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Allergen-Specific Immunotherapy and Biologics

Long-Term, Real-World Effectiveness of Allergen Immunotherapy in Children and Adolescents With Allergic Rhinitis and Asthma

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ABSTRACT

Background: Respiratory allergies often begin in childhood and can progress over time, leading to increased disease burden. Allergen immunotherapy (AIT) is the only causal treatment for allergic respiratory diseases with disease-modifying potential. While randomised trials support its efficacy in controlling allergic rhinitis (AR) and asthma symptoms, long-term real-world data in children remain limited.

Methods: This paediatric study ($n = 11{,}036$) was conducted within the pre-defined framework of the REACT study, based on protocol-specified objectives. Children (< 18 years) with physician-diagnosed AR, with or without pre-existing asthma, were included. AIT-treated patients were matched 1:1 to non-AIT controls. Effectiveness was assessed over 9 years by comparing AR and asthma medication prescriptions, using a public database covering all reimbursable AIT products. Relative differences were calculated across the full observation period.

Results: AIT-treated children (mean age 11.4 years; 62.1% male) exhibited greater reductions in AR medication use than controls (additional 9% reduction beyond 61% in controls). In children with asthma, AIT was associated with additional reductions in asthma medication use (−21% beyond −48% in controls), severe exacerbations (−21% beyond −36%), and new oral corticosteroid prescriptions (−33% beyond −41%). Age stratification revealed more pronounced AR medication reductions in younger children (0–11 years) than in adolescents (12–17 years).

Conclusion: This large-scale, real-world study supports the long-term effectiveness of AIT in children with AR, with or without asthma. The findings reflect improved disease control and suggest a disease-modifying effect of AIT. Early intervention, particularly in younger children, may help mitigate the progression of allergic disease.

1 | Introduction

Allergic rhinitis (AR) and asthma are common chronic inflammatory diseases that can often start in childhood, affecting children and adolescents [1]. Global estimates indicate that approximately 1 in 10 children suffer from AR, with increasing prevalences in many countries [2]. AR often precedes childhood asthma; the majority of children with AR at age 4 or 8 years

showed persistent disease up to 24 years old, and 30.8% of children had developed asthma [3]. Furthermore, children with asthma and concomitant AR experience poorer asthma control, as indicated by the increased risk of hospital admission for severe asthma exacerbations [4]. Asthma is also associated with a non-negligible rate of mortality in low- and middle-income countries [5]. Type 2 inflammation involved in the allergy underlying AR and asthma increases the susceptibility to viral infections [6]. A stronger association with asthma exacerbation was observed in children with increased expression of type 2 inflammation and reduced expression of type I interferon than in children with lower and higher expression, respectively [6]. Viral respiratory infections and environmental risk factors (such as air pollution, nutrition and allergic sensitisation) in early life are crucial determinants for later chronic respiratory morbidity [7], and impaired lung function [8]. Furthermore, impaired lung function in early adulthood is associated with an increased prevalence of respiratory, cardiac and metabolic morbidity [9].

Allergen immunotherapy (AIT) is the only causal treatment for allergic respiratory diseases, such as AR and asthma, in contrast to symptom-relieving medication (e.g., antihistamines, corticosteroids and bronchodilators) which alleviate symptoms but do not target the underlying disease mechanisms. AIT has demonstrated long-term and disease-modifying effects (i.e., persistent effectiveness after treatment ends) in the treatment of AR and has the potential to halt disease progression and prevent the onset of asthma [10]. AIT builds immunological tolerance through repeated daily administration of the causative allergen [11]. For sublingual immunotherapy (SLIT)-tablets, specifically, daily administration for 3 years is recommended to achieve a sustained, disease-modifying effect [12]. A recent review of clinical trials evaluating SQ SLIT-tablets in children (aged 5–17 years) with AR, with or without asthma, highlights the long-term disease-modifying properties of the treatment and underscores the clinical relevance of early intervention [13]. Additionally, treatment with the SQ SLIT-tablet reduced the risk of developing moderate–severe asthma exacerbations [14], with a potential causal mechanism linked to the enhancement of innate antiviral immunity and epithelial barrier function [15–17]. Therefore, early intervention with AIT may not only improve AR symptoms and reduce the use of symptom-relieving medication, but it may also mitigate the risk of disease progression and improve resistance to viral infection. Consequently, AIT emerges as the only treatment option to mitigate environmental risk factors and reduce the risk of viral-induced asthma exacerbations and secondary lower respiratory tract infections in children; ultimately, AIT may prevent the risk of impaired lung function development in children.

Real-world evidence (RWE) is increasingly recognised as a valuable complement to data from clinical trials [18]. The REAl-world effeCtiveness in allergy immunoTherapy (REACT) study—a large, retrospective cohort study including more than 45,000 AIT-treated subjects with AR, with or without asthma matched to non-AIT control subjects—demonstrated the long-term sustained effectiveness of AIT over a 9-year period [19]. Significant reductions in AR and asthma prescriptions were observed in the AIT-treated group compared to matched controls, alongside a reduced risk of asthma exacerbations and hospitalisations [19]. Research suggests that a crucial window of opportunity exists in early childhood within which interventions could potentially halt the progression of allergic disease [20]. Consequently, initiating AIT early in the disease course has the potential to reduce the risk of new allergen sensitisations and the onset of asthma.

In the REACT study framework, outcomes including a paediatric sub-study were pre-defined per protocol. This article reports data from this paediatric study with the aim of characterising the real-world long-term effectiveness of all AIT products prescribed in a large public health system to children with AR, with or without pre-existing asthma.

2 | Methods

2.1 | Study Design and Dataset

The methods, pre-specified analyses and findings of the main REACT study (ClinicalTrials.gov identifier: NCT04125888) and subgroup analyses have been published previously (see Appendix S1 for a brief overview) [19, 21–22]. The study was based on a publicly accessible and independently maintained German health insurance database, which is neither proprietary nor pharmaceutical-owned. These health insurances cover 90%–95% of the population and are public, meaning they are paid for by the government. The database is maintained and accessed by public organisations. This ensured a high degree of transparency, reproducibility and real-world relevance. As the REACT study was a retrospective analysis of anonymized administrative data, informed consent was not required.

