.7%	104	0.7%	203	0.7%
SLIT-t + SLIT-t	7	0.02%	2	0.01%	5	0.02%
SLIT-t + SCIT	41	0.09%	13	0.09%	25	0.09%
SLIT-t + SLIT-d	32	0.07%	11	0.08%	19	0.07%
SLIT-d + SCIT	11	0.02%	4	0.03%	4	0.02%
Switch based on allergen	873	1.9%	281	1.9%	507	1.9%
Switch based on route of administration	251	0.5%	83	0.6%	143	0.5%
*Continuous variables are presented as means $\pm$ standard deviations (SD); # Categorical variables are presented as n %; AIT: allergen immunotherapy; SLIT-t sublingual immunotherapy tablet; SCIT subcutaneous immunotherapy; SLIT-d sublingual immunotherapy drops. Monotherapy: index-AIT prescriptions for one allergen only; Co-administration $\geq$ one prescription for a non-index AIT (based on allergen), in patients who have not discontinued the index-AIT. Any overlap between a new, non-index AIT and the index-AIT must last beyond 90 days (or until the end of follow-up if remaining follow-up time is <90 days), before it is recorded as a co-administration. For the analysis of co-administration of AIT, only pre-specified combinations factoring in the route of administrations were reported. In addition to the above, co-administration for SCIT was also captured, when as at least one prescription for a non-index-AIT prescription (without time requirements) and a least one procedure code for two AIT injections given on the same day was recorded >90 days after initiation of index-AIT. The time period of >90 days after initiation was needed to mitigate faster up-dosing regimen that may require more than one SCIT injections/day. Switch based on allergen / route of administration): a non-index AIT prescription within 90 days after the index-AIT was prescribed the last time and if no overlap of >90 days was recorded (co-administration).						

Figure S4 Subject disposition over time in the main cohort

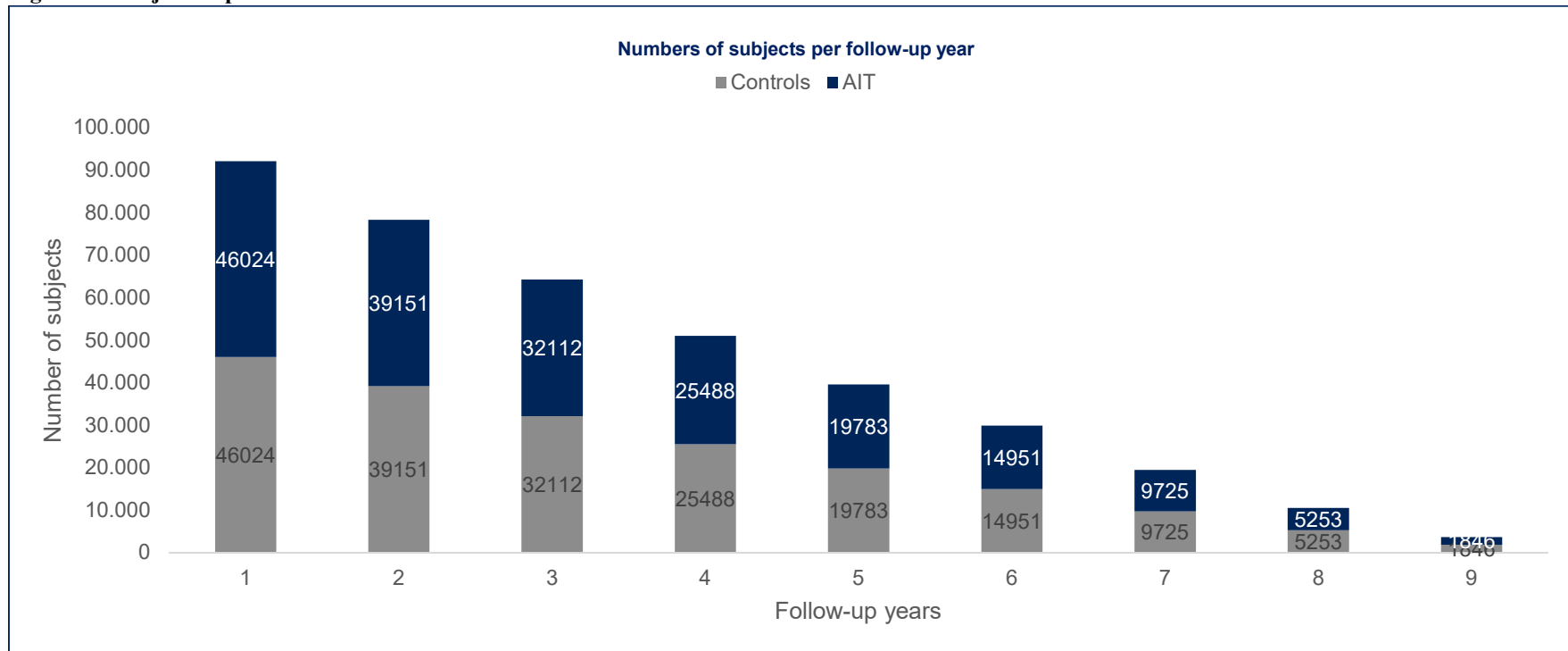


Table S5 Subjects with AR and asthma prescriptions in follow-up year 1-9

Main (N=46024)							
	N	%	N	%	OR	95% CI	p-value
Subjects with AR Rx#	AIT N=46024		Control N=46024		AIT vs. Control		
Year 1	18682	41%	15982	35%	1.28	1.25;1.32	<.0001
Year 2	12815	33%	11337	29%	1.19	1.16;1.23	<.0001
Year 3	9289	29%	8487	26%	1.13	1.09;1.17	<.0001
Year 4	6588	26%	6207	24%	1.08	1.04;1.13	0.0001
Year 5	4557	23%	4572	23%	1.00	0.95;1.04	0.8673
Year 6	3250	22%	3238	22%	1.01	0.95;1.06	0.8774
Year 7	1943	20%	1952	20%	0.99	0.93;1.07	0.886
Year 8	990	19%	972	19%	1.02	0.93;1.13	0.6704
Year 9	334	18%	319	17%	1.06	0.89;1.25	0.546
Pre-existing asthma (N=14614)							
	N	%	N	%	OR	95% CI	p-value
Subjects with asthma Rx#	AIT N=14614		Control N=14614		AIT vs. Control		
Year 1	8800	60%	8913	61%	0.97	0.92;1.02	0.18
Year 2	6811	54%	6855	55%	0.99	0.94;1.04	0.5855
Year 3	5302	51%	5420	52%	0.96	0.91;1.01	0.104
Year 4	4025	48%	4169	50%	0.93	0.88;0.99	0.0268
Year 5	3008	46%	3177	49%	0.90	0.84;0.97	0.0033
Year 6	2206	43%	2394	47%	0.86	0.80;0.93	0.0002
Year 7	1415	43%	1440	44%	0.97	0.88;1.07	0.5491
Year 8	738	43%	730	43%	1.02	0.89;1.17	0.8089
Year 9	230	40%	241	42%	0.92	0.73;1.17	0.5478
Table shows subjects N (%), with at least one prescription for allergic rhinitis in main cohort and subjects with at least one prescription for asthma in pre-existing asthma cohort by follow-up year. # Categorical variables are presented as n (%) and as the between group odds ratio (95% CI) from pre-index year; P-values are between group comparison of AIT vs. controls; OR: odds ratio; Rx: prescriptions; AIT: allergen immunotherapy; AR: allergic rhinitis; CI: confidence intervals.							

Figure S5 The number of ambulatory care visits per subject per year in the main cohort in follow-up year 1-9

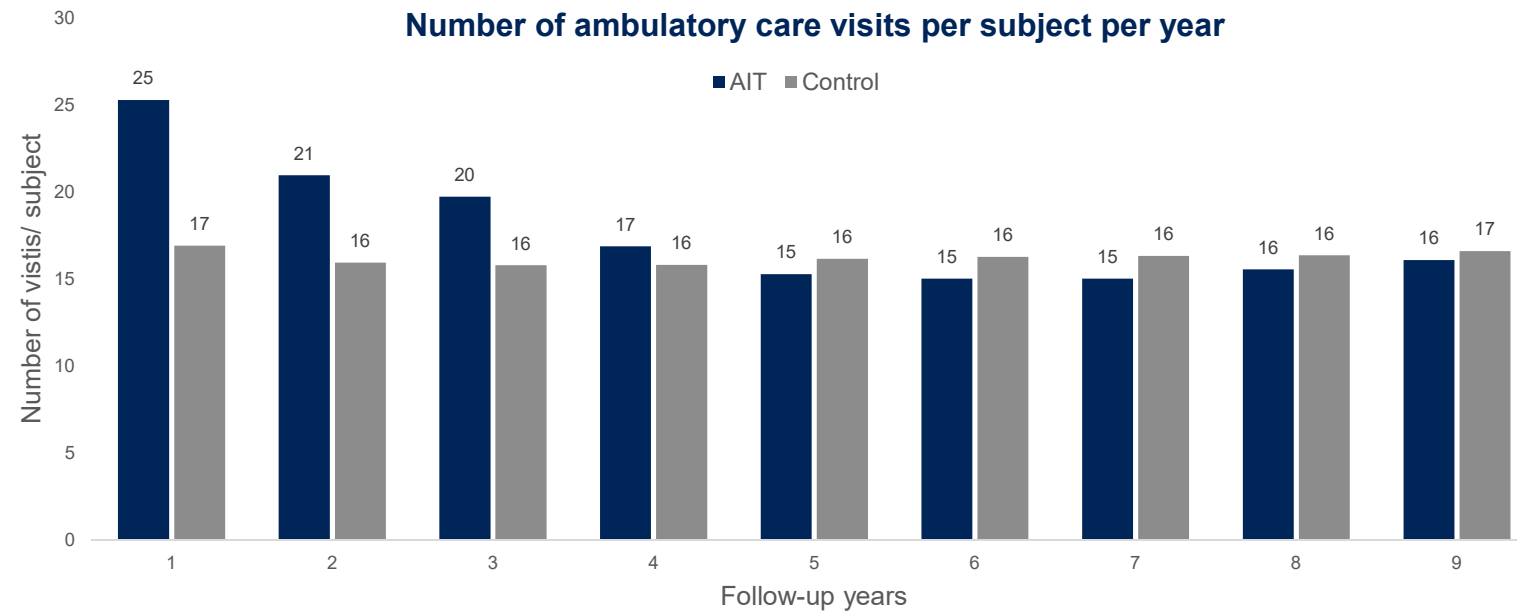


Table S6 AR prescriptions by drug class in follow-up years 1-9 in main cohort

Main									
	Rx/ subject	SD	Change from pre- index	95% CI	Rx/ subject	SD	Change from pre- index	95% CI	P value
Year 1	AIT N=46024				Control N=46024				AIT vs. Control
AR Rx*	0.944	1.692	-0.140	-0.162; -0.118	0.879	1.878	-0.155	-0.179; -0.131	<.0001
Antihistamine	0.385	1.028	-0.067	-0.080; -0.053	0.352	1.075	-0.052	-0.066; -0.038	<.0001
INCS	0.424	1.007	-0.040	-0.053; -0.028	0.373	1.047	-0.072	-0.085; -0.058	<.0001
FxDC	0.023	0.238	0.006	0.003; 0.008	0.017	0.228	0.001	-0.002; 0.004	0.0003
Year 2	AIT N=39151				Control N=39151				AIT vs. Control
AR Rx*	0.712	1.462	-0.362	-0.384; -0.340	0.717	1.649	-0.304	-0.328; -0.279	0.6714
Antihistamine	0.284	0.871	-0.171	-0.184; -0.157	0.283	0.959	-0.120	-0.134; -0.106	0.8821
INCS	0.324	0.866	-0.129	-0.142; -0.117	0.313	0.995	-0.123	-0.138; -0.109	0.1069
FxDC	0.018	0.217	0.006	0.003; 0.008	0.014	0.219	0.002	-0.001; 0.004	0.004
Year 3	AIT N= 32112				Control N= 32112				AIT vs. Control
AR Rx*	0.609	1.344	-0.458	-0.482; -0.434	0.629	1.544	-0.379	-0.406; -0.353	0.0805
Antihistamine	0.240	0.788	-0.217	-0.232; -0.203	0.250	0.895	-0.150	-0.165; -0.134	0.1404
INCS	0.292	0.843	-0.155	-0.168; -0.141	0.291	0.970	-0.143	-0.159; -0.128	0.8553
FxDC	0.019	0.211	0.012	0.009; 0.014	0.011	0.155	0.003	0.001; 0.006	<.0001
Year 4	AIT N=25488				Control N=25488				AIT vs. Control
AR Rx*	0.527	1.254	-0.526	-0.552; -0.500	0.573	1.521	-0.418	-0.448; -0.389	0.0002
Antihistamine	0.200	0.735	-0.259	-0.275; -0.243	0.226	0.858	-0.173	-0.190; -0.155	0.0002
INCS	0.268	0.795	-0.169	-0.184; -0.154	0.279	0.993	-0.148	-0.166; -0.130	0.1633
FxDC	0.021	0.235	0.020	0.017; 0.023	0.010	0.145	0.010	0.008; 0.012	<.0001
Year 5	AIT N= 19783				Control N= 19783				AIT vs. Control
AR Rx*	0.471	1.191	-0.571	-0.600; -0.542	0.533	1.504	-0.448	-0.482; -0.415	<.0001
Antihistamine	0.179	0.695	-0.282	-0.300; -0.264	0.202	0.807	-0.194	-0.213; -0.175	0.0021
INCS	0.247	0.789	-0.178	-0.195; -0.162	0.278	1.034	-0.143	-0.164; -0.122	0.0008
FxDC	0.022	0.229	0.022	0.019; 0.025	0.013	0.161	0.013	0.010; 0.015	<.0001
Year 6	AIT N=14951				Control N=14951				AIT vs. Control
AR Rx*	0.440	1.142	-0.592	-0.625; -0.559	0.499	1.372	-0.468	-0.505; -0.431	<.0001
Antihistamine	0.160	0.625	-0.305	-0.325; -0.285	0.191	0.788	-0.208	-0.230; -0.186	0.0002
INCS	0.242	0.794	-0.167	-0.186; -0.148	0.263	0.915	-0.143	-0.17; -0.12	0.0324
FxDC	0.025	0.229	0.025	0.022; 0.029	0.016	0.200	0.016	0.013; 0.019	0.0002
Year 7	AIT N=9725				Control N=9725				AIT vs. Control
AR Rx*	0.399	1.111	-0.614	-0.655; -0.574	0.454	1.315	-0.497	-0.541; -0.452	0.0018
Antihistamine	0.141	0.609	-0.313	-0.338; -0.288	0.176	0.766	-0.214	-0.241; -0.188	0.0004
INCS	0.228	0.769	-0.171	-0.194; -0.148	0.243	0.876	-0.151	-0.178; -0.124	0.2166
FxDC	0.025	0.225	0.025	0.021; 0.030	0.015	0.193	0.015	0.011; 0.019	0.0007
Year 8	AIT N=5253				Control N=5253				AIT vs. Control
AR Rx*	0.391	1.099	-0.603	-0.657; -0.549	0.428	1.288	-0.487	-0.546; -0.429	0.1178
Antihistamine	0.152	0.652	-0.291	-0.325; -0.258	0.164	0.752	-0.202	-0.236; -0.168	0.39
INCS	0.215	0.774	-0.182	-0.213; -0.150	0.238	0.885	-0.153	-0.191; -0.116	0.1558
FxDC	0.020	0.184	0.020	0.015; 0.025	0.011	0.146	0.011	0.007; 0.015	0.0097
Year 9	AIT N= 1846				Control N= 1846				AIT vs. Control
AR Rx*	0.393	1.142	-0.646	-0.741; -0.551	0.384	1.156	-0.522	-0.617; -0.427	0.8076
Antihistamine	0.175	0.787	-0.333	-0.397; -0.269	0.138	0.659	-0.250	-0.305; -0.194	0.1177
INCS	0.200	0.733	-0.183	-0.235; -0.131	0.225	0.842	-0.154	-0.214; -0.095	0.3376
FxDC	0.018	0.187	0.018	0.009; 0.026	0.014	0.169	0.014	0.006; 0.021	0.4598
*continuous variables are reported as mean $\pm$ standard deviations (SD) and as the within group absolute change (95% CI) from pre-index year. P-values are between group comparison of AIT vs. controls. Rx prescriptions are reported as Rx/subject; AIT: allergen immunotherapy; AR: allergic rhinitis; CI: confidence interval; INCS intranasal corticosteroids; FxDC: Fixed dose combination of INCS and antihistamines									

Figure S6 A, B and C: Relative change in total AR prescriptions (A), antihistamine prescriptions (B) and INCS prescriptions (C) in main cohort

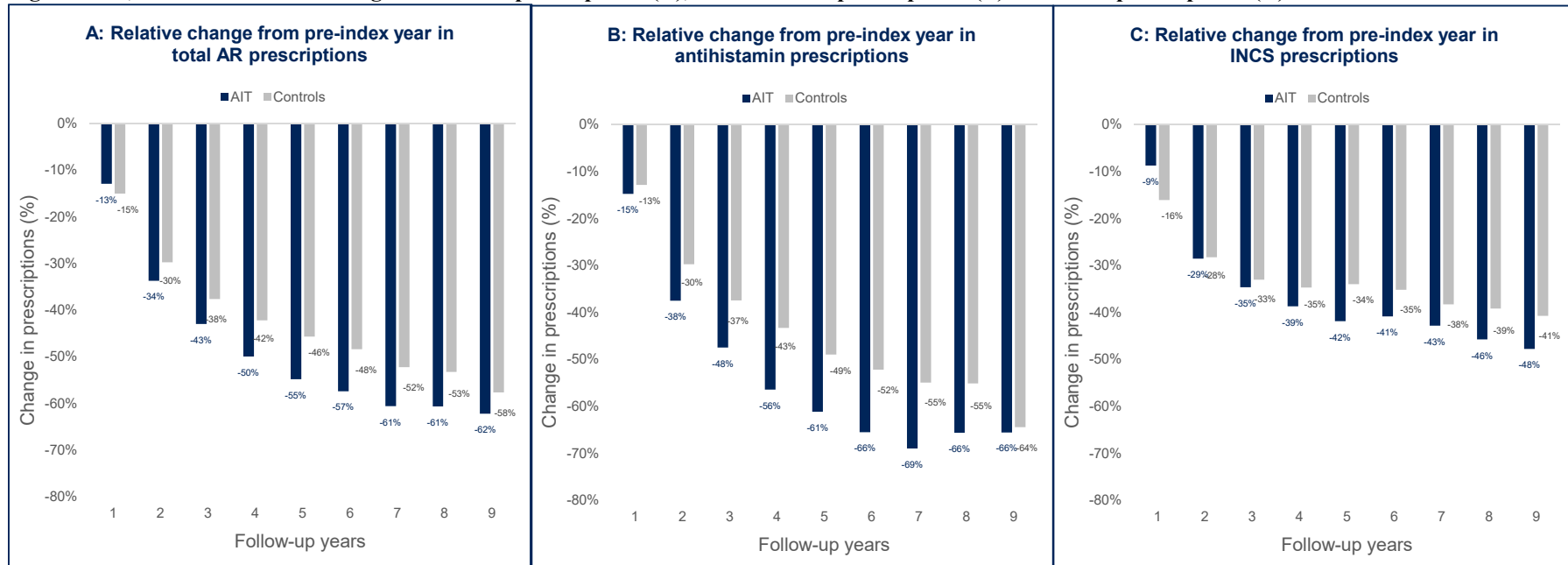


Table S7 Asthma prescriptions by drug class in follow-up years 1-9 in pre-existing asthma cohort

