Biologics and immunotherapy

Real-world, long-term effectiveness of allergy immunotherapy in allergic rhinitis: Subgroup analyses of the REACT study

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Background: Randomized controlled trials have demonstrated the efficacy of allergy immunotherapy (AIT) in allergic rhinitis (AR) and the disease-modifying effects of the SQ grass sublingual immunotherapy (SLIT) tablet.
Objective: We sought to assess real-world, long-term effectiveness and safety across AIT subgroups: route of administration, therapeutic allergen, persistence to AIT, and SQ grass SLIT tablet.
Methods: The primary outcome of AR prescriptions from a retrospective cohort study (REAl-world effeCtiveness in allergy immunoTherapy; 2007-2017) was assessed across prespecified AIT subgroups in subjects with AR with and without AIT prescriptions (controls). Safety was assessed as anaphylaxis for 2 days or less of the first AIT prescription. Subgroup follow-up continued until samples were fewer than 200 subjects.
Results: Subcutaneous immunotherapy (SCIT) and SLIT tablets showed similarly greater reductions in AR prescriptions than controls (SCIT vs SLIT tablets: year 3, *P* = .15; year 5, *P* = .43). Comparably greater reductions in AR prescriptions were observed for grass- and house dust mite–specific AIT than for controls, but significantly smaller reductions were observed for tree-specific AIT (tree vs house dust mite, and vs grass: years 3 and 5, *P* < .0001). Persistence to AIT was associated with greater reductions in AR prescriptions versus nonpersistence (persistence vs nonpersistence: year 3, *P* = .09; year 5, *P* = .006). SQ grass SLIT tablet showed sustained reductions versus controls for up to 7 years (year 3, *P* = .002; year 5, *P* = .03). Rates of anaphylactic shock were low (0.000%-0.092%), with no events for SQ SLIT tablets.
Conclusions: These results demonstrate real-world, long-term effectiveness of AIT, complement disease-modifying effects observed in SQ grass SLIT-tablet randomized controlled trials, and highlight the importance of using newer evidence-based AIT products for tree pollen AR. (J Allergy Clin Immunol 2023;152:445-52.)

Key words: Allergic rhinitis, allergy immunotherapy, cohort study, effectiveness, real-world evidence, REACT, retrospective, SQ SLIT tablet, sublingual immunotherapy

Allergic diseases are highly prevalent worldwide.[1] In particular, allergic rhinitis (AR) affects up to 30% of adults and up to 40% of children,[2-4] and is associated with negative impacts on health-related quality of life.[5,6] In addition, AR is an established risk factor for the development of other allergic diseases, such as asthma, later in life.[7] Given the high prevalence and burden of AR, there is a need for treatment options that provide long-term disease control.

Currently, allergy immunotherapy (AIT) is the only causal treatment option for allergic disease.[8,9] AIT can be administered by injection, termed subcutaneous immunotherapy (SCIT), or through the oral route as sublingual immunotherapy (SLIT).[8] Guidelines from the European Academy of Allergy and Clinical Immunology and US practice parameters recommend a minimum of 3 years of AIT treatment to achieve long-term efficacy.[8,10] Although SCIT has been used in the treatment of AR for decades,[11,12] more recently, there has been a shift toward more evidence-based AIT treatment, such as SLIT tablets.[13-15] Due to the potential for large placebo effects,[16] regulators require manufacturers of AIT products to conduct randomized, double-blind, placebo-controlled trials as proof of efficacy.[17] In line with this requirement, several large-scale, randomized, double-blind, placebo-controlled trials have been conducted to date, confirming the efficacy and safety of AIT administered as SLIT tablets.[18-28]

Randomized controlled trials (RCTs) remain the criterion standard for evaluating the efficacy of medicinal products.[29] However, they are limited by features, such as highly selected patient populations and relatively short follow-up periods,[29-31] with many RCTs assessing efficacy across either a single season or during 1-year of follow-up.[20,21,23] Three long-term RCTs in patients with AR—2 of the SQ grass SLIT tablet (1 of which was conducted in children) and the other of the Japanese cedar SLIT tablet—demonstrated efficacy during 3 years of treatment, with sustained effects for at least 2 years posttreatment.[18,22,24]

Real-world studies, which evaluate the effectiveness of treatments in real-life clinical practice, complement and extend the existing evidence from RCTs.[29] The recently published REAl-world effeCtiveness in allergy immunoTherapy (REACT) study was a large, retrospective, and propensity score–matched cohort study (2007-2017).[32,33] The study demonstrated the overall effectiveness of AIT for the treatment of AR (and asthma) in a broad population of more than 90,000 subjects during up to 9 years of follow-up.[32] AIT was consistently associated with greater reductions in AR and asthma prescriptions compared with controls (subjects with AR with no AIT prescription), and improvements in clinically relevant outcomes, such as asthma exacerbations and hospitalizations across the 9-year period.[32]

This article reports on prespecified subgroup analyses of the primary outcome from the REACT study (AR prescriptions per follow-up year) to characterize, in more detail, the real-world effectiveness of AIT. In particular, the aims were to: (1) characterize the long-term effectiveness of AIT in the treatment of AR, according to route of administration (SCIT and SLIT tablets), type of therapeutic allergen (grass, tree, and house dust mite [HDM]), and persistence to AIT treatment; (2) determine whether the evidence from real-world settings complements the favorable efficacy and safety profiles of SLIT tablets that have been established in RCTs; (3) evaluate whether the long-term, disease-modifying effect of the SQ grass SLIT tablet that has been demonstrated in RCTs is observed in a real-world setting.

