Received: 7 December 2023 | Revised: 8 March 2024 | Accepted: 19 March 2024

DOI: 10.1111/apa.17221

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

REVIEW ARTICLE

SQ sublingual immunotherapy tablets for children with allergic rhinitis: A review of phase three trials

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Funding information
ALK-Abelló

Abstract

Aim: To provide paediatricians with a summary of efficacy and safety of SQ sublingual immunotherapy (SLIT) tablets from phase three, randomised, double-blind, placebo-controlled trials in children and adolescents with allergic rhinitis or rhinoconjunctivitis, with and without asthma.

Methods: PubMed searches were conducted and unpublished data were included if necessary.

Results: Of the 93 publications, 12 were identified reporting 10 trials. One trial was excluded as paediatric-specific efficacy data were unavailable. The nine eligible trials evaluated grass, house dust mite, ragweed and tree SLIT tablets. Consistent reductions in allergic rhinitis or rhinoconjunctivitis symptoms and medication use were observed with SQ SLIT tablets versus placebo. In a five-year trial, sustained reduction of allergic rhinoconjunctivitis symptoms, asthma symptoms and medication use were observed with SQ grass SLIT tablet versus placebo. The number-needed-to-treat to prevent asthma symptoms and medication use in one additional child during follow-up was lowest in younger children. SQ SLIT tablets were generally well tolerated across trials.

Conclusion: Evidence supports use of SQ SLIT tablets in children and adolescents with allergic rhinitis or rhinoconjunctivitis, with and without asthma. Long-term data demonstrate disease-modifying effects of SQ grass SLIT tablet and suggest the clinical relevance of initiating allergy immunotherapy earlier in the disease course.

KEYWORDS
allergic rhinitis, asthma, paediatric, randomised controlled trials, sublingual allergy immunotherapy tablets

Abbreviations: AIT, allergy immunotherapy; CI, confidence interval; EAACI, European Academy of Allergy & Clinical Immunology; GAP, Grazax Asthma Prevention; OR, odds ratio; SCIT, subcutaneous immunotherapy; SD, standard deviation; SLIT, sublingual immunotherapy.

1 | INTRODUCTION

Globally, respiratory allergy is a highly prevalent, progressive disease that often begins in childhood.[1–4] Respiratory allergy manifests as allergic rhinitis, commonly known as 'hay fever',[4] allergic rhinoconjunctivitis and/or asthma.[5–7] This disease has a detrimental impact on the health-related quality of life of children and adolescents, with negative effects on emotional, physical and social well-being.[5–7] Allergic rhinitis in childhood is a recognised risk factor for the development of asthma in later life.[8] Asthma is present in up to 50% of children with allergic rhinitis.[9,10] The presence of asthma and other comorbidities can further increase the burden of disease.[4,11]

The management of allergic rhinitis in children often relies on symptom-relieving medication, such as antihistamines and/or intranasal corticosteroids.[9] However, symptom reduction alone neither addresses the cause of allergic disease nor halts the progression of disease severity and the development of asthma or other allergic diseases.[2,3] In contrast, allergy immunotherapy (AIT) targets the underlying cause of allergic disease and has the potential to alter the disease course.[2,3] By providing repeated standardised doses of relevant allergens, AIT induces clinical and immunological tolerance.[2,3] In time, this can provide long-term, sustained symptom control extending beyond the treatment period.[2,3] Considering these benefits, it has been proposed that AIT should be considered in childhood during the early stages of allergic disease to maximise the preventive effect on disease progression.[2,12]

The use of AIT in children is supported by European Academy of Allergy & Clinical Immunology (EAACI) guidelines.[2] The guidelines highlight the relevance of AIT for children with allergic rhinitis symptoms poorly controlled by symptom-relieving medication and recognise the potential for long-term disease-modifying effects.[2] In addition, a preventive effect on the development of asthma has been demonstrated in children receiving subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT) for grass or birch pollen allergy.[2,13,14] This effect persists beyond completion of three years of immunotherapy – the recommended treatment duration to achieve long-term and sustained effects.[2,13,14] Initiating pollen AIT at least two months or, optimally, four months prior to the pollen season is recommended to allow the development of immunological tolerance to the specific allergen.[2] Reductions in clinical symptoms and symptom-relieving medication use can be observed from the beginning of the first pollen season following AIT initiation.[2] Consequently, patient preference regarding the administration form of AIT (SCIT or SLIT) should be considered to ensure optimal adherence during the three-year treatment period.[2,15,16] SLIT can be administered in the form of drops or tablets.[2] Robust clinical evidence for SCIT and SLIT drops in paediatric populations is limited.[2] Conversely, the efficacy of SLIT tablets in children and/or adolescents with allergic rhinitis or rhinoconjunctivitis is well documented in the literature – particularly for fast-dissolving SLIT tablets, which have been evaluated in large randomised controlled trials.[14,17,18]