PRE-EXISTING ASTHMA									
	Rx/ subject	SD	Change from pre- index	95% CI	Rx/subject	SD	Change from pre- index	95% CI	P value
Year 1	AIT N=14614				Control N=14614				AIT vs. Control
Asthma Rx*	2.102	3.007	-0.363	-0.432;-0.294	2.241	3.255	-0.253	-0.328;-0.178	0.0001
SABA	0.743	1.413	-0.221	-0.255;-0.188	0.855	1.650	-0.125	-0.164;-0.086	<.0001
ICS	0.451	1.081	-0.114	-0.139;-0.089	0.434	1.074	-0.106	-0.132;-0.080	0.1835
ICS/LABA	0.673	1.493	0.023	-0.009;0.056	0.685	1.491	0.006	-0.028;0.040	0.4828
LTRA	0.131	0.704	-0.036	-0.053;-0.020	0.133	0.701	-0.020	-0.036;-0.003	0.8808
LABA	0.069	0.517	-0.001	-0.013;0.010	0.084	0.629	-0.004	-0.018;0.011	0.0289
Anticholinergics	0.010	0.198	0.001	-0.004;0.005	0.015	0.240	0.006	0.001;0.011	0.0405
Biologics	0.004	0.206	0.002	-0.002; 0.006	0.004	0.140	0.001	-0.002; 0.004	0.8420
LAMA/LABA	0.00	0.018	0.000	0.000; 0.001	0.000	0.030	0.000	0.000; 0.001	0.3458
Year 2	AIT N=12537				Control N=12537				AIT vs. Control
Asthma Rx*	1.834	2.875	-0.649	-0.723;-0.576	2.029	3.208	-0.486	-0.567;-0.405	<.0001
SABA	0.671	1.370	-0.305	-0.341;-0.270	0.787	1.651	-0.203	-0.245;-0.161	<.0001
ICS	0.360	0.958	-0.210	-0.236;-0.185	0.352	0.950	-0.202	-0.228;-0.175	0.4932
ICS/LABA	0.596	1.394	-0.048	-0.082;-0.014	0.647	1.440	-0.023	-0.059;0.013	0.0045
LTRA	0.112	0.627	-0.060	-0.078;-0.043	0.110	0.640	-0.044	-0.061;-0.027	0.8576
LABA	0.061	0.468	-0.014	-0.026;-0.002	0.076	0.562	-0.016	-0.031;-0.001	0.0203
Anticholinergics	0.011	0.196	0.004	0.000;0.008	0.020	0.285	0.012	0.007;0.018	0.0053
Biologics	0.005	0.237	0.003	-0.001;0.008	0.006	0.206	0.004	0.000;0.008	0.9547
LAMA/LABA	0.001	0.059	0.001	0.000; 0.002	0.003	0.145	0.002	0.000; 0.005	0.3034
Year 3	AIT N=10370				Control N=10370				AIT vs. Control
Asthma Rx*	1.666	2.713	-0.825	-0.904;-0.746	1.880	3.083	-0.630	-0.718;-0.542	<.0001
SABA	0.618	1.289	-0.361	-0.400;-0.322	0.725	1.579	-0.264	-0.310;-0.219	<.0001
ICS	0.308	0.863	-0.274	-0.301;-0.247	0.316	0.920	-0.250	-0.279;-0.221	0.4883
ICS/LABA	0.554	1.338	-0.076	-0.112;-0.039	0.613	1.387	-0.031	-0.070;0.007	0.0019
LTRA	0.095	0.590	-0.079	-0.098;-0.060	0.097	0.611	-0.059	-0.078;-0.041	0.8805
LABA	0.060	0.475	-0.021	-0.035;-0.008	0.076	0.582	-0.023	-0.040;-0.005	0.029
Anticholinergics	0.013	0.210	0.005	0.000;0.010	0.018	0.271	0.010	0.004;0.016	0.0855
Biologics	0.004	0.176	0.003	-0.001; 0.007	0.005	0.171	0.003	0.000; 0.007	0.9362
LAMA/LABA	0.002	0.79	0.002	0.000; 0.003	0.004	0.182	0.004	0.000; 0.007	0.2978
Year 4	AIT N=8338				Control N=8338				AIT vs. Control
Asthma Rx*	1.565	2.654	-0.913	-1.001;-0.825	1.807	3.047	-0.665	-0.762;-0.568	<.0001
SABA	0.678	1.261	-0.395	-0.438;-0.352	0.692	1.555	-0.279	-0.329;-0.228	<.0001
ICS	0.281	0.812	-0.306	-0.336;-0.276	0.294	0.876	-0.282	-0.314;-0.249	0.2919
ICS/LABA	0.529	1.302	-0.078	-0.118;-0.038	0.604	1.406	-0.013	-0.056;0.029	0.0003
LTRA	0.087	0.565	-0.092	-0.113;-0.071	0.087	0.559	-0.063	-0.083;-0.043	0.9890
LABA	0.058	0.466	-0.025	-0.040;-0.010	0.077	0.582	-0.026	-0.046;-0.007	0.0188
Anticholinergics	0.011	0.191	0.003	-0.003;0.008	0.024	0.305	0.015	0.007;0.022	0.001
Biologics	0.006	0.182	0.004	0.000; 0.009	0.003	0.128	0.002	-0.001; 0.005	0.2369
LAMA/LABA	0.002	0.106	0.002	0.000; 0.005	0.002	0.073	0.002	0.001;0.004	0.9319
Year 5	AIT N=6545				Control N=6545				AIT vs. Control
Asthma Rx*	1.445	2.490	-1.022	-1.119;-0.926	1.740	2.964	-0.763	-0.872;-0.653	<.0001
SABA	0.530	1.168	-0.429	-0.476;-0.382	0.657	1.517	-0.320	-0.377;-0.263	<.0001
ICS	0.249	0.789	-0.347	-0.381;-0.313	0.263	0.841	-0.315	-0.351;-0.278	0.3345
ICS/LABA	0.502	1.227	-0.095	-0.139;-0.051	0.610	1.382	-0.015	-0.063;0.033	<.0001
LTRA	0.079	0.542	-0.103	-0.127;-0.079	0.076	0.499	-0.082	-0.105;-0.060	0.7121
LABA	0.055	0.469	-0.029	-0.046;-0.012	0.070	0.534	-0.034	-0.054;-0.013	0.0916
Anticholinergics	0.013	0.200	0.004	-0.003; 0.010	0.032	0.375	0.021	0.011;0.031	0.0003
Biologics	0.006	0.187	0.005	0.001; 0.010	0.003	0.163	0.002	-0.002; 0.006	0.3704
LAMA/LABA	0.002	0.077	0.002	0.000; 0.004	0.004	0.119	0.004	0.002; 0.007	0.1635
Year 6	AIT N=5092				Control N=5092				AIT vs. Control

Asthma Rx*	1·325	2·426	-1·110	-1·219;-1·001	1·655	2·946	-0·845	-0·970;-0·721	<·0001
SABA	0·485	1·136	-0·473	-0·527;-0·419	0·614	1·461	-0·369	0·433;-0·304	<·0001
ICS	0·220	0·739	-0·366	-0·404;-0·329	0·230	0·766	-0·351	-0·392;-0·311	0·4935
ICS/LABA	0·475	1·170	-0·109	-0·157;-0·061	0·609	1·409	0·008	-0·046;0·063	<·0001
LTRA	0·061	0·457	-0·112	-0·138;-0·087	0·073	0·535	-0·090	-0·116;-0·064	0·2325
LABA	0·053	0·467	-0·033	-0·052;-0·013	0·061	0·504	-0·047	-0·071;-0·024	0·3807
Anticholinergics	0·015	0·241	0·006	-0·002;0·014	0·032	0·335	0·020	0·009;0·031	0·0028
Biologics	0·003	0·0095	0·002	-0·001; 0·005	0·005	0·181	0·004	-0·002;0·009	0·4097
LAMA/LABA	0·003	0·096	0·003	0·000; 0·006	0·010	0·192	0·010	0·005; 0·015	0·0190
Year 7	AIT N=3260				Control N=3260				AIT vs. Control
Asthma Rx*	1·329	2·542	-1·086	-1·223;-0·949	1·575	2·826	-0·903	-1·056;-0·751	0·0002
SABA	0·482	1·211	-0·459	-0·526;-0·393	0·598	1·485	-0·390	-0·472;-0·309	0·0006
ICS	0·214	0·760	-0·351	-0·398;-0·304	0·210	0·708	-0·369	-0·418;-0·319	0·8004
ICS/LABA	0·484	1·189	-0·113	-0·174;-0·051	0·570	1·346	-0·012	-0·078;0·053	0·0062
LTRA	0·059	0·472	-0·119	-0·152;-0·086	0·062	0·469	-0·100	-0·131;-0·069	0·7722
LABA	0·052	0·439	-0·033	-0·056;-0·010	0·071	0·590	-0·033	-0·064;-0·003	0·1216
Anticholinergics	0·017	0·252	0·006	-0·006;0·017	0·034	0·358	0·026	0·013;0·039	0·0278
Biologics	0·001	0·055	0·000	-0·003; 0·003	0·001	0·043	0·001	0·000; 0·003	1·0000
LAMA/LABA	0·006	0·218	0·006	-0·001; 0·014	0·011	0·295	0·011	0·004; 0·018	0·3688
Year 8	AIT N=1709				Control N=1709				AIT vs. Control
Asthma Rx*	1·353	2·552	-0·992	-1·179;-0·806	1·530	2·851	-0·896	-1·106;-0·686	0·0555
SABA	0·468	1·155	-0·462	-0·552;-0·372	0·582	1·514	-0·403	-0·520;-0·287	0·0138
ICS	0·198	0·690	-0·338	-0·398;-0·278	0·202	0·735	-0·359	-0·426;-0·292	0·8478
ICS/LABA	0·527	1·249	-0·043	-0·128;0·042	0·563	1·333	-0·013	-0·103;0·077	0·4117
LTRA	0·054	0·434	-0·118	-0·162;-0·073	0·050	0·383	-0·091	-0·129;-0·054	0·6478
LABA	0·054	0·434	-0·016	-0·045;0·013	0·055	0·495	-0·045	-0·085;-0·006	0·9707
Anticholinergics	0·022	0·270	0·005	-0·014;0·023	0·043	0·385	0·035	0·015;0·054	0·0569
Biologics	0·001	0·048	-0·001	-0·005;0·004	0·001	0·034	0·001	0·000;0·003	1·0000
LAMA/LABA	0·012	0·281	0·012	-0·001; 0·026	0·012	0·206	0·012	0·002;0·022	1·0000
Year 9	AIT N=571				Control N=571				AIT vs. Control
Asthma Rx*	1·331	2·651	-1·030	-1·361;-0·699	1·511	2·735	-1·063	-1·433;-0·693	0·258
SABA	0·443	1·131	-0·464	-0·613;-0·316	0·532	1·340	-0·501	-0·684;-0·318	0·2239
ICS	0·172	0·620	-0·343	-0·439;-0·247	0·198	0·782	-0·452	-0·577;-0·327	0·5295
ICS/LABA	0·553	1·271	-0·056	-0·210;0·098	0·601	1·298	0·096	-0·059;0·252	0·5342
LTRA	0·063	0·481	-0·123	-0·207;-0·039	0·037	0·308	-0·124	-0·187;-0·061	0·2720
LABA	0·044	0·397	-0·023	-0·069;0·024	0·056	0·474	-0·093	-0·179;-0·007	0·6359
Anticholinergics	0·040	0·402	0·012	-0·034;0·058	0·042	0·382	0·030	-0·005;0·065	0·9398
Biologics	0·004	0·084	0·004	-0·003;0·010	0·0	0·00	0·000	0·000;0·000	0·3177
LAMA/LABA	0·009	0·139	0·009	-0·003; 0·020	0·004	0·059	0·004	-0·001; 0·008	0·4051
*Continuous variables are presented as means ± standard deviations (SD) and as the within group absolute change (95% CI) from pre-index year; P-values are between group comparison of AIT vs. controls. Prescriptions are reported as Rx/subject; AIT: allergen immunotherapy; CI: confidence intervals; SABA: short-acting beta2-agonists, ICS: inhaled corticosteroids; LABA: long-acting beta2-agonists; LTRA: leukotriene receptor antagonists, LAMA: long-acting muscarinic antagonists.									

Figure S7 A, B, C and D: Relative change in total asthma prescriptions (A), SABA prescriptions (B), ICS prescriptions (C) and ICS/LABA prescriptions (D) in asthma cohort

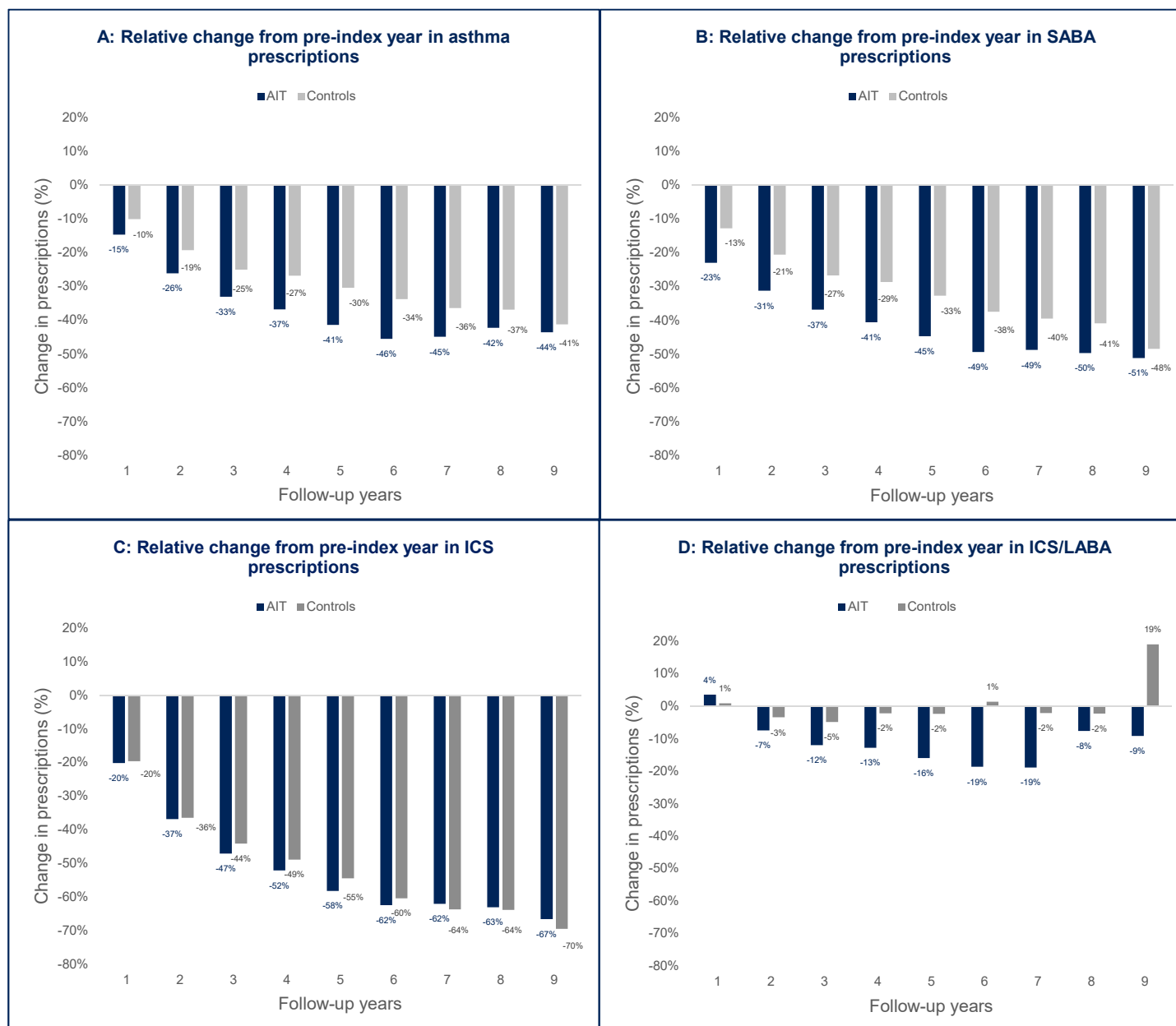


Table S8 Time-to-first improvement of asthma in the pre-existing asthma cohort

	AIT			Control			HR	95% CI	Log-rank	Kolmogorov-type
	Subjects in analysis	Subjects with events		Subjects in analysis	Subjects with events		AIT vs. control		p-value	supremum test
Asthma Improvement#	14614	5740	39%	14614	4562	31%	1.29	1.24;1.34	<.0001	<.0001
# Categorical variables are presented as n (%); Time to asthma improvement: Decrease in asthma treatment step in subjects with pre-existing asthma; Treatment step 1: Asthma diagnosis in the absence of controller asthma medication; Treatment step 2: Monotherapy with either low dose ICS or LTRA; Treatment step 3: Dual therapy or therapy with medium-high ICS, LABA or methylxanthine; Treatment step 4: Triple therapy or therapy with anti-IgE or anti-IL-5; The Cox Constant Proportional Hazards method was used to estimate the ratio of treatment effects and 95% confidence intervals. The proportional hazard assumption was tested using the Kolmogorov-type supremum test. AIT: allergen immunotherapy; HR: hazard ratio; IL: interleukin; CI: confidence interval; SABA: short-acting beta2-agonists; ICS: inhaled corticosteroids; LABA: long-acting beta2-agonists; LTRA: leukotriene receptor antagonists.										

Figure S8 Kaplan Meier curve; Time-to-first improvement of asthma in the pre-existing asthma cohort

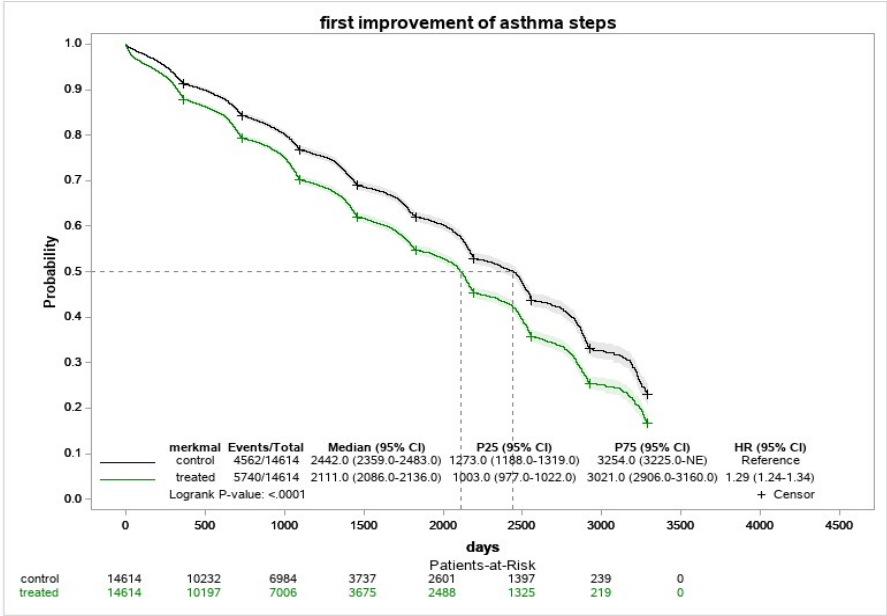


Table S9 Time-to-any improvement of asthma in the pre-existing asthma cohort

	AIT			Control			HR	95% CI	p-value
	Subjects in analysis	Subjects with events		Total events	Subjects in analysis	Subjects with events		Total events	AIT vs. control
Asthma Improvement#	14614	5740	39%	8925	14614	4562	31%	6915	1·19 1·15;1·23 <·0001
# Categorical variables are presented as n (%); Time to asthma improvement: Decrease in asthma treatment step in subjects with pre-existing asthma; Treatment step 1: Asthma diagnosis in the absence of controller asthma medication; Treatment step 2: Monotherapy with either low dose ICS or LTRA; Treatment step 3: Dual therapy or therapy with medium-high ICS, LABA, or methylxanthine; Treatment step 4: Triple therapy or therapy with anti-IgE or anti-IL-5; AIT: allergen immunotherapy; IL: interleukin; HR: hazard ratio; CI: confidence interval; SABA: short-acting beta2-agonists, ICS: inhaled corticosteroids; LABA: long-acting beta2-agonists; LTRA: leukotriene receptor antagonists.									