METHODS

These analyses were conducted on protocol-defined, prespecified AIT subgroups of the REACT study (NCT04125888)—a retrospective cohort study that evaluated claims data from approximately 5.9 million individuals in a German health insurance database (Betriebkrankenkasse).[32] The data source, protocol, analysis plan, and findings of the REACT study have been published separately.[32,33] Briefly, insurance claims data for the study period (January 1, 2007, to December 31, 2017) were reviewed, and subjects with a confirmed diagnosis of AR (with or without asthma) who had received a prescription for AIT were identified for evaluation.[32] Subjects were included if they had received at least 2 prescriptions of the same AIT during the first year after the index date (ie, date of the first AIT prescription).[32] All available AIT products (except venom) were included.[32] Subjects who had received AIT

prescriptions were matched 1:1 to a control group of subjects with AR who had not received a prescription for AIT, using propensity score matching.[32] The primary outcome of the REACT study was the number of AR prescriptions in each follow-up year during a 9-year period.[32] The published findings of the main REACT study report data for the overall AIT and control groups across all 9 years of follow-up (as well as data from year 3 for all subgroups of subjects).[32]

The present analyses further evaluated the data for key prespecified subgroups from the REACT study. Subgroups were based on different AIT variables: (1) route of AIT administration—SCIT and SLIT-tablet subgroups; (2) type of therapeutic allergen—grass, tree, and HDM subgroups; (3) persistence to AIT treatment—persistent and nonpersistent subgroups (persistence was defined as 2 prescriptions for the index AIT within 2 consecutive follow-up years). An additional prespecified subgroup of interest comprised subjects who were prescribed the SQ grass SLIT tablet.

The prespecified AIT subgroups were formed by dividing the pairs of matched subjects with AR (AIT and controls) from the main REACT study cohort according to the type of AIT treatment (by route of administration and by allergen at the index date), persistence, and SQ grass SLIT tablet.[32] Within each AIT subgroup, rematching was not performed (ie, SCIT subjects were not matched with SLIT-tablet subjects, persistent subjects were not matched with nonpersistent subjects, etc). The AIT subgroups were not mutually exclusive and were, therefore, not subdivided into further subgroups (eg, subjects in each of the allergen subgroups were not divided by route of administration—they could have received SCIT or SLIT). Subjects who could not be clearly allocated to 1 subgroup within each AIT variable at the index date (eg, those initiating AIT treatment for multiple allergens) were excluded.

For each subgroup, effectiveness was evaluated as the change in the number of AR prescriptions from the preindex year (baseline) to each follow-up year (years 1-9). The safety of AIT was assessed by the incidence of anaphylaxis related to AIT initiation, which was defined as presence of the *International Statistical Classification of Diseases and Health-Related Problems, Tenth Revision* diagnosis code for anaphylactic shock (T78.2, T80.5, T88.6) within 2 days of the index date.[32]

To account for the gradual reduction in sample size over time, data were truncated if the number of subjects in a subgroup was fewer than 200 in any follow-up year. For the most part, data were analyzed descriptively. Statistical testing for significant differences across AIT subgroups was performed *post hoc* for selected key follow-up years—at the end of the recommended minimum duration of AIT treatment (follow-up year 3) and at 2 years after completion of a 3-year treatment period (follow-up year 5), as used in previous RCTs evaluating the disease-modifying effects of AIT.[18,22,24]

RESULTS
Baseline demographics and clinical characteristics

In the REACT study, a total of 46,024 subjects with AR with an AIT prescription were matched 1:1 with control subjects with AR without an AIT prescription.[32] A breakdown of the number of subjects per prespecified AIT subgroup is presented in Fig 1. Baseline demographics for the main REACT study cohort have been published separately.[32] For the AIT subgroups, the baseline characteristics were generally similar, even though the AIT subgroups were not separately matched and minor intergroup differences were observed (Table I).

Long-term effectiveness: Route of administration

In the main REACT study, the AIT and control cohorts showed reductions in AR prescriptions during the follow-up period, but the reductions were consistently greater in the AIT group across all follow-up years.[32] When dividing the AIT group by route of administration, the mean number of AR prescriptions in the preindex year was similar across the SCIT (1.06), SLIT-tablet (1.16), and control (1.03) groups. During 8 years of follow-up, SCIT and
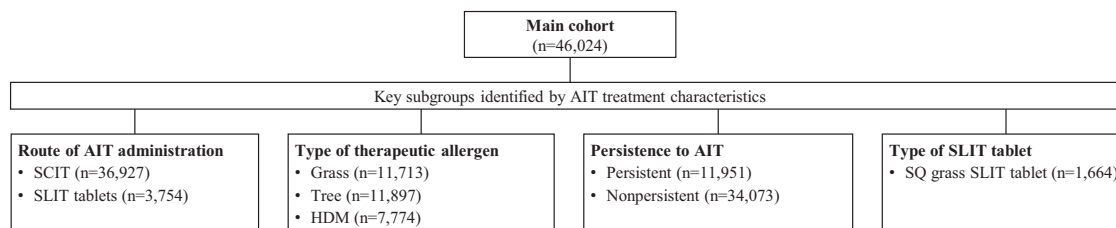
FIG 1. Prespecified subgroups based on AIT treatment characteristics. AIT subgroups were formed by dividing pairs of matched AR subjects (AIT and controls) from the main REACT study; therefore, each subgroup also included an equal number of matched AR control subjects. Persistence was defined as 2 prescriptions for the index AIT within 2 consecutive follow-up years. The data shown in this figure have been published previously,[32] and have been reproduced here for completeness.