Key notes

- This review provides paediatricians with a summary of the evidence for SQ sublingual immunotherapy (SLIT) tablets in children and adolescents with respiratory allergy.
- In placebo-controlled, phase three trials, SQ SLIT tablets reduced symptoms and medication use, and the SQ grass SLIT tablet demonstrated disease-modifying effects, particularly in younger children.
- Evidence supports the use of SQ SLIT tablets in children and adolescents and suggests that earlier initiation may be clinically relevant.

Fast-dissolving SLIT tablets have been developed with standardised extracts of common respiratory allergens – grass, ragweed, tree (birch homologous group[19]), Japanese cedar pollens and house dust mite[18,20–23] – using a freeze-drying process (lyophilisation).[24–26] In vitro studies suggest that, compared with conventional compressed tablets, freeze-dried tablets dissolve more rapidly upon sublingual administration, allowing for complete allergen release before swallowing.[24–26] The rapid dissolution of SQ SLIT tablets may be especially relevant for children, for whom adhering to prolonged sublingual holding times can be challenging.[26]

This review summarises the clinical evidence for fast-dissolving SLIT tablets in children and/or adolescents with respiratory allergy, focusing on data from pivotal, phase three, randomised, double-blind, placebo-controlled trials.

2 | METHODS

A search of PubMed was conducted on the 27th of October 2022. The search terms comprised ((SQ SLIT tablet) OR (sublingual immunotherapy tablet)) AND (trial) AND (child*). Resulting articles were screened to identify English language publications reporting efficacy and safety results from phase three, randomised, double-blind, placebo-controlled trials of fast-dissolving SLIT tablets in children and/or adolescents aged <18 years with respiratory allergy. Information extracted from peer-reviewed publications was supplemented by other relevant publications. Unpublished data were provided by ALK-Abelló.

3 | RESULTS

A total of 93 publications were identified, of which 81 were excluded during screening: 56 did not report the results of a phase three trial,

22 did not concern a fast-dissolving SLIT tablet and 3 were not in the English language. Therefore, 12 publications reporting the results from 10 phase three trials were included.[14,17,18,27–35] Key details of the designs of the clinical trials are reported in Table S1.

The 10 trials included children and/or adolescents aged 5–17 years treated with fast-dissolving SLIT tablets. Four trials used the 75 000 SQ-T/2800 BAU grass SLIT tablet, three used the 12 SQ-HDM or 6 SQ-HDM dose of the house dust mite SLIT tablet, one used the 12 SQ-Amb ragweed SLIT tablet, one used the 12 SQ-bet tree (birch homologous group) SLIT tablet, and one used the 5000 JAU Japanese cedar SLIT tablet. SQ is the dose unit for the grass, ragweed, tree and house dust mite SLIT tablets.[20–23] SQ is a method for standardisation on biological potency, major allergen content and complexity of the allergen extract.[21–23] Efficacy data from the Japanese cedar SLIT tablet trial in patients aged 5–64 years are not available for the paediatric population alone.[18,31,32] Therefore, findings from this trial are not summarised in the present review.