This paediatric sub-study was based on a pre-specified, protocol-defined cohort of 11,036 children (< 18 years) with AR, with or without asthma, from the main REACT study, and followed a strict per-protocol approach [19]. In the AIT cohort, 97.5% of children were treated with single allergen treatment [22]. The AIT children were matched 1:1 to a control group of children with AR who had not been prescribed AIT, using propensity score matching, to adjust for confounding factors and to provide a minimally biased estimate of treatment effect [19]. Subjects for whom no suitable match was found were excluded from the study [19]. In this sub-study, matched AIT and control subjects from the main REACT paediatric cohort were divided into two sub-cohorts based on the presence or absence of pre-existing asthma at the index date, without rematching. This resulted in three cohorts for analysis: (1) the main paediatric cohort, (2) the AR with pre-existing asthma sub-cohort, and (3) the AR without pre-existing asthma sub-cohort. Additionally, the asthma sub-cohorts were stratified by age at the index date, also without rematching: (1) younger children (0–11 years); (2) adolescents (12–17 years). Due to not being rematched, differences in subpopulation sizes were expected.

2.2 | Outcomes

Effectiveness outcomes were pre-specified in the study protocol and evaluated using a per-protocol approach. The primary outcome was the change in the number of AR prescriptions per subject from the pre-index year (baseline) to each follow-up year (Years 1–9) in the main paediatric cohort. The pre-index

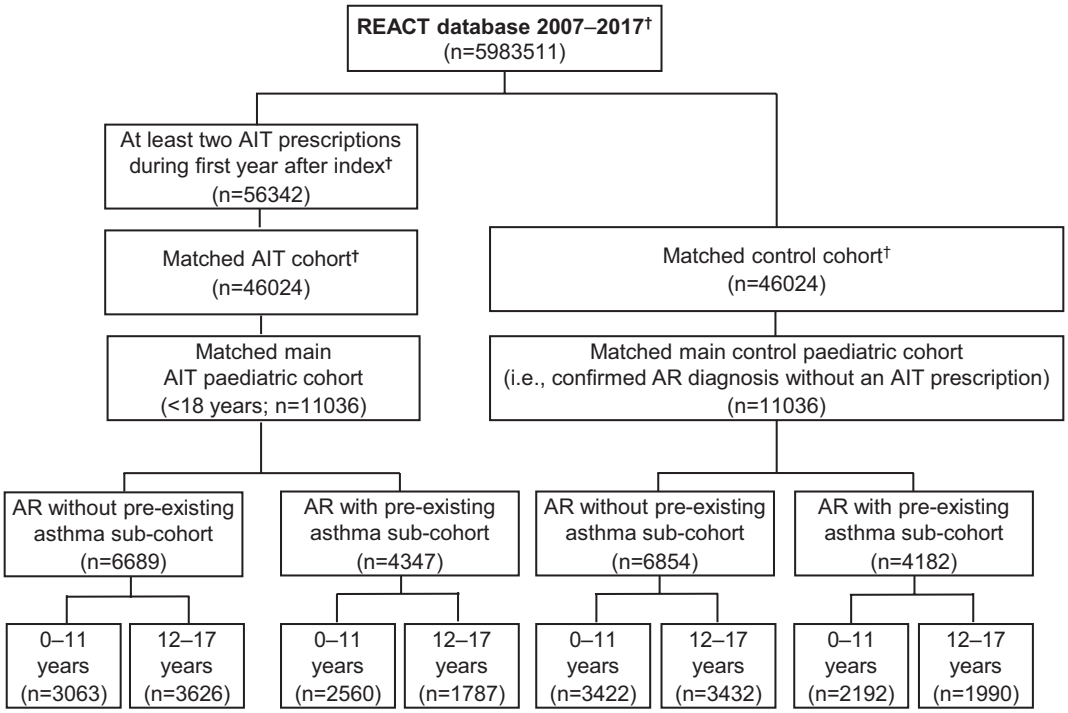

FIGURE 1 | Main paediatric cohort (pre-defined per protocol) and asthma sub-cohorts from the REACT database. †Previously published data [19]. AIT subjects in the main paediatric cohort were matched 1:1 with non-AIT control subjects from the main REACT study. Matched subjects were divided into two sub-cohorts based on the presence or absence of pre-existing asthma at the index date, without rematching. Asthma sub-cohorts were stratified by age at the index date, without rematching. AIT, allergen immunotherapy; AR, allergic rhinitis; REACT, REAl-world effeCtiveness in allergy immunoTherapy.

year was defined as the year prior to AIT initiation (for the AIT group). In children with pre-existing asthma, changes in asthma prescriptions and the number of severe asthma exacerbations (see definition in Appendix S1) were also assessed.

2.3 | Statistical Analysis

All statistical analyses followed the study's pre-specified, per-protocol design. Outcomes were assessed as absolute and relative changes in AR prescriptions per subject from baseline (pre-index year) to each follow-up year, both within and between groups (AIT vs. controls) (see Appendix S1). A linear mixed-effects model with fixed effects for group, follow-up year, and their interaction, plus a random intercept for individuals, was used to evaluate outcomes. Subgroup analyses for pre-existing asthma included asthma status and its interactions as fixed effects. Age-based subgroup analyses used a similar model, replacing asthma status with age group (younger children vs. adolescents). Identical models were applied to the asthma sub-cohort after appropriate sub-setting. All models were pre-defined based on data structure and summary characteristics.

The absolute change in the number of prescriptions per follow-up year and the corresponding between-group *p*-values reported were derived from the models used in the analyses. Specifically, after fitting the model, we used emmeans (Version 1.8.2) to estimate group means across follow-up years and then performed contrast tests to compare AIT-treated versus control groups at each time point, providing both estimated differences and corresponding *p*-values. To mitigate the gradual reduction in sample size over time, reported data were truncated if the number of subjects in a subgroup was fewer than 200 in any follow-up year.

A sensitivity analysis evaluated severe asthma exacerbations and, more specifically, those defined by new oral corticosteroid prescriptions in subjects with pre-existing asthma. Numerical data were converted into a binary classification (Yes/No) to highlight shifts in the presence or absence of exacerbations, rather than changes in absolute counts.

All statistical analyses were performed in R (Version 4.2.2) using lme4 (Version 1.1–30) and emmeans (Version 1.8.2).

2.4 | Role of the Funding Source

This study was funded by ALK-Abelló, Hørsholm, Denmark, who assumes overall responsibility for the trial and has been involved in trial design and conduct, data analysis and interpretation.

3 | Results

Figure 1 presents a breakdown of the number of subjects (AIT and controls) forming the main paediatric cohort and asthma sub-cohorts, including stratification by age.