TABLE I. Baseline demographics by subgroup, according to the different AIT variables

| Characteristics | Route of AIT administration | | Type of therapeutic allergen | | | Persistence to AIT | | Type of SLIT tablet | Control groups | |
	SCIT (n = 36,927)	SLIT tablet (n = 3,754)	Grass (n = 11,713)	Tree (n = 11,897)	HDM (n = 7,774)	Persistent (n = 11,951)	Nonpersistent (n = 34,073)	SQ grass SLIT tablet (n = 1,664)	Main REACT cohort control*† (n = 46,024)	SLIT-tablet control‡ (n = 3,754)
Age (y), mean ± SD	29.8 ± 16.2	27.1 ± 15.3	25.3 ± 14.6	35.9 ± 16.9	26.8 ± 15.6	29.2 ± 17.1	29.6 ± 16.0	27.4 ± 15.3	29.5 ± 17.4	29.3 ± 17.4
Sex: male, n (%)	19,567 (53.0)	2,035 (54.2)	6,675 (57.0)	5,818 (48.9)	4,081 (52.5)	6,594 (55.2)	17,816 (52.3)	920 (55.3)	24,134 (52.4)	1,992 (53.1)
Key comorbidities, n (%)										
Asthma	12,157 (32.9)	1,070 (28.5)	3,275 (28.0)	4,171 (35.1)	2,528 (32.5)	3,874 (32.4)	10,994 (32.3)	488 (29.3)	15,213 (33.1)	1,210 (32.2)
Conjunctivitis	8,127 (22.0)	781 (20.8)	2,749 (23.5)	2,907 (24.4)	1,240 (16.0)	2,660 (22.3)	7,341 (21.5)	349 (21.0)	10,126 (22.0)	804 (21.4)
Eczema	9,602 (26.0)	894 (23.8)	2,837 (24.2)	3,252 (27.3)	2,110 (27.1)	3,131 (26.2)	8,778 (25.8)	397 (23.9)	12,868 (28.0)	973 (25.9)
Health care utilization, mean ± SD										
Ambulatory care (visits)	15.79 ± 12.34	14.47 ± 12.00	14.02 ± 11.16	16.42 ± 12.87	16.57 ± 12.92	15.20 ± 12.17	15.73 ± 12.31	14.31 ± 12.04	17.92 ± 16.57	17.64 ± 16.25
Hospitalizations (events)	0.20 ± 0.62	0.20 ± 0.61	0.18 ± 0.59	0.19 ± 0.59	0.26 ± 0.72	0.19 ± 0.58	0.20 ± 0.63	0.18 ± 0.55	0.21 ± 0.66	0.21 ± 0.65
Sick leave (d)	0.73 ± 1.40	0.67 ± 1.37	0.63 ± 1.33	0.80 ± 1.39	0.69 ± 1.44	0.65 ± 1.28	0.74 ± 1.42	0.68 ± 1.38	0.75 ± 1.55	0.71 ± 1.45
Total duration of index AIT§ treatment (d), mean ± SD	561.0 ± 272.1	481.5 ± 309.4	533.5 ± 285.0	555.8 ± 286.4	569.0 ± 275.1	817.3 ± 278.2	454.9 ± 218.1	555.4 ± 343.7	—	—
AR prescriptions, mean ± SD	1.06 ± 1.66	1.16 ± 1.78	1.11 ± 1.69	0.94 ± 1.52	1.22 ± 1.84	1.17 ± 1.83	1.05 1.66	1.19 ± 1.78	1.03 ± 1.88	1.00 ± 1.84
Antihistamine	0.44 ± 1.04	0.49 ± 1.10	0.52 ± 1.10	0.43 ± 1.00	0.33 ± 1.00	0.51 ± 1.17	0.43 ± 1.02	0.54 ± 1.20	0.40 ± 1.10	0.39 ± 1.08
INCS	0.47 ± 0.92	0.49 ± 1.01	0.41 ± 0.84	0.40 ± 0.81	0.65 ± 1.11	0.46 ± 0.94	0.47 ± 0.92	0.48 ± 0.95	0.44 ± 1.09	0.42 ± 1.02

INCS, Intranasal corticosteroid.

*Baseline demographics for the REACT study cohort (control group) have been published previously,[32] and have been reproduced here for completeness.

†For certain AIT variables (route of AIT administration, type of therapeutic allergen, and persistence to AIT), the main REACT cohort control group (ie, matched subjects who did not receive an AIT prescription) acted as the controls for the corresponding subgroup analyses.

‡For the AIT variable, type of SLIT tablet, the SQ grass SLIT-tablet group was compared with control subjects from the overall SLIT-tablet group.

§The index AIT was defined as the first AIT that was prescribed during the study period (excluding venom AIT).

SLIT-tablet subgroups showed comparable reductions in the number of AR prescriptions (year 3, P = .15; year 5, P = .43) (Fig 2; see Table E1 in this article's Online Repository at www.jacionline.org). During years 1 to 3, the reduction in AR prescriptions with SLIT tablets was numerically greater than the reduction observed with SCIT (Fig 2; Table E1). Thereafter, during years 4 to 8, the changes in AR prescriptions showed a similar trend in the 2 subgroups (Fig 2; Table E1).