3.1 | Efficacy and safety assessments

3.1.1 | Efficacy for allergic rhinitis or rhinoconjunctivitis

All trials evaluated the efficacy of SQ SLIT tablets for the treatment of allergic rhinitis. In the pollen trials, efficacy was evaluated during the peak and/or entire pollen season. Daily treatment was initiated 8–20 weeks prior to the expected start of the entire pollen season and continued throughout the season.[17,27–30]

In most trials, the primary efficacy endpoint was the total combined score, which is calculated based on a self-reported daily symptom score and daily medication score (Figure 1).[17,28–30,33–35]

Most pollen trials followed children and adolescents for a single season and house dust mite trials had a duration of one year. One long-term trial, with a five-year duration, was identified – the Grazax Asthma Prevention (GAP) trial. The GAP trial, which enrolled children with grass pollen ARC, used a visual analogue scale, instead of the daily symptom score, to assess the efficacy of the SQ grass SLIT tablet.[14] Across all trials, children and adolescents had free access to symptom-relieving medication and medication use was self-reported as part of the daily medication score.[14,17,27–30,33–35]

3.1.2 | Efficacy for concomitant asthma

In trials permitting inclusion of children and adolescents with concomitant asthma, controlled asthma was a requirement for enrolment. Five trials explored the effect of SQ SLIT tablets on pre-existing asthma.[17,27,28,30,33] Four of these trials used the asthma daily symptom score, which was calculated based on the severity of three or four symptoms: cough, wheeze, chest tightness or shortness of breath, and exercise-induced asthma symptoms.[17,27,28,33]

The GAP trial evaluated the effect of the SQ grass SLIT tablet on the risk of developing asthma as the primary outcome.[14] Children

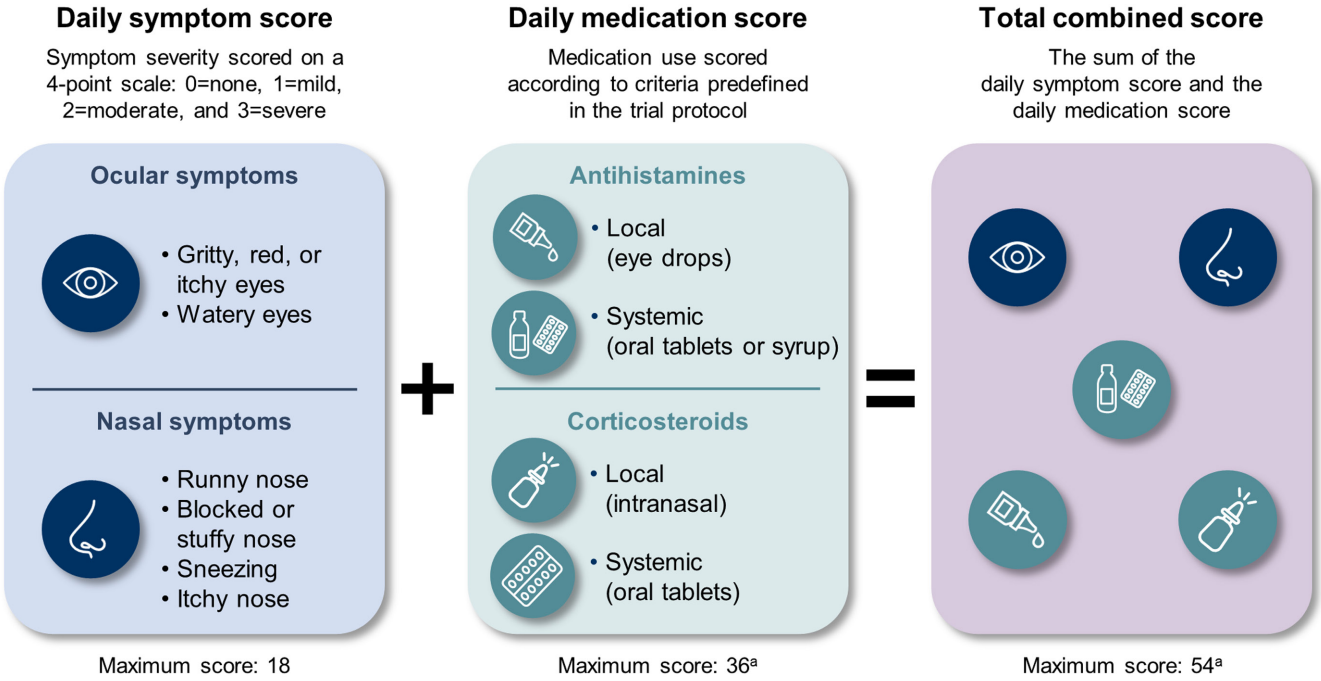

FIGURE 1 Key efficacy measures in phase three clinical trials of SQ SLIT tablets in children and adolescents with allergic rhinitis or rhinoconjunctivitis.[17,27–30,33–35] [a]Different symptom-relieving medication were permitted in individual trials. Therefore, the maximum daily medication score and total combined score varied. In the pollen trials, the severity of both ocular and nasal symptoms was scored. In the house dust mite trials, the severity of nasal symptoms only was scored and, therefore, the total combined score was defined as the total combined rhinitis score.