Table S10 Time-to-first worsening of asthma defined by a 3-point composite endpoint

	AIT			Control			HR	95% CI	Log-rank p-value	Kolmogorov-type supremum test p-value
	Subjects in analysis	Subjects with event		Subjects in analysis	Subjects with event					
Worsening of asthma#	41751	7813	19%	41751	7836	19%	1·00	0·96;1·03	0·7761	0·004
New onset of asthma	27039	1148	4·2%	27039	950	3·5%	1·22	1·12;1·32	<·0001	0·342
Increased asthma treatment step	14614	3808	26%	14614	4100	28%	0·91	0·87;0·95	<·0001	0·044
Severe asthma exacerbations	41751	4542	11%	41751	4564	11%	1·00	0·96;1·04	0·8129	0·361
#Categorical variable are presented as n (%); Time to asthma worsening: 3-point composite of either an increase in asthma treatment step in subjects with pre-existing asthma or new onset of asthma in subjects without asthma or a severe asthma exacerbation; Treatment step 1: Asthma diagnosis in the absence of controller asthma medication; Treatment step 2: Monotherapy with either low dose ICS or LTRA; Treatment step 3: Dual therapy or therapy with medium-high ICS, LABA or methylxanthine; Treatment step 4: Triple therapy or therapy with anti-IgE or anti-IL-5; New onset of asthma: At least one asthma diagnosis and two prescriptions of SABA/ICS within a post-index follow-up year. Severe asthma exacerbation: 3-point composite of either new systemic corticosteroid prescription, status asthmaticus recorded in ambulatory care or hospitalisation for asthma. The Cox Constant Proportional Hazards method was used to estimate the ratio of treatment effects and 95% confidence intervals. The proportional hazard assumption was tested using the Kolmogorov-type supremum test. AIT: allergen immunotherapy; IL: interleukin; HR: hazard ratio; CI: confidence interval; SABA: short-acting beta2-agonists, ICS: inhaled corticosteroids; LABA: long-acting beta2-agonists; LTRA: leukotriene receptor antagonists.										

Figure S9 Kaplan Meier curve; Time-to-first worsening of asthma in the pre-existing asthma cohort

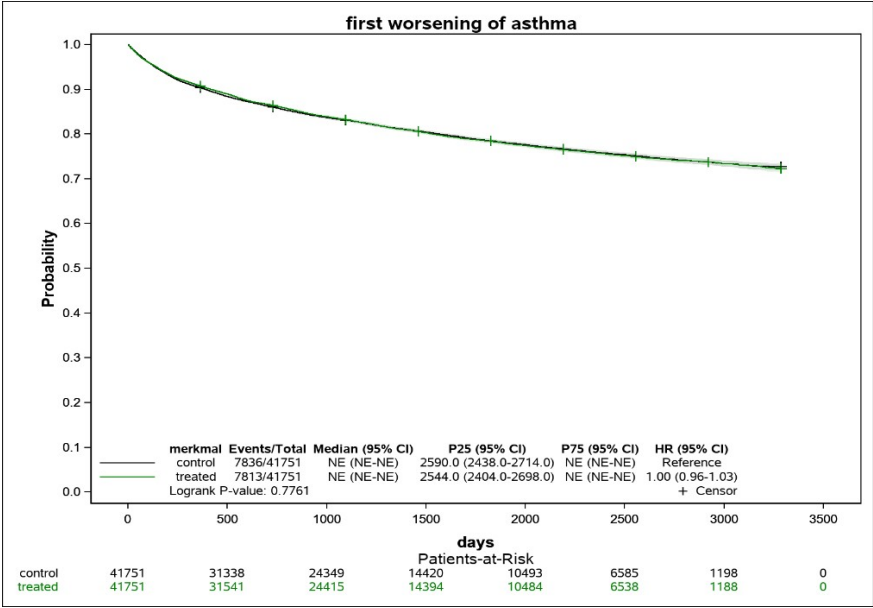


Table S11 Time-to-any worsening of asthma defined by a 3-point composite endpoint

	AIT				Control				HR	95% CI	p-value
	Subjects in analysis	Subjects with events		Total events	Subjects in analysis	Subjects with events		Total events			
Asthma worsening#	41751	7813	19%	25852	41751	7836	19%	26561	0·98	0·97;1·00	0·0357
New onset of asthma	27039	1148	4·2%	6926	27039	950	3·5%	5747	1·01	0·97;1·04	0·7988
Increased asthma treatment step	14614	3808	26%	8521	14614	4100	28%	9039	0·99	0·96;1·02	0·4224
Severe asthma exacerbations	41751	4542	11%	10838	41751	4564	11%	12164	0·95	0·92;0·97	<·0001
# Categorical variables are presented as n (%); Time to asthma worsening: 3-point composite of either an increase in asthma treatment step in subjects with pre-existing asthma or new onset of asthma in subjects without asthma or a severe asthma exacerbation. Treatment step 1: Asthma diagnosis in the absence of controller asthma medication; Treatment step 2: Monotherapy with either low dose ICS or LTRA; Treatment step 3: Dual therapy or therapy with medium-high ICS, LABA or methylxanthine; Treatment step 4: Triple therapy or therapy with anti-IgE or anti-IL-5; New onset of asthma: At least one asthma diagnosis and two prescriptions of SABA/ICS within a post-index follow-up year. Severe asthma exacerbation: 3-point composite of either new systemic corticosteroid prescription, status asthmaticus recorded in ambulatory care or hospitalisation for asthma. AIT: allergen immunotherapy; IL: interleukin; HR: hazard ratio; CI: confidence interval; SABA: short-acting beta2-agonists, ICS: inhaled corticosteroids; LABA: long-acting beta2-agonists; LTRA: leukotriene receptor antagonists.											

Table S12 Time-to-first severe asthma exacerbation in the pre-existing asthma cohort

	AIT			Control			HR	95% CI	Log-rank	Kolmogorov-type
	Subjects in analysis	Subjects with events		Subjects in analysis	Subjects with events		AIT vs. control		p-value	supremum test
Severe asthma exacerbation#	14614	3694	25%	14614	3893	27%	0·94	0·90; 0·98	0·0072	0,579
#Categorical variables are presented as n (%); Severe asthma exacerbation: 3-point composite of either new systemic corticosteroid prescription, status asthmaticus recorded in ambulatory care or hospitalisation for asthma. The Cox Constant Proportional Hazards method was used to estimate the ratio of treatment effects and 95% confidence intervals. The proportional hazard assumption was tested using the Kolmogorov-type supremum test. AIT: allergen immunotherapy; HR: hazard ratio; CI: confidence interval.										

Figure S10 Kaplan Meier curve; Time-to-first severe asthma exacerbation in the pre-existing asthma cohort

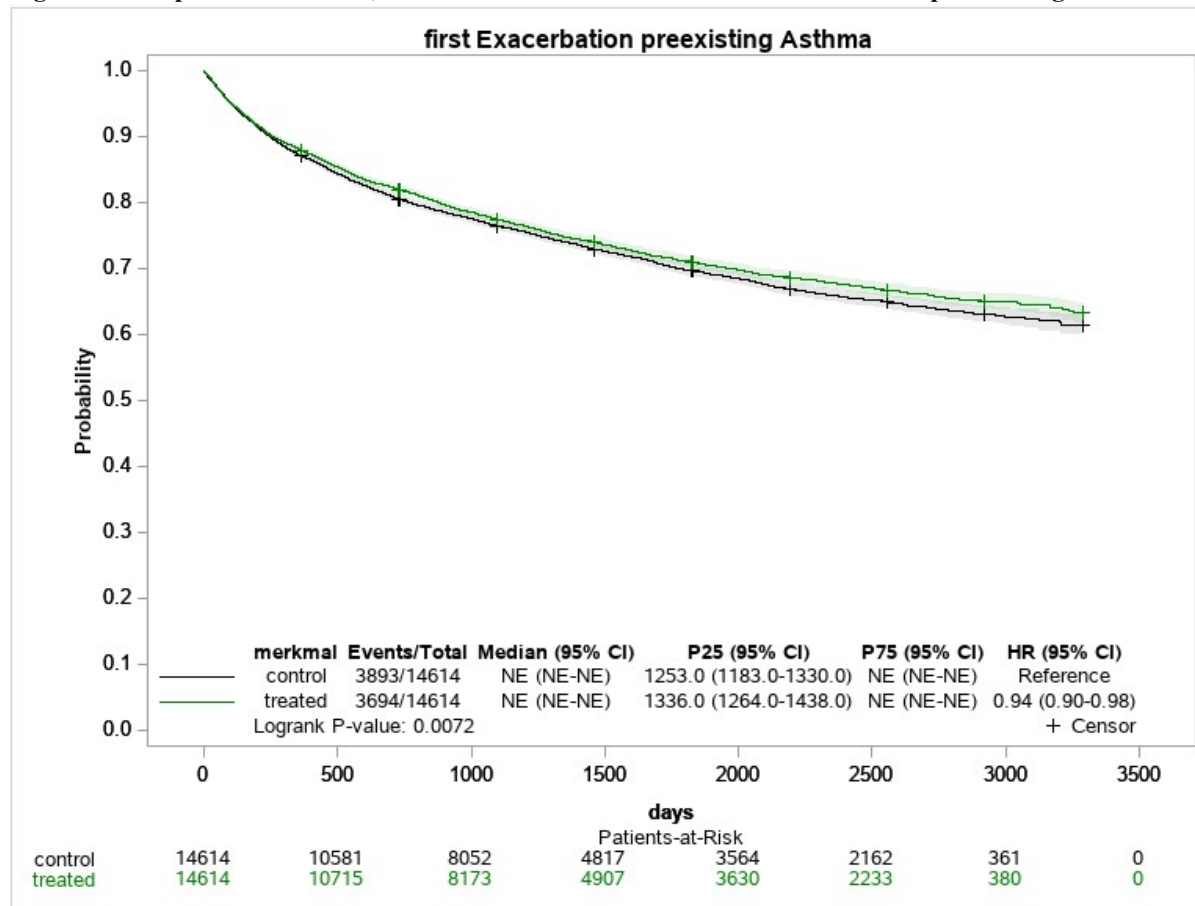


Table S13 Time-to-any severe asthma exacerbation in the pre-existing asthma cohort

	AIT				Control				HR	95% CI	p-value
	Subjects in analysis	Subjects with events		Total events	Subjects in analysis	Subjects with events		Total events			
Severe asthma exacerbation	14614	3694	25%	9307	14614	3893	27%	11137	0.92	0.90;0.95	<0.0001
# Categorical variables are presented as n (%); Severe asthma exacerbation: 3-point composite of either new systemic corticosteroid prescription, status asthmaticus recorded in ambulatory care or hospitalisation for asthma. AIT: allergen immunotherapy; HR: hazard ratio; CI: confidence interval											

Table S14 Severe asthma exacerbations by components in follow-up years 1-9 in pre-existing asthma cohort

Pre-existing asthma									
	Event/ subject	SD	Change from pre- index	95% CI	Events/ subject	SD	Change from pre-index	95% CI	P value
Year 1	AIT N= 14614				Control N= 14614				AIT vs. Control
Total exacerbations*	0.19	0.62	-0.03	-0.04; -0.01	0.20	0.67	-0.02	-0.04; -0.004	0.1560
Oral corticosteroids Rx	0.15	0.51	-0.03	-0.04;-0.01	0.18	0.62	-0.02	-0.04;-0.01	<.0001
Hospitalisation with asthma diagnosis	0.034	0.29	0.000	-0.006; 0.007	0.016	0.17	0.002	-0.002; 0.006	<.0001
Status asthmaticus	0.009	0.15	0.001	-0.003; 0.004	0.008	0.13	0.000	-0.002;0.003	0.4414
Year 2	AIT N= 12537				Control N= 12537				AIT vs. Control
Total exacerbations*	0.16	0.58	-0.06	-0.07;-0.04	0.19	0.68	-0.03	-0.05; -0.01	<.0001
Oral corticosteroids Rx	0.12	0.49	-0.05	-0.06;-0.04	0.17	0.64	-0.03	-0.05; -0.01	<.0001
Hospitalisation with asthma diagnosis	0.027	0.26	-0.004	-0.01;0.002	0.015	0.16	0.002	-0.002; 0.006	<.0001
Status asthmaticus	0.009	0.15	0.000	-0.003; 0.004	0.006	0.10	-0.001	-0.004; 0.001	0.0778
Year 3	AIT N= 10370				Control N= 10370				AIT vs. Control
Total exacerbations*	0.15	0.57	-0.06	-0.08; -0.05	0.17	0.65	-0.04	-0.06; -0.02	0.0020
Oral corticosteroids Rx	0.12	0.48	-0.06	-0.07; -0.05	0.16	0.60	-0.04	-0.06; -0.02	<.0001
Hospitalisation with asthma diagnosis	0.025	0.25	-0.002	-0.008; 0.005	0.013	0.16	0.001	-0.003; 0.005	<.0001
Status asthmaticus	0.007	0.12	-0.002	-0.006; 0.001	0.005	0.10	-0.002	-0.005; 0.001	0.1738
Year 4	AIT N= 8338				Control N= 8338				AIT vs. Control
Total exacerbations*	0.14	0.55	-0.06	-0.08;-0.04	0.17	0.65	-0.04	-0.06;-0.02	0.0041
Oral corticosteroids Rx	0.11	0.46	-0.06	-0.08; -0.05	0.15	0.63	-0.04	-0.06; -0.02	<.0001
Hospitalisation with asthma diagnosis	0.026	0.25	0.004	-0.002; 0.011	0.011	0.14	0.002	-0.001; 0.006	<.0001
Status asthmaticus	0.006	0.13	-0.003	-0.007; 0.001	0.004	0.08	-0.003	-0.006; 0.000	0.2034
Year 5	AIT N= 6545				Control N= 6545				AIT vs. Control
Total exacerbations*	0.13	0.53	-0.06	-0.08;-0.04	0.18	0.66	-0.02	-0.04;0.004	<.0001
Oral corticosteroids Rx	0.11	0.47	-0.06	-0.08;-0.04	0.17	0.64	-0.02	-0.04;0.003	<.0001
Hospitalisation with asthma diagnosis	0.017	0.19	0.004	-0.001; 0.010	0.011	0.13	0.004	0.000; 0.008	0.0357
Status asthmaticus	0.007	0.12	-0.002	-0.006; 0.003	0.001	0.04	-0.004	-0.006; -0.001	0.0005
Year 6	AIT N= 5092				Control N= 5092				AIT vs. Control
Total exacerbations*	0.12	0.52	-0.06	-0.08;-0.04	0.17	0.63	-0.04	-0.06;-0.01	<.0001
Oral corticosteroids Rx	0.11	0.47	-0.06	-0.08;-0.04	0.15	0.60	-0.04	-0.07; -0.02	<.0001
Hospitalisation with asthma diagnosis	0.014	0.18	0.005	-0.001; 0.011	0.010	0.13	0.005	0.001; 0.009	0.1821
Status asthmaticus	0.005	0.11	-0.006	-0.011; 0.000	0.005	0.10	-0.001	-0.005; 0.003	0.9243
Year 7	AIT N 3260				Control N= 3260				AIT vs. Control
Total exacerbations*	0.12	0.53	-0.07	-0.09;-0.04	0.16	0.62	-0.05	-0.08; -0.02	0.0087
Oral corticosteroids Rx	0.10	0.50	-0.06	-0.09; -0.04	0.15	0.60	-0.05	-0.08;-0.02	0.0009
Hospitalisation with asthma diagnosis	0.014	0.16	0.006	-0.001; 0.012	0.007	0.13	0.002	-0.003; 0.007	0.0762
Status asthmaticus	0.004	0.10	-0.008	-0.015; -0.001	0.003	0.06	-0.002	-0.005; 0.002	0.6471
Year 8	AIT N= 1709				Control N= 1709				AIT vs. Control

Total exacerbations*	0·12	0·55	-0·06	-0·10;-0·03	0·16	0·63	-0·04	-0·08;0·000	0·0828
Oral corticosteroids Rx	0·10	0·48	-0·06	-0·10;-0·03	0·15	0·62	-0·04	-0·08;0·002	0·0096
Hospitalisation with asthma diagnosis	0·018	0·22	0·011	0·000; 0·022	0·007	0·10	0·000	-0·006; 0·006	0·0712
Status asthmaticus	0·005	0·14	-0·011	-0·023; 0·001	0·002	0·04	-0·003	0·007; 0·001	0·3172
Year 9	AIT N= 571				Control N= 571				AIT vs. Control
Total exacerbations*	0·12	0·55	-0·06	-0·13;0·01	0·19	0·75	-0·02	-0·10;0·06	0·0535
Oral corticosteroids Rx	0·11	0·48	-0·04	-0·10; 0·02	0·19	0·73	-0·002	-0·08;0·08	0·0312
Hospitalisation with asthma diagnosis	0·007	0·12	-0·002	-0·014; 0·011	0·002	0·04	-0·011	-0·020; -0·001	0·3173
Status asthmaticus	0·002	0·04	-0·016	-0·032; 0·001	0·002	0·04	-0·005	-0·013; 0·002	1·0000
*Continuous variables are presented as mean ± standard deviations (SD) and changes as the within group absolute change (95% CI) from pre-index year; P-values are between group comparison of AIT vs. controls; Severe asthma exacerbation: 3-point composite of either new systemic corticosteroid prescription, status asthmaticus recorded in ambulatory care or hospitalisation for asthma Systemic corticosteroid prescription: New prescription of oral, intravenous, or subcutaneous corticosteroid, Status asthmaticus: Status asthmaticus recorded in ambulatory care; Hospitalisation for asthma: Hospitalisation with an asthma diagnosis as the main diagnosis; AIT: allergen immunotherapy; CI: confidence interval; Rx: prescription									

Table S15 Time-to-first onset of asthma in the no asthma cohort

	AIT			Control			HR	95% CI	Log-rank	Kolmogorov-type
	Subjects in analysis n	Subjects with events		Subjects in analysis	Subjects with events		AIT vs. control		p-value	supremum test
New onset of asthma#	27039	1148	4.2%	27039	950	3.5%	1.22	1.12;1.32	<.0001	0.342
#Categorical variables are presented as n (%); New onset of asthma: At least one asthma diagnosis and two prescriptions of SABA/ICS within a post-index follow-up year. The Cox Constant Proportional Hazards method was used to estimate the ratio of treatment effects and 95% confidence intervals. The proportional hazard assumption was tested using the Kolmogorov-type supremum test. AIT: allergen immunotherapy; HR: hazard ratio; CI confidence interval; SABA: short-acting beta2-agonists; ICS: inhaled corticosteroids.										