Long-term effectiveness: Type of therapeutic allergen

Dividing the AIT group by type of allergen showed comparably greater reductions in AR prescriptions than controls across AIT subgroups specific to grass and to HDM allergen during years 2 to 9 (grass- vs HDM-specific AIT: year 3, P = .62; year 5, P = .17) (Fig 3; see Table E2 in this article's Online Repository at www.jacionline.org). In contrast, the tree-specific AIT subgroup showed no difference in the reduction in AR prescriptions compared with the control group (Fig 3; Table E2). At years 3 and 5, the reductions in AR prescriptions in subjects who received tree-specific AIT were statistically significantly lower than those

observed in subjects who received grass-specific or HDM-specific AIT (tree- vs grass-specific AIT and tree- vs HDM-specific AIT, P < .0001 for both comparisons).

Long-term effectiveness: Persistence to treatment

A greater reduction in AR prescriptions was shown in persistent and nonpersistent groups compared with controls. However, during 9 years of follow-up, the effect was most pronounced in subjects who were persistent to AIT treatment compared with subjects who were nonpersistent to AIT (Fig 4; see Table E3 in this article's Online Repository at www.jacionline.org). At year 3, the reduction in AR prescriptions was numerically greater for persistent versus nonpersistent subjects (P = .09). At year 5, the reduction in AR prescriptions was statistically significantly greater for persistent subjects versus nonpersistent subjects (P = .006).

Long-term effectiveness: SQ grass SLIT tablet

The overall SLIT-tablet group showed numerically greater reductions in AR prescriptions compared with controls (Fig 5; see Table E4 in this article's Online Repository at www.jacionline.
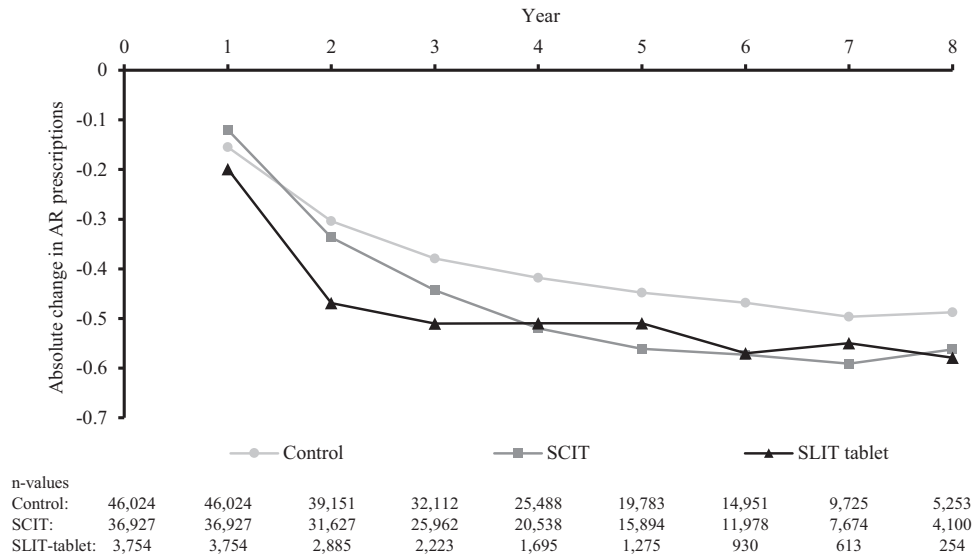
FIG 2. Absolute change in AR prescriptions, compared with the pre–index year, by route of AIT administration. Due to small sample size (n < 200), the analysis was truncated at year 8. The main control group of the REACT study[32] acted as the controls for this subgroup analysis. Mean number of AR prescriptions in the pre–index year: control = 1.03; SCIT = 1.06; SLIT tablet = 1.16.
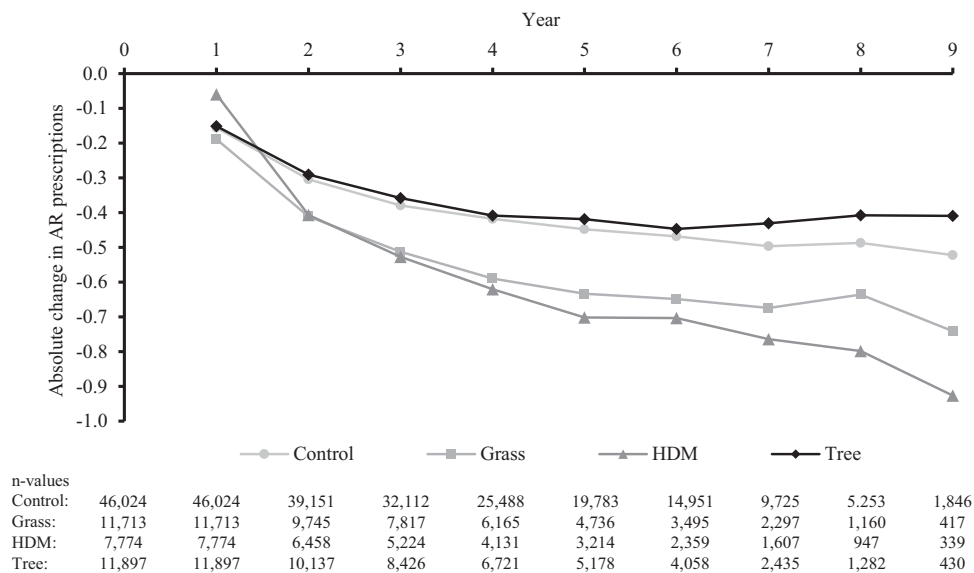

FIG 3. Absolute change in AR prescriptions, compared with the pre–index year, by type of therapeutic allergen. The main control group of the REACT study[32] acted as the controls for this subgroup analysis. Mean number of AR prescriptions in the pre–index year: control = 1.03; grass = 1.11; tree = 0.94; HDM = 1.22.

org), with the SQ grass SLIT-tablet group showing numerically greater reductions compared with the overall SLIT-tablet group during years 2 to 7 (Fig 5; Table E4). Compared with SLIT-tablet controls, the SQ grass SLIT-tablet group was associated with statistically significant reductions in AR prescriptions at year 3 (*P* = .002) and year 5 (*P* = .03), with sustained reductions across the available 7 years of follow-up (Fig 5; Table E4).