TABLE 1 Key baseline demographics and clinical characteristics of children and/or adolescents aged <18 years included in the trials.

Allergen	Grass				Ragweed	Tree	House dust mite		
Trial identifier	**GT-12**[27]	**P05239**[28]	**P08067**[a,29]	**GAP**[14]	**P008**[17]	**TT-04**[a,30]	**P001**[a,33]	**TO-203-3-2**[a,34]	**TO-203-3-3**[35]
Number of randomised subjects aged < 18 years (% of trial population)	253 (100)	345[b] (100)	283 (18.9)	812 (100)	1025 (100)	60 (9.5)	189 (12.8)	206 (21.8)	458[c] (100)
Age range of the child and adolescent population (years)	5–16	5–18[b]	5–17	5–12	5–17	12–17	12–17	12–17	5–17
Mean age, years (SD)	10.1 (3.0)	12.3 (3.0)	12.3 (3.3)	8.6 (2.1)	12.1 (3.2)	14.0 (1.7)	14.8 (1.7)	14.0 (1.6)	10.8 (2.9)
Male, %	66	65	49	63	63	47	41	46	66
Mean duration of allergic rhinitis or rhinoconjunctivitis, years (SD)	3.5 (2.5)	6.5 (3.6)	6.1 (3.7)	3.4 (1.9)	5.1 (3.2)	7.1 (3.2)	8.3 (3.9)	6.2 (3.4)	5.2 (3.0)
Asthma at baseline, %	42[d]	26	24	–[e]	43	44	31	–[e]	3.5
Monosensitisation, %	18	11	15	35	22	24	24	18	27
Polysensitisation, %	82	89	85	65	78	76	76	82	73

Note: Where baseline data are not available for the entire population, baseline data for the SQ SLIT tablet group only are presented. 'Tree' refers to the birch homologous group (birch, alder, hornbeam, hazel, oak and beech).[19]

Abbreviations: GAP, Grazax Asthma Prevention; SD, standard deviation; SLIT, sublingual immunotherapy.

[a]Baseline data are reported for the entire study population (adults and children and/or adolescents), except for mean age and duration of allergic rhinitis or rhinoconjunctivitis, which was calculated post hoc for the subgroup of children and/or adolescents.

[b]One patient was aged 18 years.

[c]Randomised to the 6 SQ-HDM dose of SLIT tablet or placebo.

[d]Information regarding asthma status at baseline was unavailable for two patients.

[e]Patients with asthma at baseline were excluded.