Baseline demographics and clinical characteristics are presented in Table 1 (and according to age in Table S1). In the main

TABLE 1 | Key baseline demographics for the main paediatric cohort and pre-existing asthma sub-cohort.

Main paediatric cohort overview (matched)[a]		
	AIT (*N* = 11,036)	**Control (*N* = 11,036)**
Mean age, years (SD)	11.4 (3.3)	11.0 (4.1)
Median age, years (IQR)	11 (9–14)[b]	11 (8–14)
Sex[c]		
Male	6855 (62.1%)[b]	7147 (64.8%)
Female	4181 (37.9%)	3889 (35.2%)
Age group		
Children (0–11 years)	5623 (51.0%)[b]	5614 (50.9%)
Adolescents (12–17 years)	5413 (49.0%)[b]	5422 (49.1%)
Key comorbidities		
Asthma	4347 (39.4%)	4182 (37.9%)
Eczema	3221 (29.2%)	3641 (33.0%)
Duration of AIT treatment, mean (SD)		
Days on index AIT[d]	559.1 (271.2)	—
Days on any AIT	844.9 (453.1)	—
AR prescriptions, mean (SD)		
Any	1.7 (2.1)	1.7 (2.3)
AH	0.8 (1.4)	0.8 (1.4)
INCS	0.4 (0.8)	0.3 (0.8)

Pre-existing asthma sub-cohort overview		
	AIT (*N* = 4347)	**Control (*N* = 4182)**
Asthma prescriptions, mean (SD)[e]		
Any	3.4 (3.4)	3.1 (3.7)
SABA	1.4 (1.6)	1.3 (1.7)
ICS	0.9 (1.4)	0.8 (1.4)
ICS + LABA	0.7 (1.5)	0.6 (1.4)
Severe asthma exacerbations[f], mean (SD)		
All exacerbations	0.3 (0.6)	0.2 (0.6)
Emergency department visits	0.01 (0.1)	0.01 (0.2)
Hospitalisations	0.08 (0.4)	0.03 (0.2)
New oral corticosteroid prescriptions	0.2 (0.5)	0.1 (0.5)
Lower respiratory tract infections, mean (SD)		
Pneumonia diagnosis	0.07 (0.3)	0.08 (0.4)
Antibiotics prescription	0.05 (0.4)	0.06 (0.4)

Note: Data are *n* (%), unless otherwise stated.
Abbreviations: AH, antihistamine; AIT, allergen immunotherapy; AR, allergic rhinitis; BKK, Betriebkrankenkasse; ICD-10-GM, International Classification of Diseases, German Modification; ICS, inhaled corticosteroid; INCS, intranasal corticosteroid; IQR, interquartile range; LABA, long-acting β2-agonist; PSM, propensity score matching; SABA, short-acting β2-agonist; SD, standard deviation.
[a]AIT and control subjects in the main paediatric cohort were matched using PSM.
[b]Previously published data [22].
[c]Sex of subjects was obtained from the BKK database [19]; data were collected during subject visits to a primary or secondary healthcare setting.
[d]Index AIT was defined as the first AIT (excluding venom AIT) prescribed during the study period [19].
[e]Data presented for the mean of the baseline in follow-up Year 1.
[f]A severe asthma exacerbation was defined as: (1) a new oral corticosteroid prescription for an asthma diagnosis according to the ICD-10-GM (new is defined as more than 7 days since the last prescription); (2) emergency department visits based on the ICD-10-GM diagnostic code J46 for status asthmaticus; (3) hospitalisation based on the ICD-10-GM diagnostic code J45.x for asthma [19]. Unless otherwise specified, the term 'severe asthma exacerbations' represents a composite variable consisting of the three events described.

paediatric cohort, 51.0% of AIT subjects ($n = 5623/11036$) were aged 0–11 years, and 39.4% ($n = 4347/11036$) had pre-existing asthma. Overall, the number of any AR and asthma prescriptions per subject was comparable across the AIT and control groups for all cohorts. There was a higher number of short-acting β2-agonist (SABA) and inhaled corticosteroid (ICS) prescriptions in younger children compared to adolescents, but prescriptions of ICS + long-acting β2-agonist (LABA) were balanced between the age groups. Younger children also experienced a higher frequency of severe asthma exacerbations compared to adolescents.

For the main paediatric cohort, the number of AR prescriptions per subject decreased in both the AIT and control groups over the 9-year follow-up (Figure 2A; Tables S2 and S3); significantly greater reductions were observed for AIT versus controls in Years 2–8. On average, AIT-treated children showed a 9% greater reduction in AR medication use beyond the 61% for controls. Notably, in Year 3, the absolute difference between the groups was −0.08 (−0.13, −0.02; $p = 0.0114$), corresponding to a further 12% reduction for AIT relative to controls. In Year 5, the absolute difference was −0.15 (−0.22, −0.08; $p < 0.0001$), equating to a 13% greater reduction for AIT relative to controls. By Year 8, the absolute difference was −0.12 (−0.23, −0.01; $p = 0.0344$), reflecting a 16% reduction for AIT relative to controls. In children with pre-existing asthma, the number of asthma prescriptions per subject declined in both groups across the 8-year follow-up period, with more pronounced reductions in the AIT group (Figure 2B; Tables S2 and S3). On average, AIT was associated with greater reductions in asthma medication prescriptions (21% beyond 48% with controls). Between-group differences were significant during Years 2–8,