Figure S11 Kaplan Meier curve; Time-to-first onset of asthma in the no asthma cohort

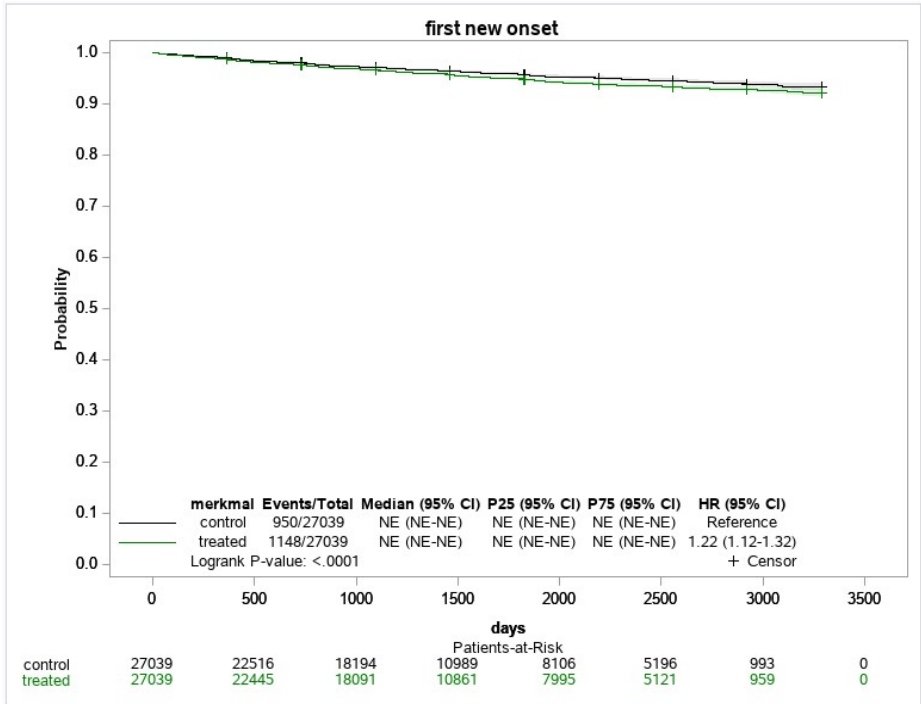


Figure S12 A and B: Ambulatory care visits (A) and change in asthma medication (B) in the no asthma cohort

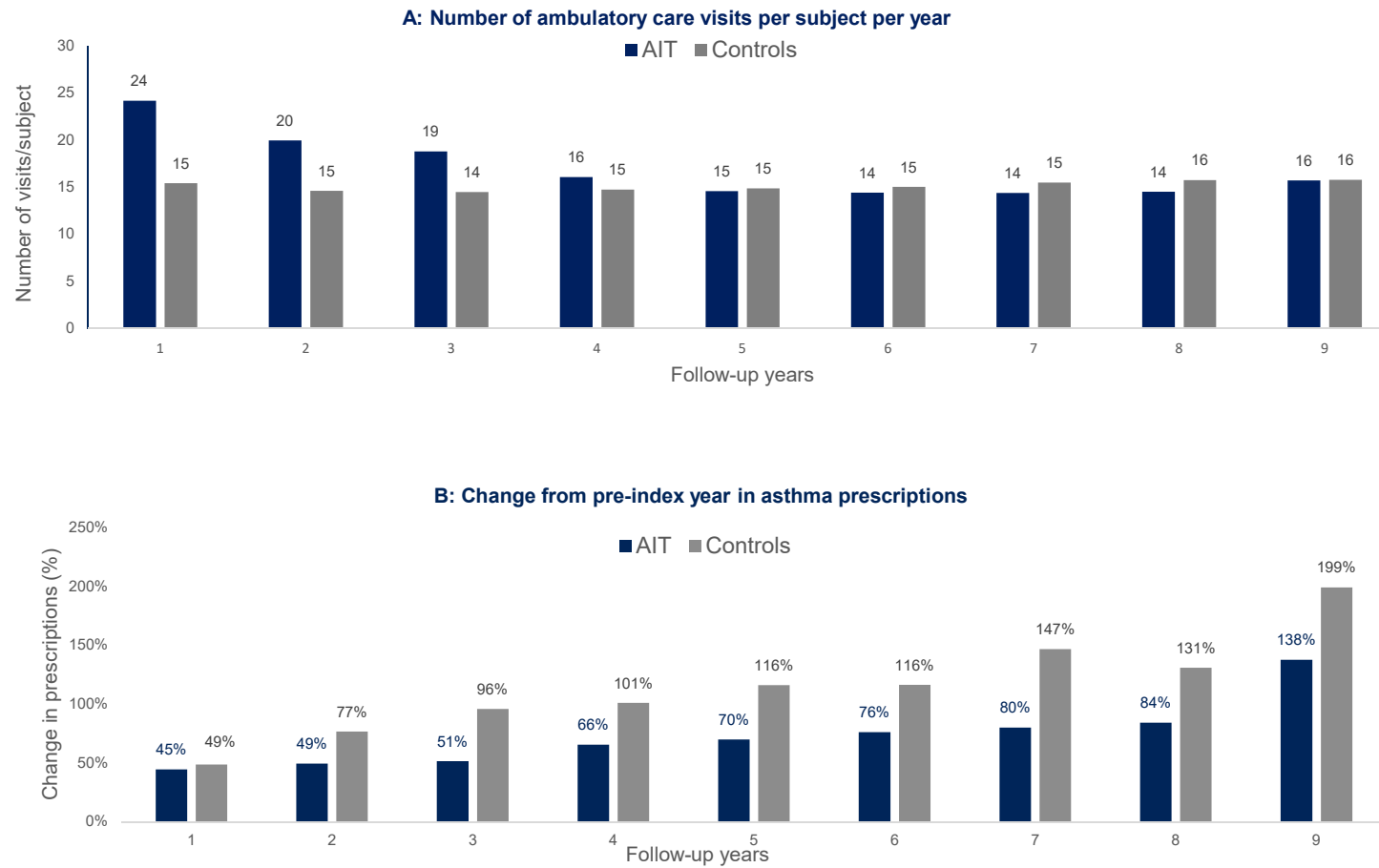


Figure S11: Panel A shows ambulatory care visits/ subject over time in the AIT-group (blue) and controls (grey) and Panel B shows relative changes in asthma prescriptions from pre-index year over time in the AIT-group (blue) and controls (grey) in the no asthma cohort.

Table S16: Subjects with events of health care resource utilisation, sick leave, and biologic prescriptions in main cohort in year 3, 5, and 9

Year 3							
	N	%	N	%	OR	95% CI	p-value
	AIT N= 32112		Control N= 32112		AIT vs. Control		
Ambulatory care visits total#	31543	98%	30912	96%	2.15	1.95; 2.38	<.0001
Otolaryngologist visits	13340	42%	8734	27%	1.90	1.84; 1.97	<.0001
Pulmonologist visits	14375	45%	11129	35%	1.53	1.48; 1.58	<.0001
General practitioner visits	21125	66%	22448	70%	0.83	0.80; 0.86	<.0001
Internist visits	13389	42%	12615	39%	1.11	1.07; 1.14	<.0001
Other specialist visits	27420	85%	27290	85%	1.03	0.99; 1.08	0.1519
Hospital visits total#	5088	16%	5501	17%	0.91	0.87; 0.95	<.0001
Inpatient visits	3199	10%	3700	12%	0.85	0.81; 0.89	<.0001
Outpatient visits	2471	8%	2585	8%	0.95	0.90; 1.01	0.0978
Surgical procedures	166	0.5%	160	0.5%	1.04	0.84; 1.29	0.7813
Sick leave#	10963	34%	10667	33%	1.04	1.01; 1.08	0.0138
Biological drug prescriptions#	14	0.04%	15	0.05%	0.93	0.45; 1.93	1.0000
Year 5							
	N	%	N	%	OR	95% CI	p-value
	AIT N= 19783		Control N= 19783		AIT vs. Control		
Ambulatory care visits total#	18980	96%	18986	96%	0.99	0.90; 1.10	0.8985
Otolaryngologist visits	5757	29%	5227	26%	1.14	1.09; 1.19	<.0001
Pulmonologist visits	7663	39%	7031	36%	1.15	1.10; 1.19	<.0001
General practitioner visits	13309	67%	14137	71%	0.82	0.79; 0.86	<.0001
Internist visits	8066	41%	8174	41%	0.98	0.94; 1.02	0.2742
Other specialist visits	16471	83%	16642	84%	0.94	0.89; 0.99	0.0207
Hospital visits total#	3247	16%	3566	18%	0.89	0.85; 0.94	<.0001
Inpatient visits	2022	10%	2353	12%	0.84	0.79; 0.90	<.0001
Outpatient visits	1621	8%	1702	9%	0.95	0.88; 1.02	0.147
Surgical procedures	86	0.4%	71	0.4%	1.21	0.89; 1.66	0.2628
Sick leave#	7103	36%	6840	35%	1.06	1.02; 1.11	0.0058
Biological drug prescriptions#	10	0.05%	5	0.03%	2.00	0.68; 5.85	0.3017
Year 9							
	N	%	N	%	OR	95% CI	p-value
	AIT N= 1846		Control N= 1846		AIT vs. Control		
Ambulatory care visits total#	1757	95%	1760	95%	0.97	0.71; 1.31	0.877
Otolaryngologist visits	474	26%	475	26%	1.00	0.86; 1.16	1.000
Pulmonologist visits	691	37%	665	36%	1.06	0.93; 1.22	0.3934
General practitioner visits	1299	70%	1370	74%	0.83	0.71; 0.95	0.01
Internist visits	847	46%	835	45%	1.03	0.90; 1.17	0.7162
Other specialist visits	1514	82%	1523	83%	0.97	0.82; 1.15	0.7304
Hospital visits total#	290	16%	333	18%	0.85	0.71; 1.01	0.0649
Inpatient visits	194	11%	244	13%	0.77	0.63; 0.94	0.0126
Outpatient visits	133	7%	127	7%	1.05	0.82; 1.35	0.7478
Surgical procedures	14	0.8%	9	0.5%	1.56	0.67; 3.61	0.4034
Sick leave#	792	43%	724	39%	1.16	1.02; 1.33	0.025

Biological drug prescriptions#	0	0%	1	0·05%	·	·	1·0000
# Categorical variables are presented as n (%); and changes as the within group odds ratio (95% CI) from pre-index year; P-values are between group comparison of AIT vs. controls. Only selected years are presented: Year 3 = expected end of treatment; Year 5 = duration of long-term RCTs investigating disease-modification, Year 9 = last year of observation. Ambulatory care visits: Number of subjects with ambulatory care visits in total and by specialist (otolaryngology, pulmonology, general practitioners, internal medicine) vs. non-specialist (others); Hospital visits: number of subjects with a hospital visit (total) and Inpatient/ Outpatient; Surgical procedures: Number of subjects with surgical ear-nose-throat (ENT) procedures of the nose and sinuses; Sick leave: number of subjects on sick leave; Biological drug prescriptions: number of subjects with biologics Rx. AIT: allergen immunotherapy; Rx: prescription; OR: odds ratio; CI: confidence interval; RCT: randomised controlled trial.							

Table S17 Events of health care utilisation, sick leave, biologics prescriptions in main cohort in year 3, 5, and 9

Year 3									
	Mean	SD	Change from pre-index	95% CI	Mean	SD	Change from pre-index	95% CI	P value
	AIT N= 32112				Control N= 32112				AIT vs. Control
Ambulatory care visits*	19·7	13·7	3·96	3·76;4·16	15·8	15·7	-2·26	-2·51;-2·01	<·0001
Otolaryngologist visits	2·7	4·63	1·28	1·22;1·34	0·8	2·05	-0·48	-0·52;-0·44	<·0001
Pulmonologist visits	2·4	4·43	1·16	1·10;1·21	0·9	2·42	-0·21	-0·25;-0·17	<·0001
General practitioner visits	4·0	5·40	0·44	0·37;0·52	4·3	5·88	-0·17	-0·26;-0·07	<·0001
Internist visits	2·6	4·82	0·84	0·77;0·90	2·0	4·37	0·05	-0·02;0·12	<·0001
Other specialist visits	7·9	9·18	0·25	0·12;0·39	7·8	10·71	-1·45	-1·62;-1·28	0·1004
Hospital visits total*	0·27	0·79	0·09	0·08;0·10	0·29	0·83	0·11	0·09;0·12	<·0001
Hospital visits inpatient	0·13	0·46	0·02	0·01;0·02	0·15	0·51	0·03	0·02;0·04	<·0001
Length of inpatient stay days	0·92	6·24	0·20	0·11;0·28	1·26	8·41	0·38	0·27;0·49	<·0001
Hospital visits outpatient	0·14	0·58	0·07	0·06;0·08	0·14	0·58	0·08	0·07;0·09	0·5274
Surgical procedures events	0·013	0·21	-0·02	-0·02;-0·01	0·013	0·21	-0·01	-0·02;-0·01	0·7905
Sick leave events*	0·79	1·48	0·09	0·07;0·11	0·82	1·58	0·08	0·06;0·10	0·02
Sick leave days*	8·3	30·3	1·29	0·84;1·74	9·0	33·0	1·29	0·80;1·78	0·0088
Biological drug prescriptions*	0·002	0·11	0·001	0·000;0·003	0·003	0·17	0·002	0·000;0·004	0·35
Year 5									
	Mean	SD	Change from pre-index	95% CI	Mean	SD	Change from pre-index	95% CI	P value
	AIT N= 19783				Control N=19783				AIT vs. Control
Ambulatory care visits*	15·3	14·0	-0·64	-0·90;-0·38	16·1	16·4	-2·03	-2·35;-1·71	<·0001
Otolaryngologist visits	1·0	2·62	-0·41	-0·46;-0·36	0·7	1·88	-0·54	-0·59;-0·49	<·0001
Pulmonologist visits	1·3	3·16	0·03	-0·02;0·09	0·9	2·25	-0·23	-0·28;-0·18	<·0001
General practitioner visits	3·9	5·15	0·23	0·13;0·33	4·6	6·12	0·06	-0·06;0·18	<·0001
Internist visits	2·0	4·00	0·23	0·15;0·30	2·2	5·16	0·23	0·14;0·33	0·0039
Other specialist visits	7·0	9·00	-0·72	-0·89;-0·55	7·8	11·16	-1·55	-1·77;-1·33	<·0001
Hospital visits total*	0·28	0·82	0·14	0·13;0·15	0·32	0·90	0·18	0·16;0·19	<·0001
Hospital visits inpatient	0·13	0·47	0·02	0·01;0·03	0·17	0·56	0·05	0·04;0·06	<·0001
Length of inpatient stay days	0·95	6·30	0·24	0·13;0·35	1·49	9·03	0·64	0·49;0·78	<·0001
Hospital visits outpatient	0·15	0·61	0·12	0·11;0·13	0·15	0·61	0·13	0·12;0·14	0·2644
Surgical procedures events	0·011	0·19	-0·02	-0·02;-0·01	0·009	0·17	-0·02	-0·02;-0·01	0·1929
Sick leave events*	0·85	1·53	0·16	0·13;0·19	0·87	1·62	0·16	0·13;0·19	0·215
Sick leave days*	8·8	30·1	2·10	1·54;2·66	9·6	33·6	2·14	1·51;2·77	0·0156
Biological drug prescriptions*	0·002	0·10	0·002	0·000;0·003	0·002	0·11	0·001	-0·001;0·003	0·641
Year 9									
	Mean	SD	Change from pre-index	95% CI	Mean	SD	Change from pre-index	95% CI	P value
	AIT N=1846				Control N=1846				AIT vs. Control
Ambulatory care visits*	16·1	15·2	-1·73	-2·70;-0·76	16·6	15·3	-3·33	-4·34;-2·32	0·3082
Otolaryngologist visits	0·8	1·97	-0·82	-1·00;-0·65	0·6	1·62	-0·78	-0·95;-0·60	0·0111
Pulmonologist visits	1·1	2·77	0·43	0·29;0·58	0·8	2·41	0·30	0·16;0·44	0·0044

General practitioner visits	4·4	5·45	0·24	-0·11;0·59	5·0	6·01	-0·12	-0·52;0·29	0·0017
Internist visits	2·4	4·32	0·61	0·34;0·88	2·5	4·60	0·46	0·17;0·76	0·7622
Other specialist visits	7·4	9·76	-2·19	-2·83;-1·54	7·7	9·64	-3·20	-3·87;-2·52	0·399
Hospital visits total*	0·26	0·85	0·14	0·10;0·18	0·30	0·82	0·18	0·14;0·22	0·1795
Hospital visits inpatient	0·13	0·47	0·02	-0·003;0·05	0·18	0·52	0·07	0·04;0·10	0·0078
Length of inpatient stay days	0·87	4·86	0·08	-0·23;0·39	1·19	5·87	0·54	0·22;0·85	0·066
Hospital visits outpatient	0·13	0·58	0·11	0·09;0·14	0·13	0·56	0·11	0·09;0·14	0·728
Surgical procedures events	0·017	0·22	-0·01	-0·03;0·01	0·008	0·12	-0·02	-0·03;-0·003	0·1153
Sick leave events*	1·06	1·70	0·40	0·30;0·49	1·02	1·78	0·28	0·18;0·39	0·484
Sick leave days*	9·8	27·1	2·30	0·37;4·23	10·2	26·3	3·38	1·77;4·98	0·6583
Biological drug prescriptions*	0	0	0	0	0·003	0·12	0·003	-0·003;0·008	0·3174
*Continuous variables are reported as mean ± standard deviations (SD); and changes as the within group absolute change (95% CI) from pre-index year; P-values are between group comparison of AIT vs. controls; Ambulatory care visits: number of ambulatory care visits in total and by specialist (otolaryngology, pulmonology, general practitioners, internal medicine) vs. non-specialist (others); Hospital visits: number hospital visits (total) and number of inpatient / outpatient visits, and length of stays in days; Surgical procedures: Number of surgical procedures of the nose and sinuses; Sick leave: number of events of sick leave and days on sick leave; Biological drug prescriptions: number biologics Rx. Only selected years are presented: Year 3 = expected end of treatment; Year 5 = duration of long-term RCTs investigating disease-modification, Year 9 = last year of observation; AIT: allergen immunotherapy; CI: confidence interval; Rx: prescriptions; RCT: randomised controlled trial.									