Safety

The safety profile of AIT was as expected, with an overall low rate of anaphylactic shock within 2 days of the first AIT

prescription. SLIT tablets showed a numerically lower incidence of anaphylactic shock than SCIT (0.027% and 0.081%, respectively) (Fig 6). Within the type of therapeutic allergen variable, reported rates of anaphylactic shock ranged from 0.051% for grass allergen to 0.092% for tree allergen (Fig 6). No cases of anaphylactic shock were reported with any SQ SLIT tablets (grass or HDM).

DISCUSSION

These prespecified subgroup analyses of the REACT study further characterize the long-term, real-world effectiveness of
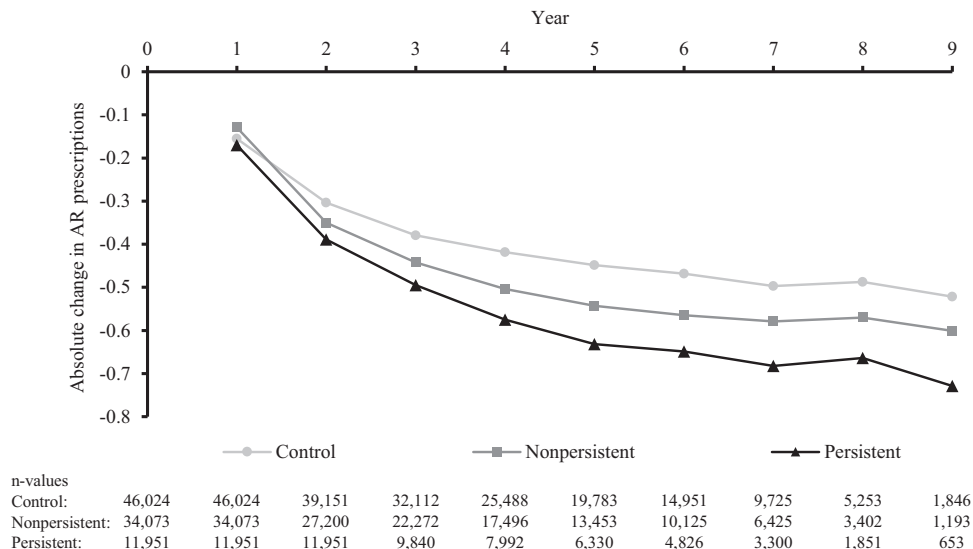
FIG 4. Absolute change in AR prescriptions, compared with the pre–index year, by persistence to AIT. The main control group of the REACT study[32] acted as the controls for this subgroup analysis. Persistence was defined as 2 prescriptions for the index AIT within 2 consecutive follow-up years. Mean number of AR prescriptions in the pre–index year: control = 1.03; persistent = 1.17; nonpersistent = 1.05.
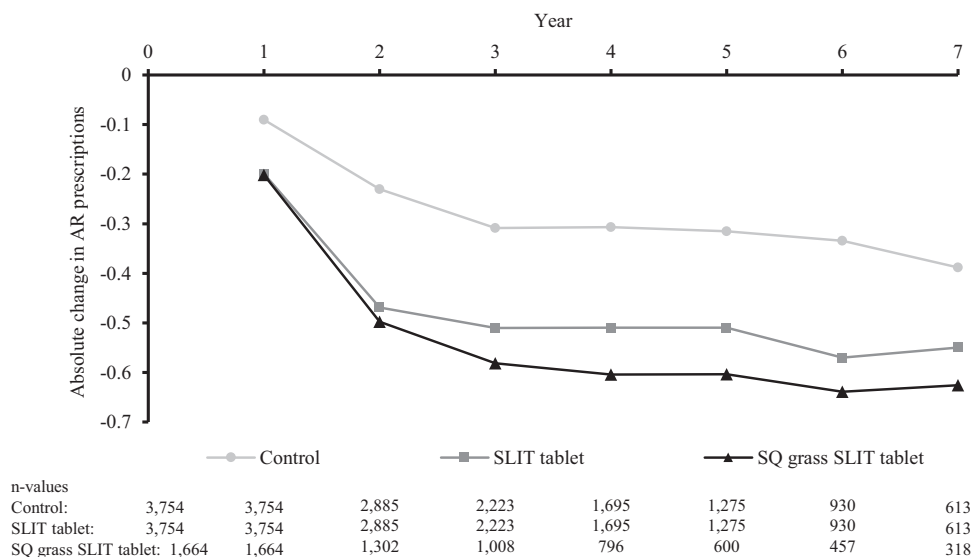

FIG 5. Absolute change in AR prescriptions, compared with the pre–index year, for SLIT tablets and the SQ grass SLIT tablet. Due to small sample size (n < 200), the analysis was truncated at year 7. The control group of the SLIT-tablet subgroup acted as the controls for this subgroup analysis. Mean number of AR prescriptions in the pre–index year: SLIT-tablet control = 1.00; SLIT tablet = 1.16; SQ grass SLIT tablet = 1.19.