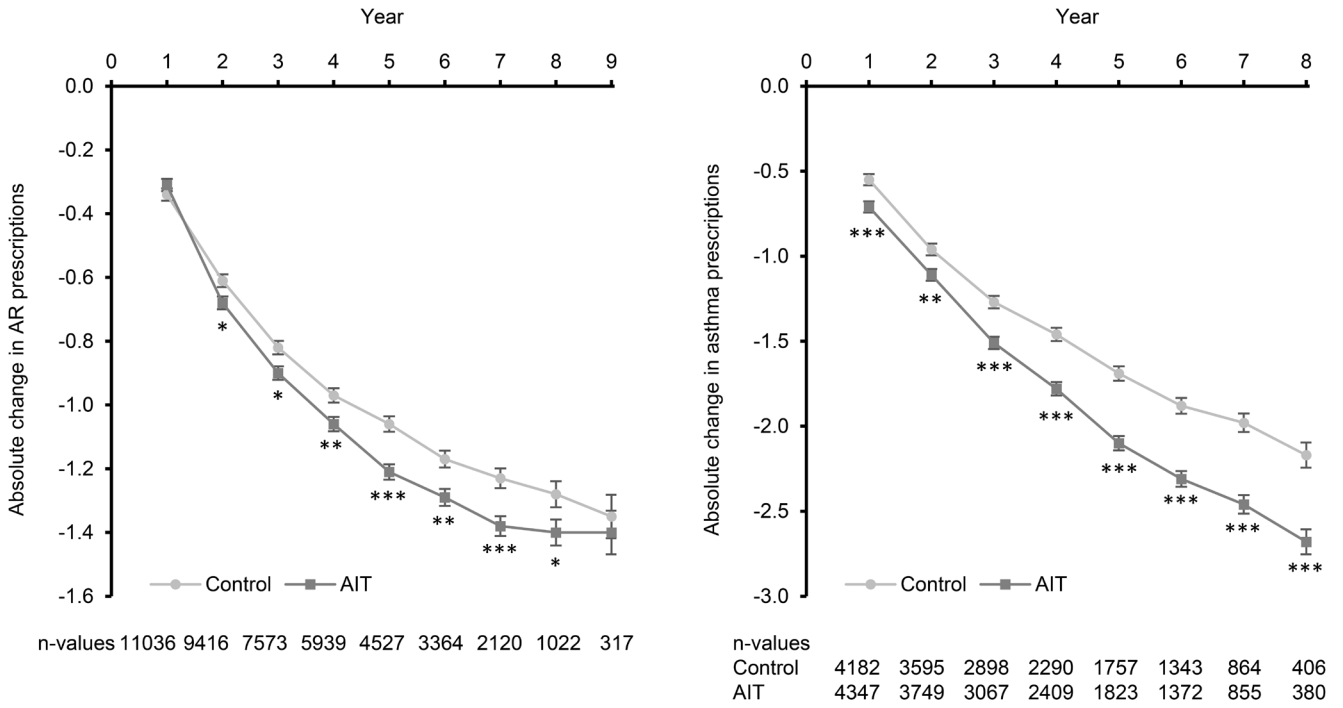

FIGURE 2 | Key outcomes: Absolute change from pre-index year in AR prescriptions overall (main paediatric cohort) and in asthma prescriptions overall (pre-existing asthma sub-cohort). (A) AR prescriptions in the main paediatric cohort. (B) Asthma prescriptions in the pre-existing asthma sub-cohort. Due to small sample size ($n < 200$), the analysis was truncated at Year 8. Data presented are mean (SE). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ versus non-AIT controls. Absolute difference (AIT minus control) with 95% CI and p-values are presented in Table S2. Mean number of prescriptions in the pre–index year for AR: AIT = 1.7, control = 1.7; for asthma: AIT = 3.4, control = 3.1. AIT, allergen immunotherapy; AR, allergic rhinitis; CI, confidence interval; SE, standard error.

with an absolute difference of −0.24 (−0.34, −0.14; $p < 0.0001$) in Year 3, corresponding to a 16% greater reduction for AIT relative to controls. In Year 5, the absolute difference was −0.41 (−0.53, −0.29; $p < 0.0001$), equating to a further 23% reduction for AIT versus controls. By Year 8, the absolute difference was −0.51 (−0.72, −0.30; $p < 0.0001$), reflecting a 22% greater reduction for AIT compared to controls.

The overall results were consistent across key drug classes for AR and asthma prescriptions (Figure 3). The AIT group showed consistently greater reductions than controls in antihistamine (AH) and INCS prescriptions per subject across Years 2–9, with significant differences at most time points (Figure 3A; Table S4). Averaged across the entire follow-up period, AIT was associated with a further 12% reduction in AH prescriptions beyond the 64% reduction observed in controls, while INCS prescriptions were reduced by an additional 28% beyond the 42% reduction in controls. In children with pre-existing asthma, the AIT group experienced significantly greater reductions in medication use than controls across the full follow-up period (Figure 3B; Table S4). Compared to controls, AIT-treated children showed a further 28% reduction in SABA prescriptions beyond the 45% reduction in controls, while ICS prescriptions decreased by an additional 10% beyond the 62% reduction observed in controls. The greatest difference in the reduction was observed for ICS + LABA prescriptions, where AIT was associated with a 62% greater reduction beyond the 19% reduction in controls, suggesting a downward shift towards ICS and SABA use (Figure 3B; Table S4).

For severe asthma exacerbations, AIT was associated with greater reductions than controls during Years 2–7, with statistically significant differences in Years 2, 4–7 (Figure 4; Table S3). Over the entire follow-up period, AIT resulted in a 21% greater reduction in severe asthma exacerbations relative to controls, in addition to the 36% reduction observed in the control group. A similar trend was observed for new oral corticosteroid prescriptions, where AIT demonstrated significantly greater reductions than controls in Years 2, and 4–7 (Figure 4; Table S3). On average, AIT led to a 33% greater reduction in new oral corticosteroid prescriptions beyond the 41% reduction observed in controls throughout follow-up.

Reductions in AR prescriptions per subject were more pronounced in younger children (0–11 years) than in adolescents (12–17 years) following AIT (Figure S1; Tables S5 and S6). Over the follow-up period, younger children showed an additional 9% reduction relative to controls, beyond the 57% reduction from baseline, while adolescents had a further 3% reduction, on top of a 63% reduction from baseline—an effect driven by greater reductions in both AH and INCS use. In AIT-treated adolescents, significant reductions in prescriptions were not observed for AH but were noted for INCS prescriptions compared to controls during Years 2–3 and 5–6, with an average additional reduction across the observation period of 16% beyond the 51% change from baseline in controls (Figure S1; Table S6). Interaction analysis has shown that the reductions in AR prescriptions were significantly greater in younger children than in adolescents; significant interactions between treatment, follow-up time, and age group were observed from Years 1–8, with t-values indicating p-values < 0.05.