Table S18 Change from pre-index year in health care costs for the main cohort in year 3, 5, and 9

	Year 3					Year 5					Year 9				
	AIT	95% CI	Control	95% CI	p-value AIT vs. control	AIT	95% CI	Control	95% CI	p-value AIT vs. control	AIT	95% CI	Control	95% CI	p-value AIT vs. Control
Total health care costs*	721	669; 773	248	154; 342	0·0002	429	342; 516	430	311; 549	<·0001	512	294; 730	701	385; 1016	0·1806
Hospital costs, total	134	105; 163	206	165; 247	<·0001	203	147; 260	295	248; 342	0·0002	260	106; 413	319	219; 422	0·7044
Inpatient	120	91; 148	189	148; 229	<·0001	178	121; 234	270	223; 316	0·0002	237	85; 388	295	194; 396	0·6889
Outpatient	14	12; 16	17	15; 19	0·1337	26	22; 30	26	23; 28	0·4927	23	14; 32	24	15; 34	0·8225
Ambulatory care cost	88	80; 96	-16	-26; -6	<·0001	26	16; 37	15	3; 28	<·0001	123	72; 173	87	54; 121	0·5125
Prescription drug cost	462	429; 494	16	-62; 94	<·0001	157	101; 212	60	-40; 160	0·0632	136	66; 206	240	-38; 518	0·1192
Sick leave benefits	38	21; 55	42	25; 59	0·5805	43	23; 62	59	38; 80	0·0902	-6	-63; 51	54	17; 90	0·7701
*Changes in continuous variables are presented as means absolute change from pre-index year in cost Euro (EUR) and 95% CI; P-values are between group comparison of AIT vs. controls; Only selected years are presented: Year 3 = expected end of treatment; Year 5 = duration of long-term RCTs investigating disease-modification, Year 9 = last year of observation; AIT: allergen immunotherapy; CI: confidence interval; RCT: randomised controlled trial															

Table S19 Change from pre-index year in comorbidities[§] for main cohort in year 3, 5 and 9

Year 3							
	N	%	N	%	OR	95% CI	p-value
Comorbidities#	AIT N=32112		Control N=32112		AIT vs. Control		
Upper respiratory tract infection (J00 – J39)	28611	89%	24098	75%	2.72	2.60;2.84	<.0001
Asthma (J45 – J46)	11542	36%	10161	32%	1.21	1.17;1.25	<.0001
Eczema (L20 – L54)	7751	24%	7649	24%	1.02	0.98;1.06	0.3506
Bronchitis (J20 – J44)	5708	18%	6820	21%	0.80	0.77;0.83	<.0001
Conjunctivitis (H10)	6453	20%	4557	14%	1.52	1.46;1.59	<.0001
Headache (R51, G44)	2778	9%	3367	10%	0.81	0.77;0.85	<.0001
Chronic cough (R05)	1659	5%	1928	6%	0.85	0.80;0.91	<.0001
Otitis media (H65 – H67)	1468	5%	1762	5%	0.83	0.77;0.89	<.0001
Depression (F32 – F33)	2705	8%	3710	12%	0.70	0.67;0.74	<.0001
Migraine (G43)	1722	5%	2185	7%	0.78	0.73;0.83	<.0001
Year 5							
	N	%	N	%	OR	95% CI	p-value
Comorbidities#	AIT N=19783		Control N=19783		AIT vs. Control		
Upper respiratory tract infection (J00 – J39)	14959	76%	14302	72%	1.19	1.14;1.24	<.0001
Asthma (J45 – J46)	6595	33%	6186	31%	1.10	1.05;1.15	<.0001
Eczema (L20 – L54)	4335	22%	4548	23%	0.94	0.90;0.99	0.0106
Bronchitis (J20 – J44)	3307	17%	3959	20%	0.80	0.76;0.84	<.0001
Conjunctivitis (H10)	2878	15%	2543	13%	1.15	1.09;1.22	<.0001
Headache (R51, G44)	1593	8%	1971	10%	0.79	0.74;0.84	<.0001
Chronic cough (R05)	876	4%	1085	5%	0.80	0.73;0.88	<.0001
Otitis media (H65 – H67)	759	4%	857	4%	0.88	0.80;0.97	0.0137
Depression (F32 – F33)	1813	9%	2842	13%	0.70	0.66;0.75	<.0001
Migraine (G43)	1159	6%	1416	7%	0.81	0.75;0.88	<.0001
Year 9							
	N	%	N	%	OR	95% CI	p-value
Comorbidities#	AIT N=1846		Control N=1846		AIT vs. Control		
Upper respiratory tract infection (J00 – J39)	1284	70%	1270	69%	1.04	0.90;1.19	0.6431
Asthma (J45 – J46)	577	31%	558	30%	1.05	0.91;1.21	0.5209
Eczema (L20 – L54)	389	21%	400	22%	0.97	0.83;1.13	0.6881
Bronchitis (J20 – J44)	275	15%	343	19%	0.77	0.65;0.91	0.0031
Conjunctivitis (H10)	237	13%	216	12%	1.11	0.91;1.35	0.3157
Headache (R51, G44)	176	10%	185	10%	0.95	0.76;1.18	0.6576
Chronic cough (R05)	78	4%	99	5%	0.78	0.57;1.06	0.1232
Otitis media (H65 – H67)	50	3%	54	3%	0.92	0.63;1.37	0.7656
Depression (F32 – F33)	202	11%	270	15%	0.72	0.59;0.87	0.0009
Migraine (G43)	120	7%	128	7%	0.93	0.72;1.21	0.6454

§The ten most frequently reported comorbidities in the AIT group (with ICD-10 codes); # Categorical variables are presented as N (%) and changes as the within group odds ratio (95% CI) from pre-index year; P-values are between group comparison of AIT vs. controls; Only selected years are presented: Year 3 = expected end of treatment; Year 5 = duration of long-term RCTs investigating disease-modification, Year 9 = last year of observation. AIT: allergen immunotherapy; CI: confidence interval; OR: odds ratio; RCT: randomised controlled trial.

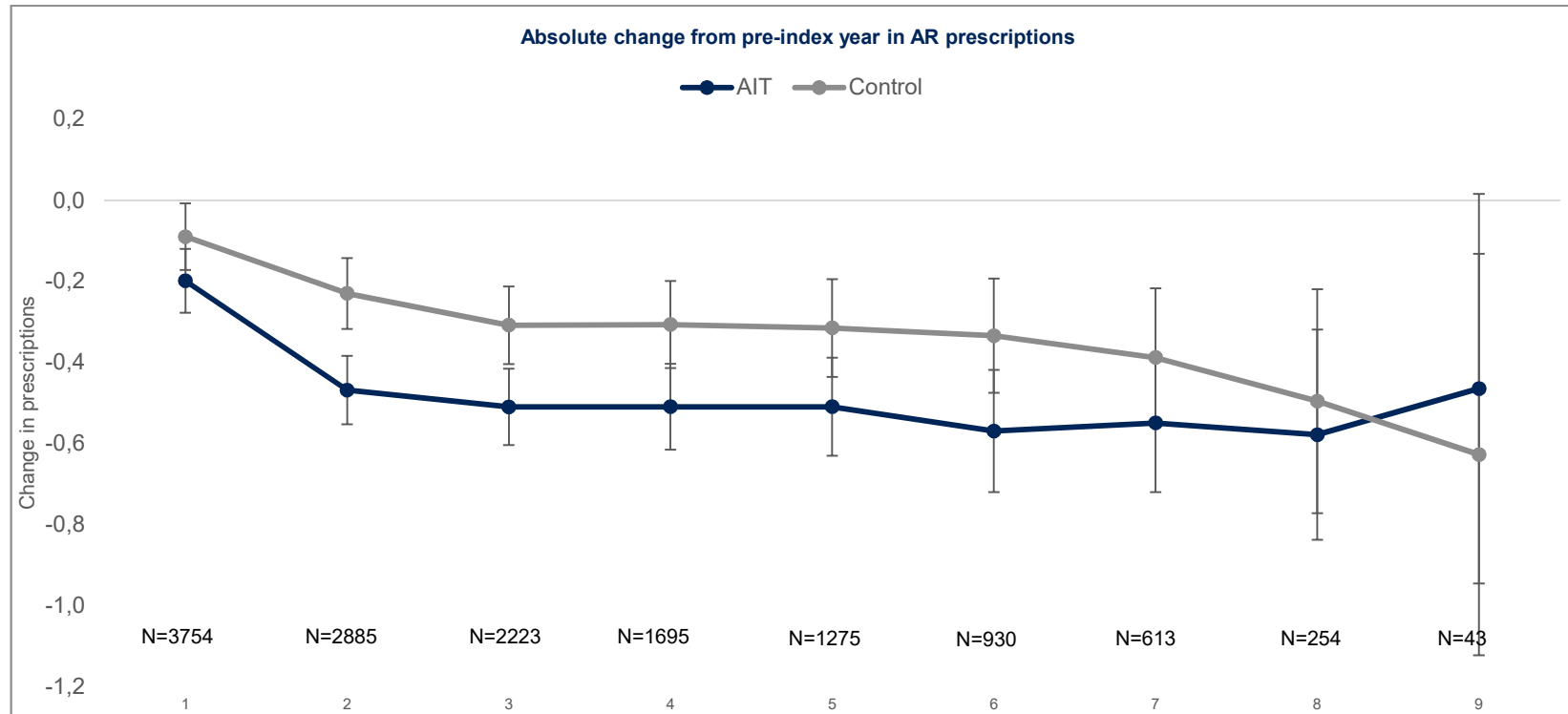
Table S20 Subgroup analyses: Change from pre-index year to year 3 in AR prescriptions

Year 3								
	Rx/ subject	SD	Change from pre- index	95% CI	Rx/ subject	SD	Change from pre-index	95% CI
Pre-existing asthma	AIT N=10370				Control N=10370			
AR Rx*	0.805	1.585	-0.587	-0.637;-0.538	0.861	1.839	-0.520	-0.576;-0.464
No asthma	AIT N=18788				Control N=18788			
AR Rx	0.482	1.126	-0.370	-0.396;-0.345	0.477	1.282	-0.300	0.328;-0.271
Adults	AIT N=21093				Control N=21093			
AR Rx*	0.483	1.165	-0.219	-0.242;-0.196	0.508	1.367	-0.187	-0.214;-0.160
Children	AIT N=7573				Control N=7573			
AR Rx*	0.831	1.536	-0.908	-0.968;-0.848	0.832	1.697	-0.811	-0.874;-0.747
Grass AIT	AIT N=7817				Control N=7817			
AR Rx*	0.597	1.3342	-0.513	-0.563;-0.465	0.654	1.649	-0.372	-0.427;-0.317
Tree AIT	AIT N=8426				Control N=8426			
AR Rx*	0.554	1.245	-0.358	-0.399;-0.316	0.541	1.401	-0.344	-0.391;-0.297
HDM AIT	AIT N=5224				Control N=5224			
AR Rx*	0.663	1.445	-0.527	-0.591;-0.464	0.698	1.614	-0.400	-0.468;-0.332
Other AIT	AIT N=7395				Control N=7395			
AR Rx*	0.634	1.377	-0.448	-0.499;-0.396	0.632	1.536	-0.358	-0.413;-0.303
Native allergens	AIT N=12216				Control N=12216			
AR Rx*	0.584	1.331	-0.454	-0.492;-0.416	0.610	1.559	-0.357	-0.399;-0.314
Allergoids	AIT N=19623				Control N=19623			
AR Rx*	0.624	1.352	-0.462	-0.493;-0.431	0.639	1.536	-0.392	-0.426;-0.359
SCIT	AIT N=25962				Control N=25962			
AR Rx*	0.599	1.326	-0.443	-0.469;-0.417	0.633	1.564	-0.388	-0.418;-0.358
SLIT drops	AIT N=3576				Control N=3576			
AR Rx*	0.672	1.416	-0.529	-0.608;-0.450	0.573	1.399	-0.359	-0.432;-0.285
SLIT tablets	AIT N=2223				Control N=2223			
AR Rx*	0.638	1.443	-0.510	-0.604;-0.416	0.646	1.460	-0.309	-0.404;-0.213
Persistent >2-year AIT	AIT N=9840				Control N=9840			
AR Rx*	0.658	1.358	-0.495	-0.540;-0.450	0.648	1.566	-0.361	-0.409;-0.314
Non-persistent <2-year AIT	AIT N=22272				Control N=22272			
AR Rx*	0.587	1.323	-0.442	-0.470;-0.414	0.620	1.534	-0.387	-0.419;-0.356
*continuous variables are reported as mean $\pm$ standard deviations (SD); prescriptions are reported as Rx/subject; children < 18 years of age, adults $\geq$ 18 years of age; HDM: house dust mite; persistent subjects: $\geq$ two index-AIT prescriptions in two consecutive follow-up years; non-persistent subjects < two index-AIT prescriptions in two consecutive follow-up years. AIT: allergen immunotherapy; AR: allergic rhinitis; CI: confidence interval; SLIT: sublingual immunotherapy; SCIT: subcutaneous immunotherapy.								

Table S21 Sensitivity analysis with different definition of asthma treatment steps

	Year 3 AIT N=10370 / Control N=10370			Year 5 AIT N=6545 / Control N=6545			Year 9 AIT N=571 / Control N=571			Time to any event		
	AIT vs. Control			AIT vs. Control			AIT vs. Control			HR	95% CI	Log-rank p-value
Asthma treatment step	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value			
≥1 step improvement	0.98	0.93;1.04	0.537	1.17	1.09;1.25	<.0001	1.21	0.96;1.52	0.1238	1.15	1.12;1.19	<.0001
≥1 step worsening	1.14	1.05;1.25	0.0017	1.01	0.91;1.12	0.9157	0.89	0.64;1.24	0.5568	1.06	1.03;1.10	0.0002
Improvement is at least one step reduction from pre-index year of at least one step. Worsening is at least one step increase. Treatment step 1: Asthma diagnosis in the absence of controller asthma medication; Treatment step 2: Monotherapy with either low dose ICS or LTRA; Treatment step 3: Dual therapy or therapy with medium-high ICS, LABA or methylxanthine; Treatment step 4: Triple therapy or therapy with anti-IgE or anti-IL-5. Only selected years are presented: Year 3 = expected end of treatment; Year 5 = duration of long-term RCTs investigating disease-modification, Year 9 = last year of observation. For time to first event analysis, the Kolmogorov-type supremum test was significant, therefore, no HR can be reported. Log-rank p-value are <.0001 for both ≥1 step improvement and ≥1 step worsening. AIT: allergen immunotherapy; ICS: inhaled corticosteroids; LTRA: leukotriene receptor antagonists; LABA: long-acting beta2-agonists; IL: interleukin; HR: hazard ratio; OR: odds ratio; RCT: randomised controlled trial; CI: confidence interval.												

Figure S13 Validation analysis; Change from pre-index year in AR prescriptions in SLIT-tablet subgroup



Change from pre-index year in AR prescriptions in the group of subjects receiving SLIT-tablets (blue) versus controls (grey). AIT: allergen immunotherapy; AR: allergic rhinitis.

Retrospective Database Study Protocol

Study Code	NI-X-04
Version	1.3
Date	16-JAN-2020

Impact of AIT on allergic rhinitis and asthma using real world evidence

Sponsor:	ALK ABELLO
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TABLE OF CONTENTS	PAGE
TITLE PAGE.....	1
TABLE OF CONTENTS	2
RESPONSIBLE PARTIES	6
PROTOCOL SYNOPSIS	7
AMENDMENT HISTORY	9
MILESTONES	10
1. BACKGROUND AND RATIONALE.....	11
1.1 Background	11
1.2 Rationale	13
2. OBJECTIVES	13
2.1 Primary Objective	13
2.2 Secondary Objectives.....	13
2.3 Exploratory Objectives	13
3. METHODOLOGY	14
3.1 General Aspects	14
3.1.1 Data Source(s).....	14
3.1.2 Approval and Data Protection.....	14
3.2 Study Design	15
3.3 Study Population	16
3.3.1 Identification and Study Period	16
3.3.2 Building of Main Study Population and Subcohorts - Identification of Patients	16
3.3.3 Inclusion and Exclusion Criteria.....	17
4. VARIABLES	19
4.1 Exposures	19
4.2 Definitions.....	19
4.2.1 Pre-existing asthma and new-onset of asthma	19
4.2.2 Treatment steps for asthma	19
4.2.3 Severe asthma exacerbation	20
4.2.4 Treatment duration.....	21
4.2.5 Co-administration and switch of AIT	22
4.2.6 Anaphylaxis related to AIT initiation	22

4.2.7	Respiratory tract infections	22
4.2.8	Costs.....	22
4.3	Outcomes	23
4.3.1	Baseline Characteristics	23
4.3.2	Variables Analyzed for Follow-up Period	24
4.3.2.1	AIT medication use	24
4.3.2.2	Primary Outcome	24
4.3.2.3	Secondary Outcomes	24
4.3.2.4	Exploratory Outcomes	25
4.3.3	Subgroups	26
5.	STATISTICAL ANALYSIS PLAN	28
5.1	Statistical Methods – General Aspects.....	28
5.2	Outcomes: Calculation of Epidemiological Measures of Interest	28
5.3	Matching	29
5.3.1	Building of Control Group.....	29
5.3.2	Matching Approach and Variables	29
5.3.3	Success of Matching	31
5.3.4	Locking of cohorts	31
5.4	Comparison of Results	31
5.4.1	Group Comparisons	31
5.4.2	Time to first and time to any analysis	32
5.5	Bias	33
5.5.1	Validation analysis	33
5.6	Sensitivity analyses	34
5.7	Limitations	34
5.8	Sample Size and Power Calculations.....	36
6.	STUDY CONDUCT AND REGULATORY DETAILS.....	37
6.1	Study Conduct.....	37
6.1.1	Study Flow Chart and Plan	37
6.1.2	Quality Control	37
6.2	Protection of Human Subjects.....	37
6.3	Collection and Reporting of Adverse Events/Adverse Drug Reactions	37
7.	ANNEXES	38
8.	LIST OF REFERENCES	41
9.	SIGNATURES.....	44

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AA	Allergic asthma
ADD	Attention deficit disorder
AE	Adverse event
AIT	Allergen immunotherapy
AR	Allergic rhinitis
ARIA	Allergic rhinitis and its impact on asthma
ATC	Anatomical therapeutic chemical (classification system)
BKK	Betriebskrankenkasse (company health insurance fund, Germany)
CCI	Charlson Comorbidity Index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DRG	Diagnosis-related groups
E	Event
EBM	Einheitlicher Bewertungsmaßstab (German system of medical remuneration for outpatient services)
FU	Follow up
FEV1	Forced expiratory volume in 1 second
GERD	Gastroesophageal reflux disease
GINA	Global Initiative for Asthma
GVP	Guideline on good pharmacovigilance practices
HRU	Healthcare resource utilization
ICD-10 (-GM)	International Statistical Classification of Diseases and Related Health Problems (revision 10) (- for Germany)
ICSR	Individual Case Safety Report
K-M	Kaplan-Meier
LOS	Length of stay
OPS	Operationen- und Prozedurenschlüssel (German procedure classification code)
PWP	The Prentice, Williams, and Peterson
PZN	Pharmazentralnummer (German drug identifier)

Abbreviation or special term	Explanation
R	Rate
SCIT	Subcutaneous immunotherapy
SD	Standard deviation
SHI	Social Health Insurance
SLIT	Sublingual immunotherapy

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PROTOCOL SYNOPSIS

Background/Rationale:

Allergic rhinitis (AR) is a symptomatic inflammatory condition of the nasal mucosa caused by allergen exposure. AR affects 23-30% of the European population and is associated with a major burden on public health, as AR can lead to limitations of quality of life and decreased productivity. AR and asthma frequently coexist, and may both be caused by allergen exposure. Allergen immunotherapy (AIT) is the only causal treatment option for AR and/or allergic asthma (AA). AIT can be administered as subcutaneous or sublingual immunotherapy (SCIT/SLIT), and SLIT is available as tablets or drops. The clinical benefits of AIT have been demonstrated in several randomized clinical trials, including phase 3 development programs. However, little is known regarding the use and effectiveness of AIT in real world clinical practice.

Objectives:

The aim of the present study is to assess the effectiveness and safety of AIT treatment on AR and asthma medication use, asthma disease (i.e. asthma prevention, asthma treatment steps and number of severe asthma exacerbations) and healthcare resource utilization (HRU) in AR patients, using real-world data from a large representative German health insurance database

Methods:

Study design: The present study is a retrospective database analysis.

Data Source(s): Information about AR patients and treatment in Germany will be obtained from the 'BKK German Sickness Fund Database' in Germany. Reimbursement data of the German statutory health system from 2007 until 2017 will be used.

Study Population: The study population consists of patients with a diagnosis of AR with or without asthma, treated with AIT (AIT treatment group), and a matched control cohort not treated with AIT (control group). The first AIT prescription is defined as the index event. Patients will be included in the analysis if they have a pre-index period of 12-months with no AIT prescriptions, and a post-index period, of at least 12-months. To evaluate the impact of AIT on asthma, two asthma subcohorts have been pre-specified based on the presence of asthma before, during or after AIT treatment.

- No asthma: No asthma before index period
- Pre-existing asthma: asthma before the index period

AIT will be identified by specific PZN and the AR diagnosis by the ICD-10-GM group J30. For dividing AR patients into the two asthma subcohorts, pre-existing asthma is defined as at

least one diagnosis from the ICD-10-GM groups J45 or J46 (excluding non-allergic asthma) or by at least two prescriptions of SABA and/or ICS within an index-year.