AIT in the treatment of AR. The findings add to the efficacy and safety profiles of AIT that have been established in RCTs, and support the robustness of the main REACT study, which demonstrated the real-world effectiveness of AIT for the treatment of AR (and asthma) during up to 9 years of follow-up.[32] In addition, the findings may provide appropriate reassurance, and confidence, that the evidence for long-term, disease-modifying effects of the SQ grass SLIT tablet is generalizable to real-life clinical practice.

The efficacy of AIT in the treatment of AR, evaluated through symptoms and medication use, is supported by various meta-analyses of data from RCTs.[34-38] Published reports of clinical trials directly comparing route of administration—SCIT versus SLIT tablets—are limited, with a recent RCT demonstrating similar efficacy for SQ grass SCIT and the SQ grass SLIT tablet after 2 years of treatment.[39] The findings of the REACT study subgroup analyses are in accordance with the RCT data and allowed for additional long-term assessment of AIT. The results
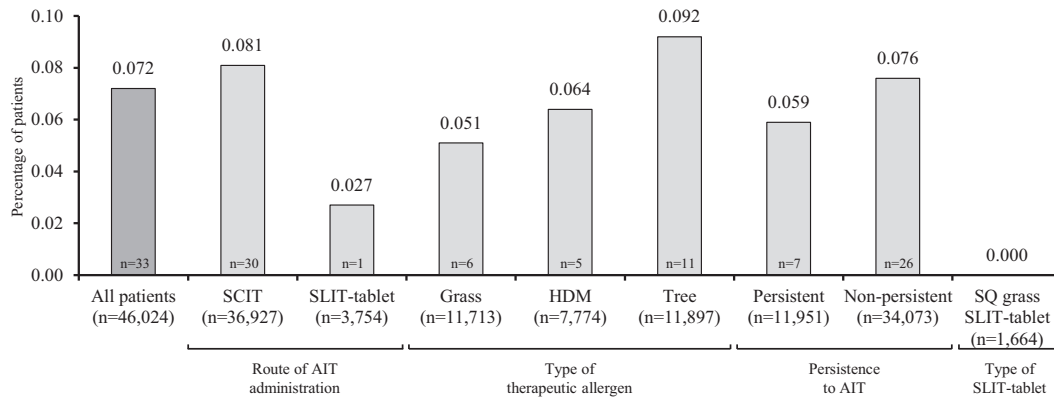
FIG 6. Incidence of anaphylactic shock within 2 days after the AIT index date. Persistence was defined as 2 prescriptions for the index AIT within 2 consecutive follow-up years.

also suggest that the onset of effectiveness, assessed by the initial rate of reduction in AR prescriptions, was faster with SLIT tablets than with SCIT.

The long-term reductions in AR prescriptions were consistent across grass and HDM allergen-specific AIT. However, a lack of effectiveness and a numerically higher rate of anaphylactic shock were observed for the tree allergen-specific AIT, highlighting an unmet need for the treatment of individuals with tree pollen allergy. Since completion of the REACT study in 2017, an SQ tree SLIT tablet has been approved in Europe and Canada for the treatment of AR triggered by pollen from trees belonging to the birch homologous group.[19,40,41] During the REACT study, the Therapy Allergen Ordinance process was launched in Germany to ensure the use of proven and tested allergens in AIT products. Although a relatively long transition period has been permitted, several AIT products have been affected by this process and have been removed from the market. Similarly, new AIT products with evidence demonstrating their efficacy and safety have entered the market.[42] Consequently, it is possible that the overall quality and, therefore, the safety and efficacy of available AIT products (including tree allergen-specific AIT) has improved since the REACT study concluded. Further studies are required to confirm the favorable efficacy and safety profile of SQ tree SLIT tablet in real-world settings.

The findings of the REACT subgroup analyses support the importance of persistence in individuals with AR—during 9 years of follow-up, subjects who were persistent to AIT showed larger reductions in AR prescriptions than nonpersistent subjects. Although there were no apparent differences between the persistent and nonpersistent subgroups at baseline, residual confounding factors that are not evident from the data may exist. For example, persistence (as well as adherence) can be affected by many factors, such as the type of AIT or allergen, and the way in which individuals access treatment (eg, prescriptions from general practitioners vs medical specialists).[43,44] Although an improvement in AR symptoms has been reported 2 to 5 months after AIT initiation,[20,21,23,25-28] treatment for at least 3 years is recommended to achieve the long-term, disease-modifying effects of AIT.[8,45] As for many chronic diseases, poor adherence and persistence to treatment are challenges in AR.[43,44,46,47] For AIT, specifically, studies have reported low rates of adherence or persistence to SCIT and SLIT treatment, particularly in real-world settings.[43,44,48-51] Consequently, there is a need to improve

real-world adherence and persistence to AIT to ensure optimal long-term outcomes.[43,44]

Interestingly, the findings of the subgroup analyses focusing on the SQ grass SLIT tablet extend the existing evidence by demonstrating sustained effectiveness of the SQ grass SLIT tablet across a longer duration of follow-up (ie, 7 years) than had previously been evaluated in RCTs (5 years).[18] The effectiveness of the SQ grass SLIT tablet appears to be driving the overall reduction in AR prescriptions in the entire SLIT-tablet subgroup, indicating possible differences in effectiveness between different SLIT-tablet products. However, elucidation of these differences is not possible with the current data set, because the overall SLIT-tablet group is composed of both the SQ grass SLIT tablet and other SLIT tablets that were available on the German market during the study period.