For younger children with pre-existing asthma, the number of asthma prescriptions per subject reduced in the AIT and control

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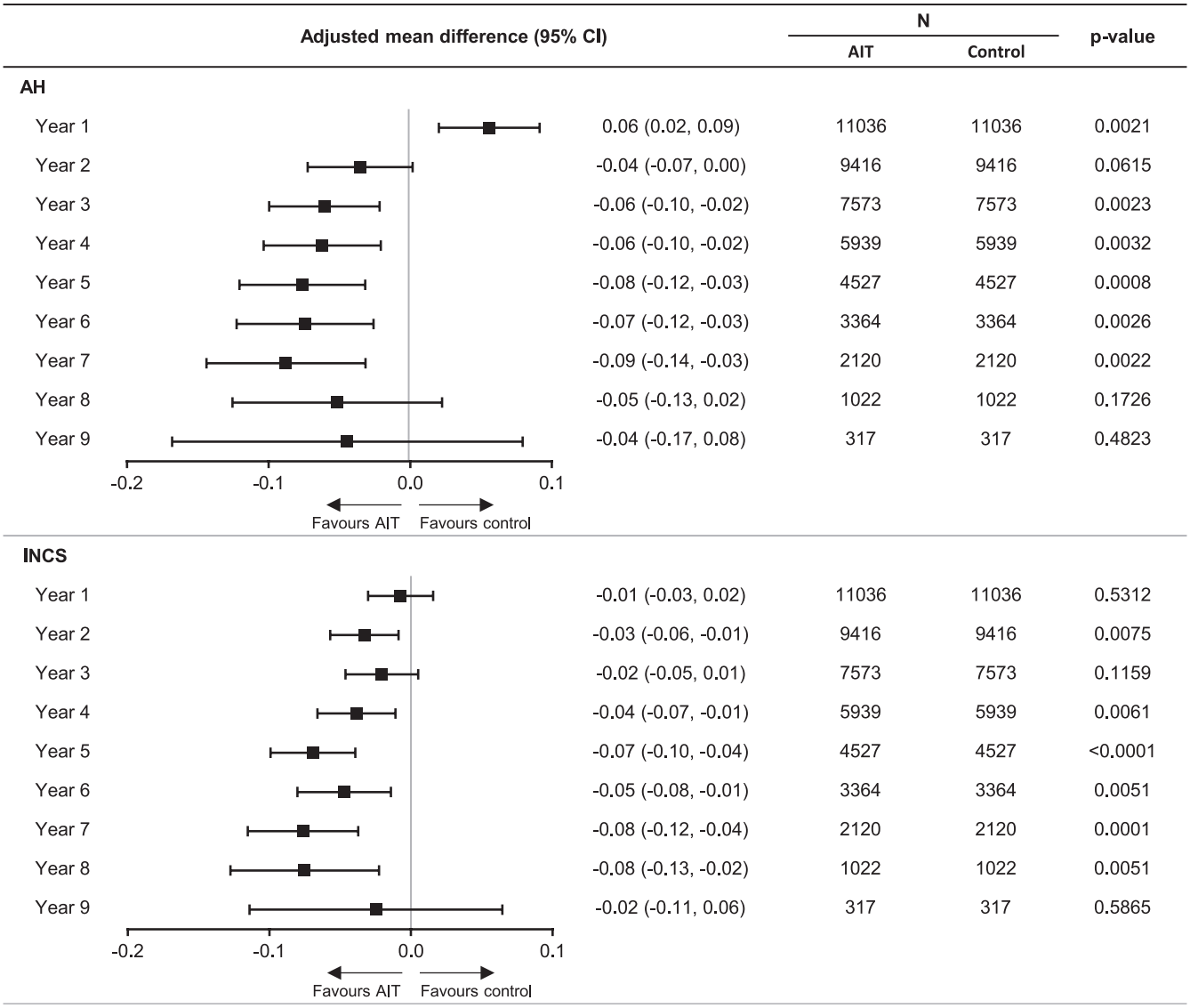

FIGURE 3 | (A) Absolute change from pre-index year in AR (main paediatric cohort) by drug class. AR prescriptions in the main paediatric cohort. Mean number of prescriptions in the pre–index year for AH: AIT = 0.8, control = 0.8; for INCS: AIT = 0.4, control = 0.3. AH = antihistamine. AIT = allergen immunotherapy. AR = allergic rhinitis. CI = confidence interval. INCS = intranasal corticosteroid. SE = standard error. (B) Absolute change from pre-index year in asthma prescriptions (pre-existing asthma sub-cohort) by drug class. Asthma prescriptions in the pre-existing asthma sub-cohort. Due to small sample size ($n < 200$), the analysis was truncated at Year 8. Mean number of prescriptions in the pre–index year for SABA: AIT = 1.4, control = 1.3; for ICS: AIT = 0.9, control = 0.8; for ICS + LABA: AIT = 0.7, control = 0.6. AIT, allergen immunotherapy; CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; SABA, short-acting β2-agonist.

groups across 8 years of follow-up, with more pronounced reductions in the AIT group, averaging an additional 10% on top of the 47% reduction observed among controls throughout the observation period (significant at Years 1 and 4–6 [Figure S2A; Table S5]). When the data were analysed by drug class, the reductions between AIT and controls were numerically greater for ICS + LABA (Years 3–7) than for ICS or SABA alone (Figure S2B–D; Table S5). In adolescents with pre-existing asthma, the AIT group had significantly greater reductions in asthma prescriptions than controls across Years 1–8, with an average additional reduction of 33% relative to controls, beyond the 49% reduction observed in controls (Figure S2A; Table S6). As with younger children, the greatest reductions between AIT and controls were observed for ICS + LABA combination therapy than for ICS or SABA alone, with significant reductions at Years 4–8 (Figure S2B–D). Across the two age categories, the data suggest a downward shift from ICS + LABA to ICS or SABA monotherapy.

Sub-cohorts with pre-existing asthma showed greater reductions from the index year in severe asthma exacerbations between the AIT and their control groups—younger children: significant difference at Years 2, 5–7; adolescents: significant difference at Years 1 and 4 only (Figure S3). Results of the sensitivity analysis showed significant and sustained reductions in severe asthma exacerbations in the AIT group compared to the control group at Years 2–7, driven by the reduction in new oral corticosteroid prescriptions (Figure S4).