Outcome(s): All endpoints will be reported and compared for each AIT treatment group and matched control groups. Endpoints will be assessed for the pre-index year and each FU-year in the post-index period. The primary outcome is AR medication use. The secondary outcomes are asthma medication use and asthma disease (i.e. asthma prevention, asthma treatment steps and number of severe asthma exacerbations), and the explorative outcomes are HRU (ambulatory care visits, hospitalizations, comorbidities, surgical procedures, sick leaves) and costs.

Statistical Analysis: A 1:1 propensity score matching (PSM) will be applied. Changes over time and by cohorts will be assessed by intra- and inter-group comparison of the results. Selected tests (Fisher's exact for categorical variables and t-test for continuous variables) will be used to check for statistically significant differences. A Kaplan-Meier curve, Hazard Ratios (HR), Cox regression and a recurrent event analysis will be conducted to estimate the impact of AIT on worsening and improvement of asthma.

AMENDMENT HISTORY

Date	Section of study protocol	Amendment or update	Reason
24.09.2019	5.3.2 - Matching Approach and Variables	Additional variables for matching added	Comorbidities should be added as variable
12.12.2019		1. Removal of new-onset asthma subcohort 2. Remove AR severity grading as an outcome. 3. More details regarding propensity score methodology included	1. Cohort can not be build without conditioning on the future 2. Initial PSM results showed that more than half the patients had no AR prescriptions in the pre-index year (likely due to OTC use) so this could not be used to define AR disease severity 3. More details regarding the propensity score matching process included, e.g. use of callipers

MILESTONES

Milestone

Protocol (including statistical analysis plan) finalized

BKK study approval

Patient Identification, matching, baseline outcomes

Primary outcome

Secondary outcome

Exploratory outcome, subgroup and sensitivity analyses

1. BACKGROUND AND RATIONALE

1.1 Background

The global prevalence of allergic rhinitis (AR) has been estimated to be as high as 40%, with 23-30 % of the European population affected [1]. AR is a symptomatic disorder of the nasal mucosa, caused by allergen-specific IgE and eosinophilic inflammation, which leads to nasal congestion/obstruction, rhinorrhoea, itchy nose and/or eyes, and/or sneezing [1]. According to the allergic rhinitis and its impact on asthma (ARIA) guidelines [2] AR is classified based on duration and severity. Based on duration, AR is subdivided into "intermittent" or "persistent" disease, and based on severity, it is subdivided into "mild" or "moderate-severe" [2]. AR is classified as intermittent when symptoms are present for <4 days a week *or* for <4 consecutive weeks, and persistent AR is characterized by symptoms lasting >4 days a week *and* for >4 consecutive weeks [2]. In mild AR, symptoms are present but are not considered troublesome and none of the following items are encountered: sleep disturbance, impairment of daily activities, leisure and/or sport or impairment of school or work performance. In contrast, moderate-severe AR is defined by the presence of one or more of these items [2]. Thus, it is possible to have mild persistent or moderate-severe persistent AR, as well as mild intermittent or moderate-severe intermittent AR [2].

AR is associated with a major burden to patients, society, and public health [3-5]. The symptoms may reduce quality of life (QOL) and decrease productivity by affecting patient's sleep, as well as their ability to concentrate and work [3]. Two systematic reviews [4,5] regarding the effect of AR on QOL showed that AR patients had a significantly reduced general and disease-specific QOL, owing to impaired physical and mental health, and that AR treatment was associated with QOL improvement [3]. Several reasons may explain the magnitude of the AR burden, including the perceptions of patients and physicians about the severity of disease [1]. Patients' perceptions about their condition vary widely and are not in agreement with the objective severity and persistence of their disease, leading to under-diagnosis and under-treatment [1]. They often do not seek medical evaluation, use over-the-counter products, and out of those who have a prescription over 50% do not fulfil it [1]. Likewise, physicians may also underestimate the severity of AR: A prospective, cross-sectional, international survey investigating the burden of allergic rhinitis in Europe showed that overall, there was a poor correlation between patients and physicians in disease severity reporting, since patients rated their disease as more severe than physicians did [6]. Moreover, although evidence-based therapies exist, there are still unmet needs in terms of administering and evaluating existing and novel therapies [1, 8].

AR frequently coexists with asthma, as 10-40% of patients with AR have asthma [7]. Asthma is a heterogeneous disease affecting 1-18% of the population in different countries. Asthma is characterized by chronic airway inflammation that leads to expiratory airflow limitation and symptoms such as wheeze, shortness of breath, chest tightness and cough [7]. Asthma is usually associated with airway hyper-responsiveness to direct or indirect stimuli combined with chronic airway inflammation, which is typically diagnosed with spirometry before and

after the administration of a bronchodilator [7]. According to the Global Initiative for Asthma (GINA) guidelines [7], the severity of asthma is assessed retrospectively from the level of treatment needed to control symptoms and exacerbations [7], as follows:

- Mild asthma: well controlled with Step 1 or Step 2 treatment, i.e. with as-needed reliever medication alone, or with low-intensity controller treatment, such as low dose ICS, leukotriene receptor antagonists or chromones
- Moderate asthma: well controlled with Step 3 treatment, e.g. low dose ICS/LABA
- Severe asthma: requires Step 4 or 5 treatment, e.g. high-dose ICS/LABA to achieve control of symptoms, or it remains uncontrolled despite this treatment.

Allergen immunotherapy (AIT) is the only causal treatment option for AR and/or allergic asthma (AA) [8]. The mode of action targets immune tolerance induction, e.g. a change in the immune response to specific antigens, which leads to sustained long-lasting therapeutic benefits after therapy discontinuation [8]. During immune tolerance induction, desensitization of FcεRI-bearing mast cells and basophils occurs, and peripheral T-cell tolerance plays a major role [8]. AIT can be administered sublingually (SLIT) as drops or tablets or subcutaneously (SCIT) for a treatment period of at least 3 years [18]. SLIT tablets are taken daily, preferably starting 12 weeks prior to the start of the pollen season. All but the first dose can be taken at home [19], as serious adverse reactions to SLIT tablets are very rare (about 1.4 in 100,000 doses), and most commonly reported adverse events are local reactions [18]. In contrast to SLIT, SCIT treatment must be administered at a medical office. The treatment regimen for SCIT consists of a dose escalation phase with weekly injections, followed by a maintenance phase with monthly injections [20]. Several different approaches may be used during the escalation phase, i.e. a "cluster" approach with several doses in a single day, a "conventional" approach with dose increases over 15 weeks, and a "rush" approach with incremental doses every 15–60 minutes over 1–3 days [21]. The safety profile of SCIT is overall favourable and well-established, however, SCIT-induced systemic reactions ranging from mild symptoms to life-threatening anaphylaxis have been reported [8]. SLIT represent 80% or more of new AIT prescriptions in some parts of the world, mainly Europe [8], whereas SLIT tablet use in the United States is more limited [22].

Systematic reviews demonstrated that SCIT compared with placebo significantly decreases symptoms and medication use and improves the QOL in AR patients [16-17]. While there is little information on the comparative efficacy of SCIT and SLIT, SLIT has been shown to be safer and has the additional benefit of easy, at home administration [3]. The SLIT tablets have consistently demonstrated clinically relevant reductions in AR symptoms and medication use in phase 3a leading to regulatory approval by e.g. EMA and FDA. The clinical development programs have demonstrated both short-term and long-term efficacy for the management of allergic rhinitis [9-15] [3]. Moreover, Moeller et al [23] reported that AIT can reduce the development of asthma in children with seasonal rhino-conjunctivitis with 20 % [23]. Valovirta et al [24] also found that treatment with grass SLIT tablet reduced the risk of asthma symptoms and the use of asthma medication, and had a positive, long-term clinical effect on rhinoconjunctivitis symptoms in children with a clinically relevant history of grass pollen allergic rhinoconjunctivitis and no medical history or signs of asthma [23,24]. According to Virchow et al [25], in adults with house dust mite allergy-related asthma not well controlled

by inhaled corticosteroids, the addition of house dust mite SLIT tablet to maintenance medications reduced the risk of asthma exacerbations [25]. Importantly, the disease-modifying effect of AIT has been demonstrated, as the clinical efficacy was sustained several years after AIT cessation (5 years and 10 years) [26, 27]. In 2018, Wahn et al [28] showed that birch pollen AIT significantly reduced AR and asthma medication intake six years after medication cessation, and significantly decreased risk of new-onset asthma medication use in the real world [28]. However, the study was limited to birch allergy. Consequently, there is a need to more broadly evaluate the safety and effectiveness of AIT in the real world.

1.2 Rationale

The aim of the present study is to assess the effectiveness and safety of AIT treatment on AR and asthma medication use, asthma disease (i.e. asthma prevention, asthma treatment steps and number of severe asthma exacerbations) and healthcare resource utilization (HRU) in AR patients, using real-world data from a large representative German health insurance database.

2. OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the impact of AIT during and after treatment on AR medication use in patients with AR with and without asthma.

2.2 Secondary Objectives

The secondary objectives of this study are to assess the impact of AIT during and after treatment on:

- change in asthma medication use
- new onset of asthma (in AR patients without pre-existing asthma)
- change in asthma treatment steps (in AR patients with pre-existing asthma)
- severe asthma exacerbations (in AR patients with asthma)

2.3 Exploratory Objectives

The explorative objectives are to explore the impact of AIT on HRU and costs in real life and differences between AIT formulations and routes of administration.

3. METHODOLOGY

3.1 General Aspects

3.1.1 Data Source(s)

Reimbursement data of the German statutory health system from 2007 until 2017 will be used. This sample consists of up to 5.2 million persons insured by a sickness fund. A detailed list of available variables within the company health insurance funds (BKK) database is provided in Annex 1. Through an anonymized internal number of identification, all patients can be tracked across all areas of services, utilized health services in hospitals, the ambulatory sector, pharmaceuticals, and sickness leave over time from 2007 until 2017. Information on drug prescriptions, hospital visits, and sickness benefits are acquired on a daily basis. Diagnoses made by practitioners in the ambulatory care are available on a quarterly basis only. The classification of the certainty of diagnosis in ambulatory care is included in Annex 1. For the analyses, only diagnoses with a certainty status G (confirmed) or Z (asymptomatic condition after a diagnosis) will be considered as confirmed diagnoses. In hospital care, all documented diagnoses will be considered as confirmed.

Information on the representativeness of the BKK Database will be provided in the study report. The database will be compared to official numbers of the entire population of the German Social Health Insurance (SHI) with respect to age, gender, region and diagnoses in inpatient and outpatient care.

3.1.2 Approval and Data Protection

This study will comply with European and German data protection regulations. All patient-level data in the database are pseudoanonymized. No direct subject contact or primary collection of individual human subject data will occur. Study results will be in tabular form and in aggregate analyses that omit subject identification, therefore informed consent is not required. Any publications and reports will not include subject identifiers.

The BKK will be informed about the project and the required approvals will be requested. All patient-level data in the database are anonymized to comply with German data protection regulations. The use of the study database for health services research is therefore fully compliant with German federal law. Institutional Review Board/ethical approval is not needed.

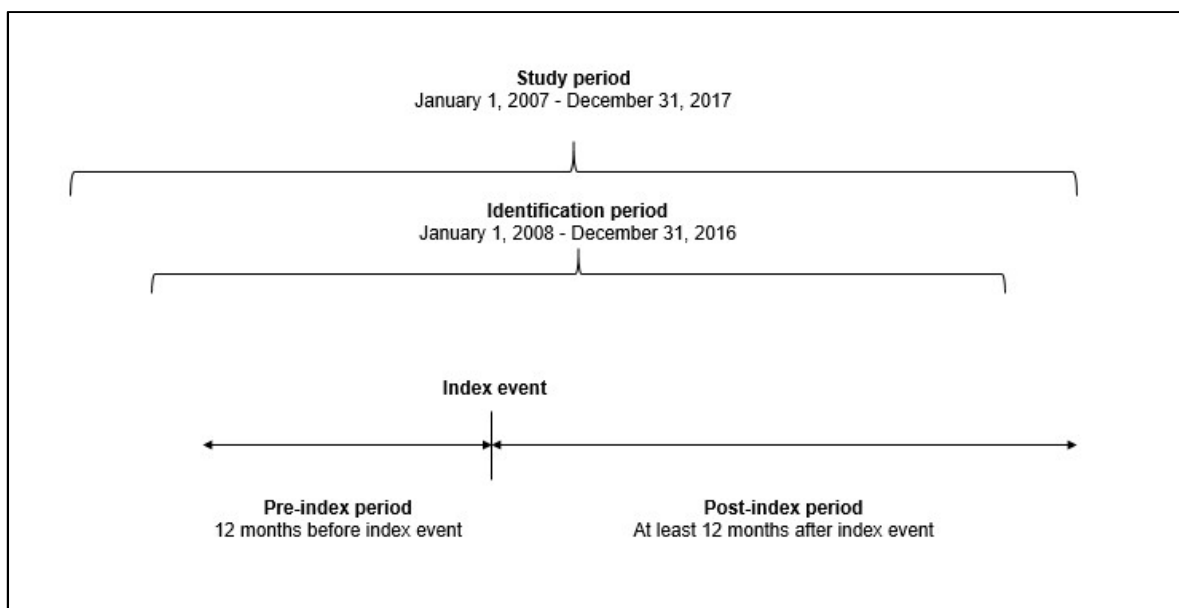
Due to a person-related pseudonym, it is possible to unambiguously identify persons in all data sets mentioned below. Thereby each insured person can be tracked cross-sectoral (cross-sectoral means they have the same pseudonym-ID in all areas (sectors) of services) and longitudinal through all areas of services refunded by statutory sickness funds. The privacy of these persons is protected at all times, as the information cannot be used to draw conclusions about any one person. It is also possible to examine the medical history of persons/patients over several quarters or years.

The database allows the analysis of patients (groups) with defined characteristics (e.g. existence of a specific disease, number and/or duration of hospitalizations, prescriptions of specific medications or any combination of these characteristics) at a specific date (index) and comparisons between patient and control groups with respect to their (group-) specific utilization of healthcare services.

3.2 Study Design

This is a retrospective cohort study of claims data. Data will be extracted between January 1, 2007, and December 31, 2017 (study period). Patients receiving venom AIT prescriptions will be excluded as these patients do not necessarily suffer from AR or asthma and are therefore not the target population for the current study. Patients will be included in the analysis if they have a pre-index period of 12-months with no AIT prescriptions, and a post-index period, of at least 12-months (see Figure 1):

Figure 1: Study design



- Identification period: January 1, 2008 - December 31, 2016
- Index event: First AIT prescription (excluding venom)
- Study period: January 1, 2007 - December 31, 2017
- Pre-index period: 12 months before index event
- Post-index period: At least 12 months after index event

3.3 Study Population

3.3.1 Identification and Study Period

The identification period for patients will be January 1, 2008, to December 31, 2016 (see Figure 1). In this period, the first AIT prescription (excluding venom AIT) will define the index event. The study period will run from January 1, 2007, to December 31, 2017. This allows the retrospective tracking for at least 12 months (pre-index period) before and the follow-up tracking for at least 12 months after the individual index event of the identified patients.

3.3.2 Building of Main Study Population and Subcohorts - Identification of Patients

The main study population (AIT treatment group) consists of AR patients with and without asthma, who has received AIT treatment in the identification period and with no AIT treatment in the pre-index period. The relevant PZN codes for the identification of AIT are shown in Annex 3. A confirmed diagnosis of AR must be recorded in the study period at any time, and pre-existing asthma will be defined based on either an asthma diagnosis and/or SABA/ICS prescriptions (see section 4.2). The relevant ICD-10-GM codes for the identification of AR and pre-existing asthma respectively, are shown in Table 1.

Table 1: Characteristics for the identification of patients with AR and pre-existing asthma

Disease	ICD-10-GM / PZN	Label
AR	J30	Vasomotor and allergic rhinitis
	J30.0	Vasomotor rhinitis
	J30.1	Allergic rhinitis due to pollen
	J30.2	Other seasonal allergic rhinitis
	J30.3	Other allergic rhinitis
	J30.4	Allergic rhinitis, unspecified
Asthma	J45	Asthma
	J45.0	Predominantly allergic asthma
	J45.8	Mixed asthma
	J45.9	Asthma, unspecified
	J46	Status asthmaticus
	PZN see Annex 2	SABA
	PZN see Annex 2	ICS

To evaluate the impact of AIT on asthma, two asthma subcohorts (see Table 2) will be specified from the main study population (AIT treatment group) based on the presence of pre-existing asthma, i.e. before the index event.

A matched main control cohort (control group), as well as matched asthma control subcohorts not treated with AIT before baseline and with at least one confirmed AR diagnosis at any time in the study period will be built. Since the AIT treatment group has an index event and the control groups do not, after matching, the controls will get the same index date as the AIT treatment patients they got matched to (for details please see section 4.3.3). Since a control could receive AIT at a later timepoint, the matched controls will be censored when they are prescribed AIT.

Table 2 shows the characteristics of AR and asthma

Table 2: Treatment and control groups

	Treatment groups	Characteristic(s)
	AIT treatment group	AR
1	No asthma	AR + no asthma
2	Pre-existing asthma	AR + pre-existing asthma
	Control groups	Characteristic(s)
	Control group	AR
1	Control - No asthma	AR + no asthma
2	Control - Pre-existing asthma	AR + pre-existing asthma

* AR diagnosis can occur either in pre- and/or post-index. For the identification at least one diagnosis at any time during the study period is sufficient.

3.3.3 Inclusion and Exclusion Criteria

The inclusion criteria for the AIT treatment group are as follows:

1. At least two index-AIT prescriptions during the first FU-year
2. At least one confirmed AR diagnosis during the study period
3. Continuous enrollment (no gaps in insurance time-defined by days) for 12 months before the index event (in the pre-index period)
4. Continuous enrollment (no gaps in insurance time-defined by days) for at least 12 months after the index event (in the post-index period)

For the control groups, the same inclusion criteria will apply, with the exception of inclusion criterion 1, i.e. controls have not received AIT before baseline.

The exclusion criterion for the AIT treatment group is as follows:

1. AIT prescription 12 months before the index event (in the pre-index period) for the AIT treatment group.

In total, the dataset consists of three AIT treatment cohorts (a main cohort and two asthma subcohorts) and three matched control cohorts (a main cohort and two asthma subcohorts):

1. The main cohorts are:
 - a. AIT treatment group
 - b. Control group
2. The two asthma subcohorts are:
 - a. No asthma
 - i. AIT treatment
 - ii. Control
 - b. Pre-existing asthma
 - i. AIT treatment
 - ii. Control

4. VARIABLES

4.1 Exposures

Not applicable.

4.2 Definitions

4.2.1 Pre-existing asthma and new-onset of asthma

Asthma is defined based on asthma diagnoses (Table 1) and/or two at least two prescriptions of SABA/ICS within an index-year. The relevant ATC codes are shown in Annex 2.

To mitigate the risk of detection bias for new-onset of asthma (see section 5.5), the definition used to form the pre-existing asthma subcohort prior to AIT initiation (pre-index period), is defined as either at least one asthma diagnosis or two prescriptions of SABA/ICS within the pre-index year, thus allowing 'borderline asthma patients' to be characterised as pre-existing asthma patients.

To further mitigate the risk of detection bias for new-onset of asthma, confirmation of new-onset of asthma (post-index period) is defined at least one asthma diagnosis and two prescriptions of SABA/ICS within a post-index follow-up year, thus requiring both an asthma diagnosis and two confirmatory prescriptions with SABA/ICS for an event of new-onset of asthma to be recorded.