AIT involves the administration of the specific type of allergen to which individuals are allergic[12] and is, therefore, associated with a risk of allergic reactions.[52] In the present analyses, a low incidence of anaphylactic shock was reported across all subgroups, with no cases reported for SQ SLIT tablets and 1 case for SLIT tablets overall (n = 1 out of 3754; 0.027%). Also, no cases of anaphylactic shock were reported with the SQ HDM SLIT tablet, although data for this subgroup were excluded from the analyses due to low patient numbers (n = 192), because the product was launched only at the very end of the study period. The incidence of local reactions, which are common following AIT,[53] and systemic reactions other than anaphylactic shock were not evaluated in this analysis. It should also be noted that the definition of anaphylaxis was limited to cases of anaphylactic shock that occurred within 2 days of the first AIT prescription (ie, cases that were likely to be associated with AIT initiation), which may have led to underestimation of the rates of anaphylactic shock. However, the results of these subgroup analyses align with the safety data from RCTs of AIT in the treatment of AR.[18-20,35,54]

The main strengths of these subgroup analyses were the large, unselected population of subjects with AR who had received an AIT prescription in real-world clinical practice, and the utilization of prespecified subgroups from the primary REACT study. The analysis was limited by the small number of subjects at the later time points in some subgroups, which resulted in truncation of data. The AIT subgroups were not mutually exclusive, and the prespecified subgroups were not further divided into other

subgroups, thereby limiting the granularity of the data. Furthermore, some AIT subjects could not be allocated to a particular subgroup (eg, due to treatment with more than 1 allergen at the index date); these subjects were likely to be very heterogeneous and, therefore, were excluded from the analyses. Similarly, subjects treated with SLIT drops were not included, given that real-world studies aim to complement existing evidence from RCTs,[29] which remains sparse for SLIT drops. Finally, rematching of AIT subjects was not undertaken for the AIT subgroups. The AIT subgroups were prespecified and were included to test the robustness of the primary outcome (AIT vs controls); therefore, AIT subjects were matched 1:1 with controls, not treated with AIT. To form the AIT subgroups, the existing matched pairs (AIT and controls) were divided by AIT treatment and persistence. Given that AIT subjects were not rematched across AIT modalities, there could, potentially, be differences between the AIT subgroups, although they appeared similar at baseline. In consideration of these limitations, the data were mainly analyzed descriptively, with *post hoc* statistical testing for key follow-up years only (year 3 and year 5). As the REACT study also demonstrated long-term and sustained effectiveness across a range of secondary asthma outcomes in the subgroup of subjects with AR with preexisting asthma, further analyses are warranted to explore these outcomes across different AIT modalities. However, the general results observed in these subgroup analyses of patients with AR align with the overall findings reported for AIT in the main REACT study,[32] lending support to the data.

In conclusion, the findings of these subgroup analyses of the REACT study describe a consistent effectiveness of AIT in the real world. The results build on existing RCT evidence for the favorable efficacy and safety profiles of SQ SLIT tablets, and extend the evidence for long-term, disease-modifying effects of the SQ grass SLIT tablet. The results also highlight an unmet need for evidence-based treatments for AR triggered by tree pollen. This need may be met by the SQ tree SLIT tablet, which, in the period after the REACT study (ie, after 2017), has demonstrated efficacy and safety in RCTs, providing an alternative treatment option for individuals with tree pollen allergy. Finally, the results also support the importance of persistence to AIT in ensuring optimal long-term outcomes for individuals with AR.

Clinical implications: Subgroup analyses of the REACT study complement the real-world effectiveness of AIT for treatment of AR, and provide real-world evidence for the long-term, disease-modifying effects of the SQ grass SLIT tablet.

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TABLE E1. Absolute change from the pre–index year to each follow-up year in mean number of AR prescriptions, by route of AIT administration

Follow-up year	Absolute change in mean number of AR prescriptions		
	Control (n = 46,024)	SCIT (n = 36,927)	SLIT tablet (n = 3,754)
1	−0.16 (−0.18, −0.13)	−0.12 (−0.14, −0.10)	−0.20 (−0.28, −0.12)
2	−0.30 (−0.33, −0.28)	−0.34 (−0.36, −0.31)	−0.47 (−0.55, −0.38)
3	−0.38 (−0.41, −0.35)	−0.44 (−0.47, −0.42)	−0.51 (−0.60, −0.42)
4	−0.42 (−0.45, −0.39)	−0.52 (−0.55, −0.49)	−0.51 (−0.62, −0.40)
5	−0.45 (−0.48, −0.41)	−0.56 (−0.59, −0.53)	−0.51 (−0.63, −0.39)
6	−0.47 (−0.51, −0.43)	−0.57 (−0.61, −0.54)	−0.57 (−0.72, −0.42)
7	−0.50 (−0.54, −0.45)	−0.59 (−0.64, −0.55)	−0.55 (−0.72, −0.38)
8	−0.49 (−0.55, −0.43)	−0.56 (−0.62, −0.50)	−0.58 (−0.84, −0.32)

Values are absolute change (lower limit of the mean, upper limit of the mean). Due to small sample size (n < 200), the analysis was truncated at year 8. The main control group of the REACT study[32] acted as the controls for this subgroup analysis.

Mean number of AR prescriptions in the pre–index year: control = 1.03; SCIT = 1.06; SLIT tablet = 1.16.