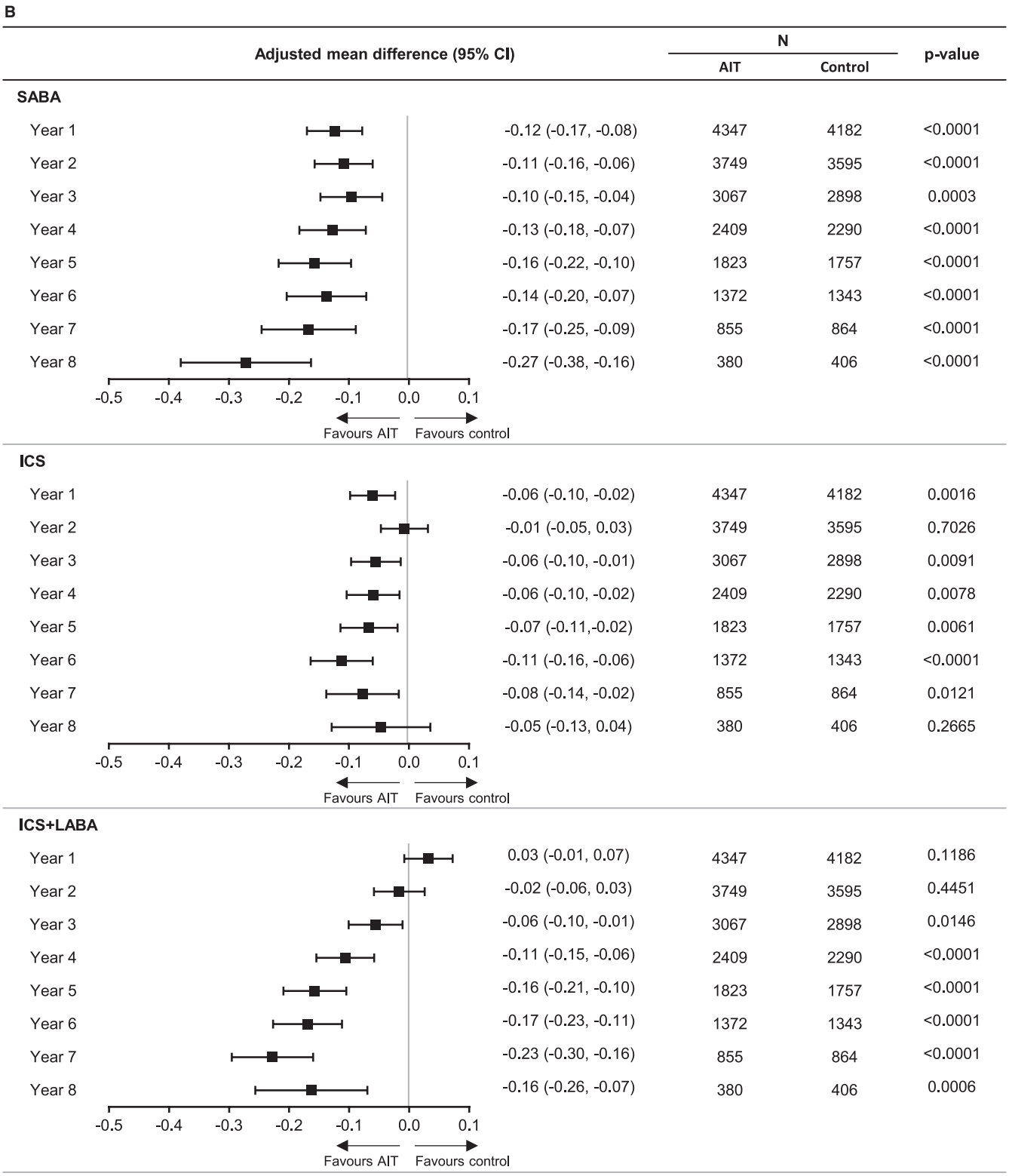

FIGURE 3 | (Continued)

4 | Discussion

To our knowledge, this pre-specified, per-protocol analysis of 11,036 children with physician-diagnosed AR, with or without pre-existing asthma, represents one of the largest real-world evaluations of AIT in paediatric patients—demonstrating sustained, long-term (up to 9 years) reductions in AR and asthma medication use, improved asthma control, and fewer asthma exacerbations compared to controls. The reduction in the use of symptom-relieving medications (AH and INCS) not only supports the findings of the REACT study [19], but also broadens the scope of the long-term evidence supporting AIT. This is further exemplified by the recent review of nine SQ-SLIT tablet randomised controlled trials (RCTs), which emphasises