4.2.2 Treatment steps for asthma

For patients who meet the criteria for pre-existing asthma (as defined in section 4.2.1.), asthma treatment steps based on medication use are used as a proxy for asthma disease severity in accordance with the (GINA) guidelines. All relevant ATC and PZN codes are shown in Annex 2. As AIT is recommended at both GINA level 3 and 4 and due to overlaps of the medium and high dose of inhaled corticosteroid dosages (ICS) in the data, the GINA level 3 and 4 will be merged into 'Asthma treatment step 3' in the analysis. In summary, four distinct treatment steps based on controller medication are defined and will be used in the analyses. Low vs. medium-high doses of ICS are shown in Annex 2 including dose adjustment for children vs. adults according to the GINA-guidelines [7]. Any ICS dose above the threshold for low dose is considered as medium or high dose. Use of reliever medication SABA, will be reported separately.

1. Asthma treatment step 1: No asthma controller medication

- asthma diagnosis in the absence of criteria for treatment step 2-4

2. Asthma treatment step 2: Monotherapy

- Monotherapy:
 - Low dose ICS or
 - LTRA

3. Asthma treatment step 3: Dual therapy and specific monotherapy

- Monotherapy:
 - Medium or high dose ICS or
 - LABA or
 - Methylxanthine
- Dual therapy – combination of:
 - Medium or high dose ICS
 - LTRA
 - LABA
 - Methylxanthine

4. Asthma treatment step 4: Triple therapy or specific monotherapy

- Monotherapy
 - anti-IgE or
 - anti-IL-5
- Triple therapy – combination of:
 - Low, medium or high dose ICS
 - LTRA
 - LABA
 - Methylxanthine
 - LAMA

For pre-existing asthma patients, the treatment steps will be determined for each patient per 12 months follow-up (follow up-year = FU-year) as the highest treatment step within a 12 month follow up period. Each FU-year is defined as 12 months from the index event or end of last FU-year. One prescription is sufficient to determine the treatment step. The comparison of the treatment step, i.e. possible changes in steps, is carried out based on the treatment step determined at baseline. I.e. the treatment step in the pre-index year will be compared with every FU-year. As medication use may fluctuate over the course of a year, treatment steps based on medication use collected from a full year, may lead to an overestimation of the asthma treatment step. Therefore, sensitivity analyses are included in the statistical analyses plan (see section 5.6), requiring an additional, confirmatory prescription for the asthma treatment steps.

4.2.3 Severe asthma exacerbation

Severe asthma exacerbations will be defined by any of the following:

- Ambulatory care: ICD-10-GM code J46 Status asthmaticus

- Hospitalization with ICD-10-GM asthma code (see Table 1) as the main diagnosis
- New prescription of oral, intravenous or subcutaneous corticosteroid with any ICD-10-GM asthma code. A prescription is defined as “new” when more than 7 days have passed since the last prescription.

The timeframe for one exacerbation (=event) is 7 days. Having at least one criterion of the above will count as one exacerbation. If more than one criterion or multiple events (e.g. hospitalizations) appears within 7 days, they will be reported as part of the same exacerbation. A new exacerbation is defined when one of the above criteria appear at least 7 days apart from the last exacerbation criterion being met.

In the hospital, the exact date of diagnosis is not documented. Therefore, the date of admission is decisive. In the outpatient (non-hospital) sector diagnoses are captured quarterly (for the same case at the same practitioner). Therefore, the first date of the relevant diagnosis/treatment will be taken into account.

The relevant ATC and PZN codes for oral, intravenous or subcutaneous corticosteroids are shown in Annex 2.

4.2.4 Treatment duration

Treatment duration of AIT will be assessed by number of days. Treatment duration will be assessed as number of days on treatment until first discontinuation of the index-AIT as well as the total sum of days on AIT treatment for each FU-index year and for the entire follow-up period. The treatment duration will be assessed separately for the index-AIT (based on allergen) and any AIT.

The date of discontinuation is the first day of the permissible gap, if the permissible gap has been exceeded. All medications will be considered to have been discontinued if gap in prescriptions > 90 days (i.e. 90 days permissible gap) with the exception of systemic corticosteroid (oral, intravenous, subcutaneous) where the permissible gap is only 7 days in accordance with the asthma exacerbation definition.

For SCIT, evaluating discontinuation using prescriptions only may be insufficient, as the SCIT treatment is administered at a medical office. Consequently, discontinuation of SCIT will require that both a gap in prescriptions and procedure codes for AIT injections (see Annex 2) exceed the 90 days permissible gap.

If a medication is re-started after being discontinued, it will be considered as a new prescription.

4.2.5 Co-administration and switch of AIT

Most patients are expected to receive AIT treatment as monotherapy. However, in polysensitized patients the index-AIT may be co-administrated or switched to a non-index AIT treatment.

Monotherapy is defined as index-AIT prescriptions for one allergen only.

Co-administration is defined as at least one prescription for a non-index AIT (based on allergen), in patients who have not discontinued the index-AIT. Any overlap between a new, non-index AIT and the index-AIT must last beyond 90 days (or until the end of follow-up if remaining follow-up time is <90 days), before it is recorded as a co-administration. For the analysis of co-administration of AIT, only pre-specified combinations factoring in the route of administrations (see section 4.3.2.1.1) will be reported.

In addition to the above, co-administration for SCIT is also captured, when as at least one prescription for a non-index-AIT prescription (without time requirements) and a least one procedure code for two AIT injections given on the same day (Annex 3) is recorded >90 days after initiation of index-AIT. The time period of >90 days after initiation is needed to mitigate faster up-dosing regimen that may require more than one SCIT injections/day.

Switch from index-AIT to non-index AIT (based on allergen and route of administration) is defined as a non-index AIT treatment provided within 90 days after the index-AIT was prescribed the last time and if no overlap of >90 days is recorded (co-administration).

4.2.6 Anaphylaxis related to AIT initiation

Anaphylaxis related to AIT initiation is defined as diagnosis code for anaphylactic shock (see Annex 2) ≤ 2 days of the first AIT prescription being filled (index date). Due to quarterly information on outpatient diagnosis an anaphylaxis will count when relevant diagnosis code for anaphylactic shock appears in index quarter.

4.2.7 Respiratory tract infections

Respiratory tract infections are defined as a diagnosis code for respiratory tract infection (see Annex 2). To evaluate the antibiotic use for respiratory tract infection, only antibiotic prescriptions filled ≤ 2 weeks of the respiratory tract diagnosis code is recorded. Due to quarterly information on outpatient diagnosis an antibiotic use for respiratory tract infection will count when antibiotic prescriptions and respiratory tract diagnosis code appear in same quarter. The relevant ATC codes are shown in Annex 2.

4.2.8 Costs

Costs will be based on the perspective of payers in the data source and will be shown as overall costs and by areas of services, which are inpatient and ambulatory care, ambulatory medication, and sick leaves.

Hospital inpatient costs are calculated by the DRG System, which includes summarized costs per hospitalization. Hospital outpatient costs are calculated per case and include all procedures, medication, and operations in total. In the ambulatory sector, each procedure and operation are billed by fee schedule items according to EBM usually on a daily basis (except laboratory results for example). Sickness benefit paid by sickness fund after 43 days of being sick. Medication costs are available as gross prices per prescription on a daily basis.

Costs will be in Euro. Due to individual FU-time all costs will be assessed per person and per FU-year. If the last FU-year is less than 365 days (366 for leap years) then the costs will be extrapolated (by assessing costs per day and multiply with number of total days of respective year).

4.3 Outcomes

4.3.1 Baseline Characteristics

- Age (in years)
- Gender (male/female)
- Geographical location (East, West, North, South)
- Time insured (from the index event to last day of insurance, in years)
- Number of prescribed AR products
 - Total
 - By class
- Number of prescribed asthma products
 - Total
 - By class
- Pre-existing asthma (y/n ; see section 4.2.1)
- Asthma treatment step for patients with pre-existing asthma (see section 4.2.2)
- Number of hospital visits
- Number of ambulatory care visits
- Number of sick leaves
- Charlson Comorbidity Index (CCI score)
- Comorbidities (see Annex 2)

4.3.2 Variables Analyzed for Follow-up Period

4.3.2.1 AIT medication use

- Number of AIT prescriptions and number of disjunct patients: A prescription will be defined as one unit/package of a product (identified by PZN). If a patient gets two units of one PZN it will be counted as two prescriptions. Information about all PZN, PZN by therapy and application form are given in Annex 3
- Duration of index-AIT treatment from index-date to end of follow-up (see section 4.2.4):
 - Number of days until first discontinuation of index-AIT
 - Total number of days on index-AIT (based on allergen) by:
 - Each follow-up year
 - Total follow-up period
- Any AIT treatment from index-date to end of follow-up (see section 4.2.4):
 - Number of different AIT treatments
 - Total number of days on any AIT treatment by:
 - Each follow-up year
 - Total follow-up period
- Number of patients with AIT prescription as:
 - Monotherapy
 - Co-administration of non-index AIT (based on allergen) and by
 - SLIT-tablets + SLIT-tablets
 - SLIT-tablets + SCIT
 - SLIT-tablets + SLIT-drops
 - SLIT-drops + SCIT
 - Switch from index-AIT to non-index AIT (based on allergen)
 - Switch from index-AIT to non-index AIT (based on route of administration)

4.3.2.2 Primary Outcome

4.3.2.2.1 AR Medication

- Number of patients with AR prescriptions by each follow-up year:
 - All AR products
 - By AR drug class (see Annex 2, 3)
- Number of prescriptions by AR drug class

4.3.2.3 Secondary Outcomes

4.3.2.3.1 Asthma Medication

- Number of patients with asthma prescriptions:

- All asthma products
 - By asthma drug class (see Annex 2, 3)
- Number of prescriptions by asthma drug class

4.3.2.3.2 Asthma disease Severity

- Number of pre-existing asthma patients:
 - By asthma treatment step (see section 4.2.2)
 - With a change in asthma treatment step from pre-index to FU-year:
 - ≥ 1 step improvement
 - ≥ 1 step worsening
 - No change in asthma treatment step
- Number of patients:
 - With a severe asthma exacerbation (see section 4.2.3)
 - By each variable of the composite for severe asthma exacerbation
- Number of events (E) and rate (R) per year of
 - Severe asthma exacerbation (see section 4.2.3)
 - By each variable of the composite for severe asthma exacerbation
- 'Time to first' and 'Time to any' worsening of asthma (days), defined as a 3-point composite:
 - No asthma subcohort: New onset of asthma (see section 4.2.1) or
 - Pre-existing asthma subcohort: Increased asthma treatment step (see section 4.2.2) or
 - Severe asthma exacerbations (see section 4.2.3)
- 'Time to first' and 'Time to any' improvement of asthma (days)
 - Pre-existing asthma subcohort: Decreased asthma treatment step (see section 4.2.2)

4.3.2.4 Exploratory Outcomes

Healthcare resource utilization (HRU):

- Ambulatory care visits:
 - Number of patients with ambulatory care visit and number of ambulatory care visits
 - Total

- By specialist¹ (otolaryngology, pulmonology, general practitioners, internal medicine) vs. non-specialist (others)
- Hospital visits:
 - Number of patients with a hospital visit and number of hospital visits
 - Inpatient
 - Outpatient
 - Number of patients with hospital inpatient stay and length of stay
- Number of patients with biologics prescription (see Annex 2)
- Number of patients with surgical procedures (see Annex 2)
 - All procedures
 - By type of procedure
- Anaphylaxis related to AIT initiation
 - Number of patients with anaphylaxis (see Annex 2 and 4.2.6)
 - Number of events of anaphylaxis
- Number of days on sick leave
- Number of patients with co-morbidities (see Annex 2)
- Number of patients with respiratory tract infections (see Annex 2 and section 4.2.7)
 - Number of antibiotic prescriptions for respiratory tract infections

Costs:

- Cost estimation
 - Total costs (all areas of service)
 - Costs by area of service:
 - Costs for treatment in the hospital (inpatient and outpatient)
 - Costs for treatment in ambulatory care
 - Costs for drug prescriptions
 - Costs for sick benefits

4.3.3 Subgroups

- Age at start of AIT:
 - Children <18 years

¹ NOTE: In Germany most of the GPs are specialized in allergic diseases. Therefore, the database does not include a dedicated group for allergy & immunology

- Adults ≥ 18 years
- AIT treatment duration:
 - Persistent patients, defined as at least two index-AIT prescriptions in two consecutive FU-years
 - Non-persistent patients, defined as less than two index-AIT prescriptions in two consecutive FU-years
- AIT route of administration (see Annex 3):
 - SCIT
 - SLIT-drops
 - SLIT-tablets
- AIT allergens (see Annex 3):
 - Tree pollen
 - Dust mite
 - Grass
 - Others
- AIT formulations (see Annex 3):
 - Native allergens
 - Allergoids
- AIT SLIT-tablets by brand (see Annex 3):
 - GRAZAX® (grass SQ SLIT tablet)
 - ACARIZAX® (HDM SQ SLIT tablet)

5. STATISTICAL ANALYSIS PLAN

5.1 Statistical Methods – General Aspects

All relevant analyses will be carried out using SAS 9.4.

To achieve the objectives of the study (see section 2) three matched AIT treatment cohorts and three matched control cohorts will be built, i.e. one main cohort and two asthma subcohorts (see section 3.3.1). The controls will be matched by propensity score-based matching (see section 5.3).

For categorical variables, distributions will be described in terms of the number of observations and proportions at the level of the variable (frequencies, percentages). Continuous variables will be summarized in terms of number of observations, mean, standard deviation (SD), median and range of values. The 25th and 75th percentiles will also be reported.

Time to event endpoints (see section 4.3.2.3.2) will be summarized using the Kaplan-Meier method, Cox regression, HR and recurrent event analysis (see section 5.4.2).

5.2 Outcomes: Calculation of Epidemiological Measures of Interest

Baseline characteristics (see section 4.3.1) will be reported for the AIT treatment group and control group, as well as for the two asthma subcohorts before matching. Data will be collected in the pre-index period. For variables that may change during the pre-index period, for example age and geographical location, the value closest to the index event will be used in the analyses.

To achieve the primary, secondary and exploratory objectives, the variables listed in the sections 4.3.2.2, 4.3.2.3 and 4.3.2.4 will be reported and compared for the AIT treatment group and matched control group, as well as the two asthma subcohorts. A pre-index vs FU-years comparison will be reported as well for all cohorts. Each 12 month follow up (follow-up = FU-year) is defined as 12 months from index event or end of last FU-year. The primary, secondary and exploratory outcomes will be assessed for each FU-year in the post-index period. AIT medication use will not be assessed for the main control group and the control subcohorts, as they have not received any AIT treatment.

In addition, six subgroups, i.e. age, treatment duration, route of administration, allergens, brand and formulation, including categories/variables of interest will be built for the main cohort (see section 4.3.3). Subgroups will be all attributed to the index AIT. The number of patients in each subgroup of each category/variable will be reported and all outcomes will be analysed for the subgroups. Results will be compared through time and by controls (see section 5.4.1). Due to data protection and privacy regulations, analysis can only be performed on subgroups with at least 6 patients. For subgroups ≤ 5 patients, only counts of patients per subgroup will be shown (no further analysis will be performed). If the matching approach will

be change (e.g. not 1:1 matching) and a subgroup of control group is not possible to define then a subgroup analysis for controls will not be part of the analysis.

The portion of patients which had more than one AIT prescription (based on route of administration or allergen) on index date, will be assigned to a new subgroup-mixed type and only counts of patients will be shown (no further analysis will be performed).

5.3 Matching

5.3.1 Building of Control Group

The AIT treatment group consists of patients with an AIT prescription and the control group consists of patients without AIT treatment before baseline. An index event (first AIT treatment) can only be observed in the AIT treatment group and not in the control group. In order to define the baseline characteristics for the matching (and afterwards to set same index date for controls), a start of the baseline has to be set. For this purpose, we match within years and set the start of the baseline on the same quarter for all treatment and control patients. The start of baseline will be defined, based on the yearly distribution of AIT index events. Baseline is observable in quarters, because outpatient diagnoses are available at quarterly basis.

After matching, the controls will get the same index date as the treatment patients they got matched to.

If a patient starts AIT before baseline, they will be a treatment case. In order to minimize the risk of confounding by indication and selection bias, the control group will consist of AR patients who have not received AIT before baseline and in the 12 month follow-up (post-index) period (see section 3.3), but who may initiate AIT at a later timepoint. If a control initiates AIT treatment after the 12 month follow-up (post-index) period, the control will be censored from the analyses from the date of AIT initiation.

5.3.2 Matching Approach and Variables

The matching between the AIT treated patients and the controls will be performed with a 1:1 propensity score matching (PSM) due to the large number of matching variables (listed below). Patients will be matched without replacement and the nearest neighbor approach will be applied. At the start the caliper value will be 0.01 and sensitivity analysis of other caliper values will be done if needed. In the following, the matching variables are listed. It is indicated whether the variable is categorical, continuous or dichotomous.

Variables for propensity score matching:

- Age (categorical)
 - <11 years

- 12-17 years
 - 18+ years
- Gender (dichotomous)
- Asthma treatment steps (categorical) (see section 4.2.2)
 - Asthma treatment step 1
 - Asthma treatment step 2
 - Asthma treatment step 3
 - Asthma treatment step 4
 - No Asthma
 - Only reliever medication
- Age (continuous)
- Geographical location (categorical)
 - East
 - West
 - South
 - North
- CCI (continuous)
- Number of prescribed AR products (continuous) (see Annex 2)
 - Total
 - By class
- Number of prescribed asthma products (continuous) (see Annex 2)
 - Total
 - By class
- Number of primary care visits (continuous)
- Number of hospitalizations (continuous)
- Number of sick leaves (continuous)
- Number of surgical procedures (continuous)
- Costs for primary care visits (continuous)
- Costs for hospitalizations (continuous)
- Costs for medication use (continuous)
- Sick leave benefits (continuous)
- Atopic dermatitis: L20 - L20.9 (dichotomous)
- Urticaria: L50 - L50.9 (dichotomous)
- Conjunctivitis: H10 – H10.9 (dichotomous)
- Acute allergic conjunctivitis: H10.1 (dichotomous)
- Entire group: J00 - J39.9 (dichotomous)
- Vasomotor rhinopathy: J.30 (dichotomous)
- Allergic rhinopathy by pollen: J30.1 (dichotomous)
- Other seasonal allergic rhinopathy: J30.2 (dichotomous)
- Other allergic rhinopathy: J30.3 (dichotomous)
- Allergic rhinopathy, unspecified: J30.4 (dichotomous)
- Predominantly allergic bronchial asthma: J45.0 (dichotomous)
- Non-allergic bronchial asthma: J45.1 (dichotomous)

- Mixed forms of bronchial asthma: J45.8 (dichotomous)
- Bronchial asthma, not specified: J45.9 (dichotomous)

If the end of the FU-time is not the same for a matched pair, then the shorter individual FU-time (in days) will be applied for both patients in the matched pair.

5.3.3 Success of Matching

The standardized differences show the differences in the characteristics of the treated patients and the controls. From an operational stand point, matching is considered as successful if the standardized differences are <10%. If not accomplished with the above approach, matching variables need to be modified (e.g. less categories, remove variables). Each modification will be documented. As soon as standardized differences are <10%, the complete documentation of the executed modification process will be finalized.

5.3.4 Locking of cohorts

The following must be documented and approved by the sponsor:

- 1) Operationally, the matching was successful, i.e. standardized differences are <10%
- 2) Clinical evaluation by the sponsor that the cohorts have been matched successfully

Only after sponsor approval of the above, will the cohorts be considered as final. The final cohorts will be locked, and the date of lock will be documented. If the matching is not successful, the matching will be optimized, and the steps repeated. Any needed updates and changes will be recorded and documented.