TABLE E2. Absolute change from the pre–index year to each follow-up year in mean number of AR prescriptions, by type of therapeutic allergen

| Follow-up year | Absolute change in mean number of AR prescriptions | | | |
	Control (n = 46,024)	Grass (n = 11,713)	Tree (n = 11,897)	HDM (n = 7,774)
1	−0.16 (−0.18, −0.13)	−0.19 (−0.23, −0.15)	−0.15 (−0.19, −0.11)	−0.06 (−0.12, 0.00)
2	−0.30 (−0.33, −0.28)	−0.41 (−0.45, −0.37)	−0.29 (−0.33, −0.25)	−0.41 (−0.47, −0.35)
3	−0.38 (−0.41, −0.35)	−0.51 (−0.56, −0.46)	−0.36 (−0.40, −0.32)	−0.53 (−0.59, −0.46)
4	−0.42 (−0.45, −0.39)	−0.59 (−0.64, −0.54)	−0.41 (−0.45, −0.36)	−0.62 (−0.69, −0.55)
5	−0.45 (−0.48, −0.41)	−0.63 (−0.69, −0.57)	−0.42 (−0.47, −0.37)	−0.70 (−0.78, −0.62)
6	−0.47 (−0.51, −0.43)	−0.65 (−0.72, −0.58)	−0.45 (−0.50, −0.39)	−0.70 (−0.79, −0.61)
7	−0.50 (−0.54, −0.45)	−0.67 (−0.76, −0.59)	−0.43 (−0.50, −0.36)	−0.76 (−0.88, −0.65)
8	−0.49 (−0.55, −0.43)	−0.64 (−0.75, −0.52)	−0.41 (−0.50, −0.31)	−0.80 (−0.94, −0.65)
9	−0.52 (−0.62, −0.43)	−0.74 (−0.93, −0.55)	−0.41 (−0.59, −0.23)	−0.93 (−1.19, −0.66)

Values are absolute change (lower limit of the mean, upper limit of the mean). The main control group of the REACT study[32] acted as the controls for this subgroup analysis. Mean number of AR prescriptions in the pre–index year: control = 1.03; grass = 1.11; tree = 0.94; HDM = 1.22.

TABLE E3. Absolute change from the pre–index year to each follow-up year in mean number of AR prescriptions, by persistence to AIT

Follow-up year	Absolute change in mean number of AR prescriptions		
	Control (n = 46,024)	Persistent (n = 11,951)	Nonpersistent (n = 34,073)
1	−0.16 (−0.18, −0.13)	−0.17 (−0.22, −0.12)	−0.13 (−0.15, −0.10)
2	−0.30 (−0.33, −0.28)	−0.39 (−0.43, −0.35)	−0.35 (−0.38, −0.32)
3	−0.38 (−0.41, −0.35)	−0.49 (−0.54, −0.45)	−0.44 (−0.47, −0.41)
4	−0.42 (−0.45, −0.39)	−0.58 (−0.62, −0.53)	−0.50 (−0.53, −0.47)
5	−0.45 (−0.48, −0.41)	−0.63 (−0.68, −0.58)	−0.54 (−0.58, −0.51)
6	−0.47 (−0.51, −0.43)	−0.65 (−0.71, −0.59)	−0.56 (−0.60, −0.53)
7	−0.50 (−0.54, −0.45)	−0.68 (−0.76, −0.61)	−0.58 (−0.63, −0.53)
8	−0.49 (−0.55, −0.43)	−0.66 (−0.76, −0.57)	−0.57 (−0.64, −0.50)
9	−0.52 (−0.62, −0.43)	−0.73 (−0.89, −0.56)	−0.60 (−0.72, −0.48)

Values are absolute change (lower limit of the mean, upper limit of the mean). The main control group of the REACT study[32] acted as the controls for this subgroup analysis.
Persistence was defined as 2 prescriptions for the index AIT within 2 consecutive follow-up years.
Mean number of AR prescriptions in the pre–index year: control = 1.03; persistent = 1.17; nonpersistent = 1.05.

TABLE E4. Absolute change from the pre–index year to each follow-up year in mean number of AR prescriptions, for SLIT tablets and the SQ grass SLIT tablet

	Absolute change in mean number of AR prescriptions		
Follow-up year	Control (n = 3754)	SLIT tablet (n = 3754)	SQ grass SLIT tablet (n = 1664)
1	−0.09 (−0.17, −0.01)	−0.20 (−0.28, −0.12)	−0.20 (−0.32, −0.08)
2	−0.23 (−0.32, −0.14)	−0.47 (−0.55, −0.38)	−0.50 (−0.63, −0.37)
3	−0.31 (−0.40, −0.21)	−0.51 (−0.60, −0.42)	−0.58 (−0.72, −0.44)
4	−0.31 (−0.41, −0.20)	−0.51 (−0.62, −0.40)	−0.60 (−0.76, −0.45)
5	−0.32 (−0.44, −0.19)	−0.51 (−0.63, −0.39)	−0.60 (−0.77, −0.43)
6	−0.33 (−0.48, −0.19)	−0.57 (−0.72, −0.42)	−0.64 (−0.83, −0.45)
7	−0.39 (−0.56, −0.22)	−0.55 (−0.72, −0.38)	−0.63 (−0.84, −0.41)

Values are absolute change (lower limit of the mean, upper limit of the mean). Due to small sample size (n < 200), the analysis was truncated at year 7. The control group of the SLIT-tablet subgroup acted as the controls for this subgroup analysis.

Mean number of AR prescriptions in the pre–index year: SLIT-tablet control = 1.00; SLIT tablet = 1.16; SQ grass SLIT tablet = 1.19.