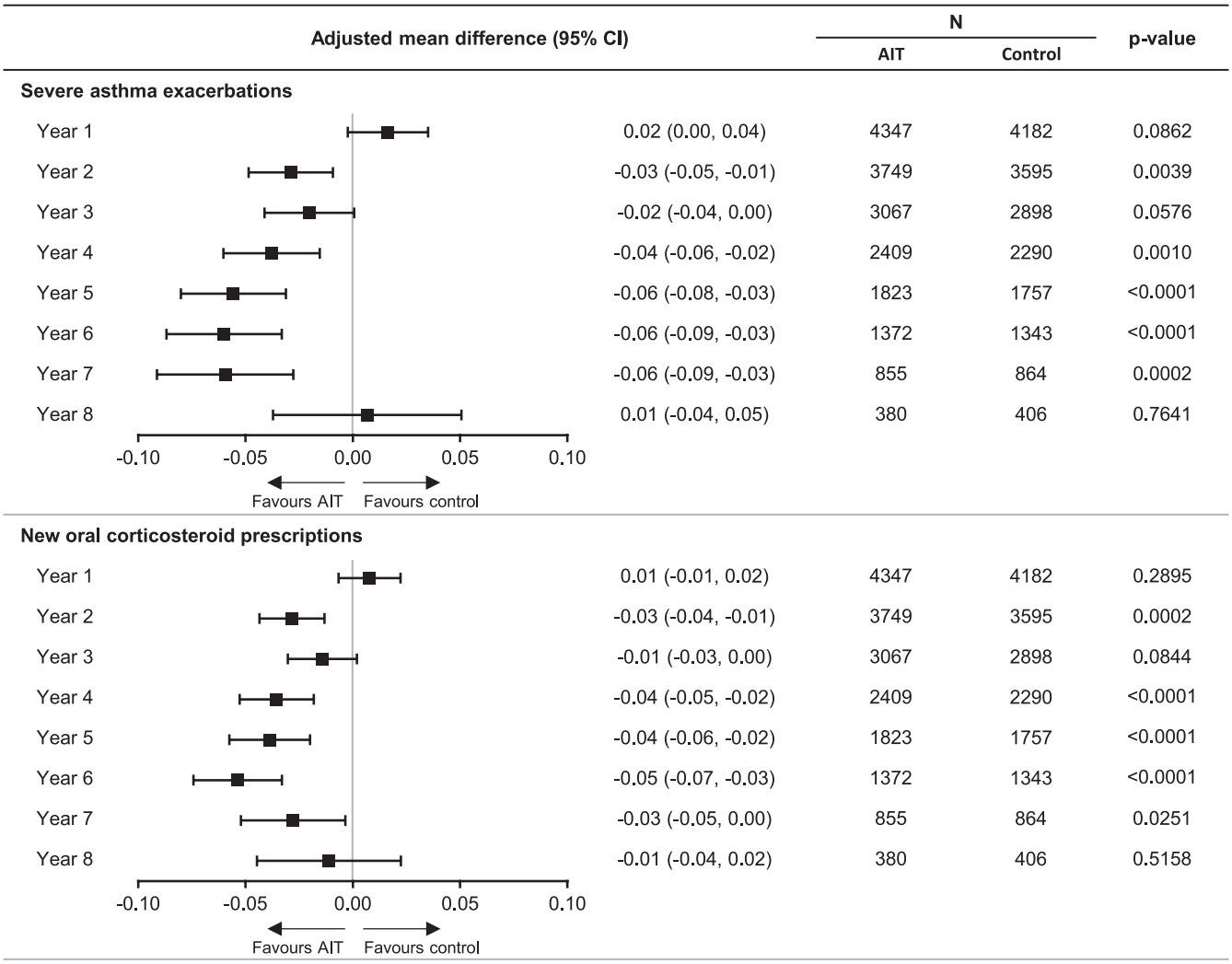

FIGURE 4 | Absolute change from pre-index year in severe asthma exacerbations and new oral corticosteroid prescriptions (pre-existing asthma sub-cohort). The new oral corticosteroid prescriptions figure has been included to show the key variable driving the reduction in severe asthma exacerbations (other variables assessed were hospitalisations and emergency department visits). Due to small sample size ($n < 200$), the analysis was truncated at Year 8. Mean number of severe asthma exacerbations and new oral corticosteroid prescriptions in the pre–index year, respectively: AIT = 0.3 and 0.2, control = 0.2 and 0.1. AIT, allergen immunotherapy; CI, confidence interval; SE, standard error.

persistent symptom management and decreased medication scores among children with AR treated with the SQ SLIT-tablets, and a lower risk of experiencing asthma symptoms/using asthma medication [13]. The real-world data also complement the findings from RCTs of AIT in adults and/or children with AR, which showed that the addition of SQ SLIT-tablets to an optimal care regimen has consistently demonstrated reductions in daily symptoms and medication scores compared to placebo—clinical trials have reported a reduction in the combined AR symptom and medication scores of up to 40% relative to placebo on top of optimised standard-of-care regimens [23–25].

In children with AR and pre-existing asthma who are treated with AIT, the data suggest improved asthma control (16%–23% greater reduction in asthma prescriptions) and a stepdown in pharmacological management of asthma (65% greater reduction in ICS + LABA), compared with controls, which support the disease-modifying effect of AIT. Of particular interest, AIT was associated with significantly greater and long-term sustained reductions in ICS + LABA use versus controls across the younger children and adolescent subgroups. These findings indicate a downward shift from combination therapy to either ICS or SABA monotherapy and, ultimately, improved asthma control, as was also shown in the main REACT analyses [19]. This downward shift resulted in younger children receiving more ICS or SABA monotherapy, thereby diminishing the disparity between the AIT and control groups in the number of prescriptions for these drugs—hence, considering our effect margins as conservative. A significant reduction in the number of asthma prescriptions between AIT and controls in adolescents (33% greater reduction than with controls), across all drug classes and for most years, was also indicative of enhanced asthma control. Consequently, AIT may contribute to improved asthma control.

Our findings from the analysis of all AIT products prescribed in a given population were further supported by recent

allergen-specific real-world data. A long-term RWE study, evaluating the efficacy of subcutaneous immunotherapy (SCIT) in children/adolescents (5–17 years) and adults, showed a 27% reduction in the risk of new-onset asthma in the AIT cohort compared to the non-AIT cohort ($p = 0.0212$), and a significantly longer time to asthma onset with AIT versus no AIT ($p = 0.001$) [26], in line with previous data in adults showing the benefits of AIT on reducing the risk of asthma exacerbations [14, 15]. In addition, the EfficAPSI study showed that exposure to SLIT liquid was associated with a 36% reduction in new asthma events compared to controls, with a consistent effect across different age groups (5–24 years, 44%; 25–39 years, 30%; 40–49 years, 40%; ≥ 50 years, 33%) and respiratory allergies (grasses, 44%; house dust mite, 37%) [27]. RWE studies such as these provide a valuable opportunity to obtain evidence for the preventative effect of AIT on developing asthma [26]; the RWE evidence generated to support the disease-modifying potential of AIT established in RCTs is essential for informing and shaping paediatric asthma guidelines.

A novel finding from this analysis is the marked and consistent steroid-sparing effect observed in the AIT-treated children. Compared to controls, AIT was associated with significant reductions in INCS prescriptions for AR (28% greater reduction than with controls), ICS + LABA prescriptions for asthma (65% reduction than with controls), and any new oral corticosteroid prescriptions for asthma exacerbations (33% greater reduction than with controls). A trial in adults and adolescents with stable HDM-induced asthma and concurrent ICS treatment (100–800 μg budesonide) has shown that ICS dosage was reduced by 42% from baseline, after 1 year of treatment with SQ HDM SLIT-tablets (6 SQ-HDM dose) [28]. A reduction in corticosteroid prescriptions is of considerable clinical relevance given the significant burden of repetitive and long-term corticosteroid exposure in children [29]. Aside from the safety benefits, a lower usage of ICS is also a marker of enhanced asthma control [30].

Previous research has established viral infection as a leading causative factor in the development of asthma exacerbation in younger children, accounting for up to 85% of events [31]. On this basis, the well documented efficacy of AIT in preventing asthma exacerbations has also been attributed to its ability to enhance bronchial epithelial antiviral immunity in addition to the suppression of allergic inflammation [10, 17]. Furthermore, airway remodelling that is associated with environmental factors, such as viral infections and allergies, is believed to begin very early in life, and lung function development trajectories are thought to be relatively fixed by the age of 8 years [8]. Early intervention with AIT could be a way to mitigate the risk of impaired early lung function development and, consequently, reduce the risk of asthma later in life [32]. Indeed, a RWE cohort study has reported that the prevalence of allergy and lower respiratory tract infections increased before the onset of severe asthma [33], suggesting that they may be risk indicators for severe asthma and that early intervention with AIT may lessen the likelihood of severe asthma symptoms. However, further research is warranted to confirm these findings.