5.4 Comparison of Results

5.4.1 Group Comparisons

Changes from the pre-index year to the individual post-index years (FU-years) will be analyzed as:

- i. Inter-group comparison, i.e. change between:
 - a. AIT treatment group vs. main control group
 - b. No asthma (AIT) vs. No asthma (control)
 - c. Pre-existing asthma (AIT) vs. pre-existing asthma (control)
- ii. Intra-group comparison, i.e. change within each cohort:
 - a. AIT treatment group
 - i. No asthma
 - ii. Pre-existing asthma

- b. Control group
 - i. No asthma
 - ii. Pre-existing asthma

To check for statistically significant differences between the groups, the Fisher's Exact test will be used for categorical variables and the t-test will be used for continuous variables.

Changes in AIT medication through time will not be compared with controls, as AIT does not exist in the pre-index period and in the control cohorts.

5.4.2 Time to first and time to any analysis

Kaplan-Meier (K-M) plots will be used to illustrate the rate of "time to first" worsening or improvement in asthma (see section 4.3.2.3.2). The K-M analysis is a method for estimating the proportion of individuals remaining in the sample at a particular time from an initiation point. This method takes into account patients lost/censoring before the study endpoint, in this case, those who ended the insurance or have reached end of the study period. The K-M analysis will be used to estimate the proportion of patients in the sample without evidence of the event at a particular time after first AIT prescription. The probability of "time to first" worsening or improvement in asthma will be calculated based on the number of patients still being followed through study period. Patients will be dropped from the risk set at the point they meet the event or censored (earliest of end of the insurance or end of the study period). Controls who subsequently initiate AIT will be also be censored (see Section 5.3.1)

Worsening or improvement in asthma will be defined as an event (see section 4.3.2.3.2) within the follow up period. Patients lost to follow-up will be censored (or dropped from the risk set) at the FU-year recorded as the end of the insurance. Patients will be followed until their condition gets worse or better, until they are censored, or until they reach the end of the variable follow-up period (up to eight years), whichever occurs first.

A K-M plot will be generated with a "time to first" curve for the 3-point composite and by each of three components which make up the composite for AIT treatment group vs. control group. The cumulative rate of "time to first" will appear in the K-M plot. The median time to event will be reported along with a 95% confidence interval (CI). By a cox proportional regression the estimated hazard ratio (HR) will be calculated.

A "time to any" analysis includes recurrent events of interest which repeated by a given individual. These events may all be of the same type, or different types. Due to a cox proportional regression, in particular the "The Prentice, Williams, and Peterson Total Time Model" (PWP total time model), the time to each event will be calculated as the time from start of treatment (index AIT) to each event separately. Similarly, to K-M, a plot will be generated as "time to any" curves for the 3-point composite and by each of three components which make up the composite (whichever occurs first) for AIT treatment group vs. control group.

5.5 Bias

The analyses will compare outcomes from the pre-index year vs. post-index FU-years and will compare outcomes between AIT treatment and control cohorts. Due to matching some treated patients will not have a suitable control and will be excluded. These excluded patients will be described or confronted with the included patients by means of descriptive statistics if appropriate. Despite the planned matching, there still is a high risk of confounding and bias occurring due to great heterogeneity. The most likely issues are highlighted below:

- **Confounding by indication:** AIT is often used in more severe AR patients. Consequently, these patients may require more AR and asthma medications and have a higher risk of new-onset of asthma compared to the control group, due to the severity of their allergy.
- **Misclassification:** The databases do not provide data on symptoms, and much of the symptomatic medication use for AR is OTC, i.e. without prescriptions. Consequently, only prescriptions are recorded and can be used as a proxy for asthma treatment steps and treatment effects which may lead to misclassification.
- **Detection bias:** Patients initiating AIT are more likely to be treated and followed by a specialist. Consequently, the AIT group may have a higher risk of getting diagnosed with new-onset of asthma and receive more prescriptions for AR and asthma due to optimized SoC.

Several steps have been taken to mitigate the high risk of bias and confounding in this study throughout the protocol. Using PSM, the AIT groups and controls should be successfully matched at the time of AIT initiation. However, additional adjustments and sensitivity analyses may be required post-hoc to further support the interpretation of the results, e.g. more visits to specialists in the AIT group could indicate differences in ‘access to care’ that could lead to detection bias.

5.5.1 Validation analysis

Due to the high risk of confounding and bias in this study (see section 5.5 and 5.7), a validation analysis has been pre-specified. This is based on previous publications, which have assessed how successful the trial design was in controlling for selection bias and confounding by comparing results from a database analysis with those seen in RCTs [29]. It has been established that SLIT-tablets reduce the use of AR medication in multiple large phase 3a RCTs [3, 9-15]. If a reduction in AR medication use is not seen in SLIT-tablet patients in the first follow-up year, it is likely that key confounders and biases have not been well controlled for. All results should be considered in this context, i.e. it is likely they are also biased and are not well controlled for confounders. Conversely, if a reduction in AR medication use is seen in SLIT-tablet patients, it provides support for the strength and validity of the matching process and the robustness of all other results.

If it is concluded that the analysis has not well controlled for bias and confounding, as seen by a lack of reduction in AR medication use in SLIT-tablet patients, the external experts and sponsor will assess if there is alternative methodology or sensitivity analyses which could better control for bias. Any additional analyses would be post-hoc and documented prior to the analysis being conducted, and would be supplemental to the pre-specified analysis.

5.6 Sensitivity analyses

Medication use will be used to assess the asthma treatment steps (see section 4.2.1 and 4.2.2). For the main analyses at least one prescription within a FU-year is sufficient to determine the treatment step. As asthma treatment may fluctuate over a full year, this approach may lead to an overestimation of treatment steps, and therefore, the asthma treatment steps will be evaluated in a sensitivity analysis that only includes medications with a confirmatory prescription (within the same drug class) in the same year, i.e. at least two prescriptions in the pre-index year and at least two prescriptions in each of the post-index FU- years.

5.7 Limitations

The study has a very large patient database with extensive hospital and prescription data that is available for evaluation. The generalisability will be comparably high, as the BKK patient pool is proved to be a good representation of the German population.

The results are unlikely to be biased by side effects, due to the large number of patients and physicians/hospitals that are included in the BKK database.

However, the general limitations of this study are:

- This study will be limited to only those individuals with statutory health insurance. Consequently, results of this analysis may not be generalizable to patients with private health insurance. However, since about 90% of the German population is covered by statutory health insurance, this is considered to be as a minor problem.
- Due to small samples of patients within (sub-) cohorts, interpretations should be done very carefully.
- As with any claims databases, the BKK Database relies on administrative claims data for clinical detail. These data are subject to data coding limitations and data entry error.
- Inpatient treatment consists of ambulatory and inpatient care. Ambulatory care is defined by an inpatient treatment without an overnight stay. Till 2011 number of hospitalizations in ambulatory care is underestimated. Medication for inpatient care is not available, unless an OPS is available. Therefore, a full analysis with respect to medications is possible only for those induced by practitioners in outpatient care.
- Doctor visits in outpatient care are underestimated in case of quarterly fixed rate. For example, a patient has a common cold, visits a doctor and blood sampling is

performed. Subsequently, the patient visits again the doctor to discuss the results. The second visit is not visible in the data since a fixed rate has been coded.

- Outpatient diagnoses are coded quarterly. It is not possible to link prescriptions from practitioners, costs or dates to the diagnosis one by one.
- Furthermore, limitations with regards to specific medical outcomes, laboratory test results and specific patient demographics or characteristics are not visible, because the following information is not captured in German sickness funds claims data: tobacco use, laboratory and diagnostic test results, race, BMI, emergency room, birth control methods, pregnancy and breast feeding, diet and exercise regimen, pre-menopausal women, male or female of no reproductive potential. Limitations lead to underestimation or overestimation depending on the criterion, respectively on the limitation.
- The data only include procedures and treatments that are reimbursed according to the German law.
- Diagnoses in outpatient care are less reliably and validly documented in German claims data than inpatient diagnoses, mainly because no coding guidelines exist. To take this bias into account only diagnoses with the supplement “gesichert” (confirmed/assured) were analyzed.

The study design limitations are:

- In inpatient care all diagnostic codes – main diagnoses, discharge diagnoses and concomitant diagnoses – are included in the analysis. Concomitant diagnoses may include suspected diagnoses, which may lead to overestimation of patient numbers.
- For the definition of exacerbations an exact date is needed. For diagnosis, a date will be approximated in outpatient care as the first visible day in quarter and in hospital care as the day of admission.
- Treatment duration will be approximated as the days between the day of prescription of one preparation to the day of the last prescription.
- Severity of disease cannot be directly determined, only inferred using proxy indicators.
- The AIT group may have a higher risk of getting diagnosed with new-onset of asthma and receive more prescriptions for AR and asthma due to being seen more often by specialist.
- Overall, a study design with an individual inclusion (between 2008 and 2016) and an individual pre-observation period (of 1 year to index quarter) and individual follow-up (at least 1 year) was chosen over fixed timelines. This study design allows a less strict inclusion criterion for the AIT cohort and the other subcohorts, where diagnosis and prescriptions can be coded anytime in the inclusion period, pre- and post-observation period. By that a larger number of patients will be included in the analysis.

5.8 Sample Size and Power Calculations

Not applicable.

6. STUDY CONDUCT AND REGULATORY DETAILS

6.1 Study Conduct

6.1.1 Study Flow Chart and Plan

As this is a retrospective database study, no study schedule/plan is foreseen. A summary of the study periods relevant for the analyses is presented in **Errore. L'origine riferimento non è stata trovata..**

6.1.2 Quality Control

All data that form the basis of this study are collected in a standard process including several checks for correctness and completeness done by several parties (the based sickness funds data pass through checks at Team Gesundheit, the health insurance companies, associations of statutory health insurance registered doctors, hospitals, offices responsible for settling claim, etc.). Since data management and data cleaning was conducted and checked, data coding and analysis can be done on a simplified, standardized and documented interface. Programming will be done by two researchers in parallel and independently, to improve accuracy. The present study does not require monitoring.

6.2 Protection of Human Subjects

Patient informed consent is not required, as this is a secondary database study. All data from the database are fully anonymized. The privacy of the persons is protected at all times, as the information cannot be used to draw conclusions about any one person.

6.3 Collection and Reporting of Adverse Events/Adverse Drug Reactions

For products with marketing authorizations in the EU/EEA, in line with regulation (e.g., GVP Module VI.C.1.2.1.2.), the reporting of adverse reactions as ICSRs is not required.

7. ANNEXES

Annex 1: List of Variables Available in the BKK Database²

Data of the insured persons:

- Anonymized health insurance identification number of the insurant
- Gender, Age (in years)
- Duration of insurance within the considered time frame
- Regional distribution (places of residence)
- Reason for end of enrollment

Outpatient/ambulatory treatment:

- Anonymized health insurance identification number of the insurant
- Diagnoses according to the International Statistical Classification of Diseases and Related Health Problems system (revision 10) (- for Germany) (ICD-10-GM) (quarterly)
- Status of certainty: confirmed (G), preliminary (V), excluded (A) and asymptomatic condition after a diagnosis (Z)
- Code identifying the group of the physician in charge
- Billed fee schedule items (*Gebührenordnungsnummern*) according to EBM (*Einheitlicher Bewertungsmaßstab*, German system of medical remuneration for outpatient services) and related costs
- Date of treatment

Inpatient treatment/Hospitalization:

- Anonymized health insurance identification number of the insurant
- Date of admission/discharge to/from hospital
- Type of treatment (ambulatory, stationary)
- Three main diagnoses (the first is the main diagnosis at discharge) (ICD-10-GM) and respective ten concomitant diagnoses for each main diagnosis
- Primary and secondary diagnoses from specialist departments (up to three departments depending on treatment)
- Billed diagnosis-related groups (DRGs) (German classification) and related costs
- Up to 30 OPS codes (Operations and Procedures Code, German classification for operations and procedures conducted in hospital) per case
- Date of treatment for OPS codes

Drug prescription data:

- Anonymized health insurance identification number of the insurant
- Anatomical therapeutic chemical (ATC) code of prescribed medications and related costs
- PZN (*Pharmazentralnummer*, German drug identifier) of prescribed medications
- Date of prescription (on a daily basis)

Sickness benefits:

- Anonymized health insurance identification number of the insurant
- First day of sick leave, last day of sick leave
- ICD-10-GM diagnoses
- Sickness benefit paid by sickness fund

² Note: Some variable-labels are better to understand in German-language terminology.

Annex 2: Identification Codes



Identification
Codes Annex 2_1501

Secondary Database Study Protocol
Study Code NI-X-04
Version 1.3
Date 16 JAN 2020

Annex 3: AIT List



AIT Lists of PZN and
more.xlsx

8. LIST OF REFERENCES

1. Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis. European Academy of Allergy and Clinical Immunology (EAACI), 2015. Available at: http://www.eaaci.org/globalatlas/ENT_Atlas_web.pdf. Accessed May 19, 2019.
2. Bousquet J, et al. Management of Allergic Rhinitis and its Impact on Asthma (ARIA) Pocket Guide. Available at: http://www.eaaci.org/attachments/768_Aria%20Pocket%20Guide.pdf. Accessed May 19, 2019.
3. Wise SK, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. International Forum of Allergy & Rhinology, Vol. 8, No. 2, February 2018.
4. Linneberg A, et al. Burden of allergic respiratory disease: a systematic review. Clin Mol Allergy 2016; 14:12.
5. Hahn-Pedersen J, et al. Systematic literature review assessing data on the burden of allergic rhinitis from a cost and quality of life perspective. Value Health. 2014;17:A602.
6. Canonica GW, et al. A survey of the burden of allergic rhinitis in Europe. Allergy 2007;62(S85):17-25.
7. Global Initiative for Asthma. Global Strategy for Asthma Management and prevention 2018 (www.ginasthma.org).
8. Burks AW, et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. J Allergy Clin Immunol 2013; 131(5): 1288–1296 e1283.
9. Radulovic S, et al. Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev 2010;(12):CD002893.
10. Di Bona D, et al. Efficacy of grass pollen allergen sublingual immunotherapy tablets for seasonal allergic rhinoconjunctivitis: a systematic review and metaanalysis. JAMA Intern Med 2015; 175:1301–1309.
11. Leatherman BD, et al. Dosing of sublingual immunotherapy for allergic rhinitis: evidence-based review with recommendations. Int Forum Allergy Rhinol 2015; 5:773–783.
12. Devillier P, et al. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. BMC Med 2014; 12:71.

13. Makatsori M, et al. Dropouts in sublingual allergen immunotherapy trials—a systematic review. *Allergy* 2014; 69:571–580.
14. Lin SY, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA* 2013; 309:1278–1288.
15. Di Bona D, et al. Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2010; 126:558–566.
16. Meadows A, et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. *Health Technol Assess* 2013;17:vi, xi-xiv, 1–322.
17. Lin SY, et al. Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review. *Comparative Effectiveness Reviews*, No. 111. Rockville, MD: Agency for Healthcare Research and Quality; 2013. <https://www.ncbi.nlm.nih.gov/books/NBK133239/>. Accessed December 19, 2017.
18. Canonica GW, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *The World Allergy Organization Journal* 2014;7(1):6.
19. Pepper, et al. Sublingual Immunotherapy for the Polyallergic Patient. *The Journal of Allergy and Clinical Immunology: In Practice* 2017;5(1):41–45.
20. van Cauwenberge P, et al. Consensus statement on the treatment of allergic rhinitis. *European Academy of Allergology and Clinical Immunology. Allergy* 2000;55(2):116–34.
21. Caminati M, et al. Incidence and risk factors for subcutaneous immunotherapy anaphylaxis: the optimization of safety. *Expert Review of Clinical Immunology* 2015;11(2):233–45.
22. Elenburg S and Blaiss MS. Current status of sublingual immunotherapy in the United States. *World Allergy Organ J* 2014;7(1):24.
23. Moeller C, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-Study). *J Allergy Clin Immunol* 2002;109:251–6.
24. Valovirta E, et al. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. *Allergy Clin Immunol* 2018; 141:529–38.

25. Virchow JC, et al. Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma. . JAMA. 2016;315(16):1715-1725.
26. Valovirta E, et al. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. Allergy 2018; 62: 529-538.
27. Jacobsen L, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy 2007; 62: 943–948
28. Wahn U, et al. Real-world benefits of allergen immunotherapy for birch pollen-associated allergic rhinitis and asthma. Allergy. 2018;1–11.
29. Smeeth et al: Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials, 2008.

9. SIGNATURES

ALK ABELLO SIGNATURE(S)

Impact of AIT on allergic rhinitis and asthma using real world evidence

This Non-Interventional, Database Study Protocol has been subjected to an internal ALK Abello review

I agree to the terms of this Study protocol.

ALK Abello representative

16 Jan 2020



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This document contains confidential information, which should not be copied, referred to, released or published without written approval from ALK Abello. Investigators are cautioned that the information in this protocol may be subject to change and revision.

This translation in German was submitted by the authors and we reproduce it as supplied. It has not been peer reviewed. Our editorial processes have only been applied to the original abstract in English, which should serve as reference for this manuscript.

Langfristige Wirksamkeit der Allergie-Immuntherapie in der klinischen Praxis bei Patienten mit allergischer Rhinitis und Asthma: Ergebnisse der REACT-Studie, einer retrospektiven Kohortenstudie

Hintergrund: Die Allergie-Immuntherapie (AIT) ist die einzige kausale Therapie von Allergien des Atemweges. Über die Evidenz aus randomisierten kontrollierten Studien (RCTs) hinausgehend, muss die langfristige Wirksamkeit der AIT auch in der klinischen Praxis nachgewiesen werden.

Methoden: REACT (Real World Effectiveness in Allergy Immunotherapy) ist eine retrospektive Kohortenstudie, die Krankenkassendaten zwischen 2007-2017 verwendet. Einschlusskriterien zur Studie waren eine gesicherte Diagnose einer allergischen Rhinitis (AR) mit oder ohne Asthma und AIT. Um vergleichbare Gruppen zu gewährleisten, wurden mit AIT behandelte Personen mittels Propensity score matching (PSM) 1:1 mit Kontrollpersonen gematcht, wobei Patientenmerkmale und potenzielle Störfaktoren berücksichtigt wurden. Die Ergebnisse wurden als Unterschiede innerhalb der Gruppe (vor versus nach AIT-Beginn) und zwischen den Gruppen (AIT versus Kontrolle) über 9 Jahre analysiert (ClinicalTrials.gov: NCT04125888).

Ergebnisse: 46024 mit AIT behandelte Personen wurden mit Kontrollpersonen gematcht und 14614 wurden in die Kohorte mit vorbestehendem Asthma aufgenommen. Die mit AIT behandelten Personen waren 29·5 (16·3) Jahre alt und 53 % waren männlich. Im Vergleich zum prä-Index Jahr war die AIT im Vergleich zu Kontrollpersonen durchweg mit einer größeren Reduktion der AR- und Asthma-Verordnungen assoziiert, einschließlich von Asthmadauermedikation und der Bedarfsmedikation. Darüber hinaus war die Wahrscheinlichkeit einer Reduktion der Asthmastufentherapie in AIT-Personen signifikant höher ($P < 0·0001$). Neben der Reduktion der Asthmabehandlung in der AIT-Gruppe wurde eine stärkere Reduktion schwerer Asthma-Exazerbationen nachgewiesen ($P < 0·05$). Pneumonien mit Antibiotikaverordnungen, Krankenhausaufenthalte und die Dauer der stationären Aufenthalte waren alle zugunsten der AIT-Gruppe reduziert.

Interpretation: Die Studie ergänzt die bestehende RCT-Evidenz für AIT, indem sie die längerfristige und nachhaltige Wirksamkeit der AIT in der realen Welt zeigt. Darüber hinaus war die AIT bei Personen mit bestehendem Asthma mit einer verringerten Wahrscheinlichkeit von Asthma-Exazerbationen und Pneumonien assoziiert.

Finanzierung: Die Studie wurde von ALK A/S finanziert.