There is compelling evidence for the beneficial effects of AIT treatment in younger children with AR [20]. The present analysis suggests that there could be greater effectiveness of AIT in younger children with AR than in adolescents, and that these younger children had a greater disease burden at baseline. Indeed, evidence supports that AIT may provide an enhanced prophylactic benefit against asthma onset in younger cohorts, highlighting a strategic window of opportunity in early childhood where intervention could pivotally influence the trajectory of asthma progression [20, 34]. However, the influence of the limited medication uses in adolescents at baseline, and any potential effect of poor adherence in this group, must be considered.

The strengths of this analysis lie in the design of the main REACT study, including pre-registration and pre-specification of all outcomes and statistical analyses [35]. The selection criteria were based on propensity score matching and defined criteria, which ensured a coherent selection of subjects in the AIT and non-AIT cohorts and created comparable groups. Additional strengths include a large sample size, use of a publicly accessible and independently maintained insurance database, inclusion of all prescribed AIT products, long-term follow-up, and consistent findings across follow-up years, outcomes, and cohorts. The fact that AR, asthma, and other comorbidities were diagnosed by a physician significantly enhances the validity of the outcome measurements compared to the use of surrogate markers as proxies for diagnosis, which are commonly employed in RWE studies [35].

Limitations of the analysis include uncertainty regarding the use of over-the-counter medications, including AH medications, as these treatment options may not be recorded in the claims database unless prescribed by the physician. Indeed, as children aged ≥ 12 years in Germany typically have to pay for AH medications even with a prescription (whereas children under 12 receive reimbursement) and many AH medications are available over-the-counter, parents of adolescents may be more inclined to purchase over-the-counter versions that do not require a prescription, potentially contributing to the low baseline prescription rate for AR observed in adolescents in our analysis. However, it is also important to acknowledge that the overall observed changes in medication use and symptom severity underlying the AIT and non-AIT groups could be influenced by factors such as regression to the mean [36]. Additionally, other factors, such as natural variations/regression in symptoms over time, changes in all types of environmental exposures (including allergen avoidance strategies) and in real-world medication behaviours, or spontaneous improvement in symptoms, might also have contributed to the observed changes in the non-AIT group. Indeed, although the reductions in AR and asthma prescriptions observed in the non-AIT group may seem unexpected, the pattern is consistent with existing RWE [37]. The perceived loss of effectiveness beyond Year 7 (particularly for asthma exacerbations and new oral corticosteroid prescriptions) should also be acknowledged. This is unlikely to be a true loss of effect, but rather a reflection of attrition bias and reduced statistical power resulting from small sample sizes due to patient dropout—a common characteristic of long-term RWE studies. In addition, survivorship bias may have influenced the results, as patients remaining in follow-up could differ from the original cohort. While adherence data were not included due to protocol restrictions precluding post hoc analyses, these outcomes have been published separately in a pre-defined REACT substudy

[21]. Disease recurrence is another possible factor contributing to the waning of treatment effect. However, long-term evidence suggests no sudden loss of efficacy for AIT 2 years after the end of a 3-year treatment course [38]; therefore, methodological explanations, rather than disease recurrence, are likely to be the main driver. Despite a smaller sample size in the cohorts (versus the main REACT study), the strength and consistency of the results favouring AIT support the benefits of AIT in children, particularly in younger children with pre-existing asthma.

5 | Conclusion

This subgroup analysis provides robust evidence for the long-term effectiveness of AIT in children with AR, including those with pre-existing asthma. AIT was associated with significant, sustained reductions in AR and asthma medication use and asthma exacerbations for up to 9 years following initiation. These findings indicate improved disease control and support the disease-modifying potential of AIT. Importantly, they suggest that early intervention may help prevent disease progression. Given the high burden of allergic disease in children, these results underscore the value of AIT as an effective, long-term treatment option for AR with and without asthma.

Author Contributions

All authors contributed to the study concept and design, and/or to the acquisition, analysis, or interpretation of data. C.W. conducted the literature search. C.W., T.S., A.K.S. and J.R.L. provided the resources for this analysis and the visualisation of the data. C.W. and J.R.L. supervised the study. C.W., T.S. and J.R.L. verified that the data in the publication are in line with the study report and outputs. C.W., T.S. and J.R.L. conducted the investigation and curated the data. C.W., T.S. and J.R.L. managed and coordinated the research activity planning of the study. J.R.L. accessed and verified the underlying data provided in the study report and outputs. C.W. prepared the initial draft. All authors had access to the trial data, reviewed the manuscript, revised the content, and approved the final version for submission. ALK-Abelló funded the study. The sponsor was involved in the study design and collection, analysis, and interpretation of data, as well as data checking of information provided in the manuscript. However, ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors. The authors were responsible for all content and editorial decisions, and received no honoraria related to the development of this publication. Professional medical writing and editorial support, according to Good Publication Practice guidelines, was provided by Emma Court PhD, and colleagues within Cambridge – a division of Prime (Knutsford, UK), funded by ALK-Abelló.

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Conflicts of Interest

C.W. is employed in the department of Global Research and Drug Discovery, ALK-Abelló. T.S. and A.K.S. are employees of ALK-Abelló. M.C. reports personal fees from ALK-Abelló during the conduct of the study; grants, personal fees, and non-financial support from Chiesi and GlaxoSmithKline, personal fees, and non-financial support from AstraZeneca, Boehringer Ingelheim, Novartis, and Zambon, and grants from the University of Ferrara (Italy), outside the submitted work. N.F. reports personal fees from Aimmune, Allergan, AstraZeneca, Grifols, Ipsen, MSD, Novartis, Sanofi Aventis, and Vertex, outside of the submitted work. J.R.L. is an employee of Novo Nordisk and a former employee of ALK-Abelló (at the time the work was conducted). C.P. reports grants from ALK-Abelló during the conduct of the study; grants and personal fees from Astra Zeneca, Chiesi, GSK, Novartis, Sanofi, and TEVA outside of the submitted work. B.F. reports personal fees from ALK-Abelló during the conduct of the study; speaker honorarium from Novartis and Merck Sharp & Dohme outside of the submitted work.

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 be accessed only by a permitted 3rd party (Team Gesundheit, Gesellschaft für Gesundheitsmanagement GmbH, Essen, Germany) for research purposes.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** all70085-sup-0001-AppendixS1.docx.