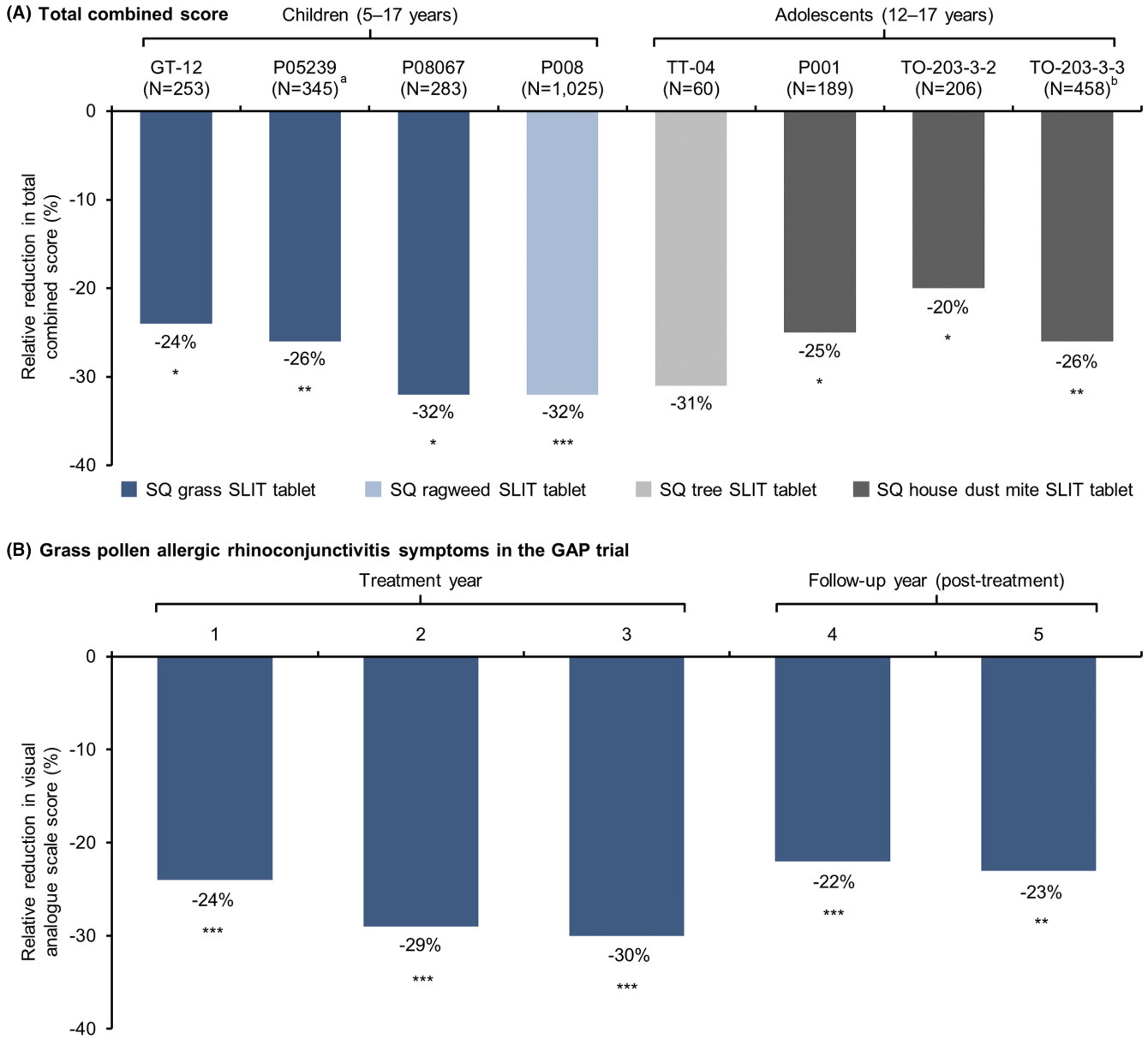

FIGURE 2 Relative reductions with SQ SLIT tablets versus placebo in (A) total combined score,[17,23,27–30,35] and in (B) grass pollen allergic rhinoconjunctivitis symptoms during the five-year GAP trial.[14] Data for Figure 2b from Valovirta et al.[14] GAP, Grazax Asthma Prevention; SLIT, sublingual immunotherapy. ***$p<0.001$, **$p<0.01$, *$p<0.05$ versus placebo. N-values in panel (a) represent the number of patients randomised. [a]One patient was aged 18 years. [b]Randomised to the 6 SQ-HDM SLIT tablet or placebo. For the pollen trials, total combined score is presented for the entire pollen season. In the house dust mite trials, the severity of nasal symptoms only was scored resulting in a total combined rhinitis score.

with allergic rhinoconjunctivitis without pre-existing asthma received blinded treatment with SQ grass SLIT tablet or placebo for three years and were monitored for a further two years after treatment completion.[14] To determine the time to onset of asthma, asthma was defined using stringent diagnostic criteria encompassing clinical symptoms, medication response, and the outcome of lung function tests.[14] The trial also investigated the development of asthma symptoms and the use of asthma medication as secondary endpoints.[14]

3.1.3 | Safety and tolerability assessments

All trials assessed the safety and tolerability of SQ SLIT tablets through unsolicited reporting of adverse events, which were assessed for severity and relation to treatment. In a ragweed trial (P008) and a house dust mite trial (P001), reports of adverse events were also actively solicited.[17,33] During the first 28 days of treatment, patients completed a SLIT report card with 15 pre-specified local allergic reactions.[17,33,36]

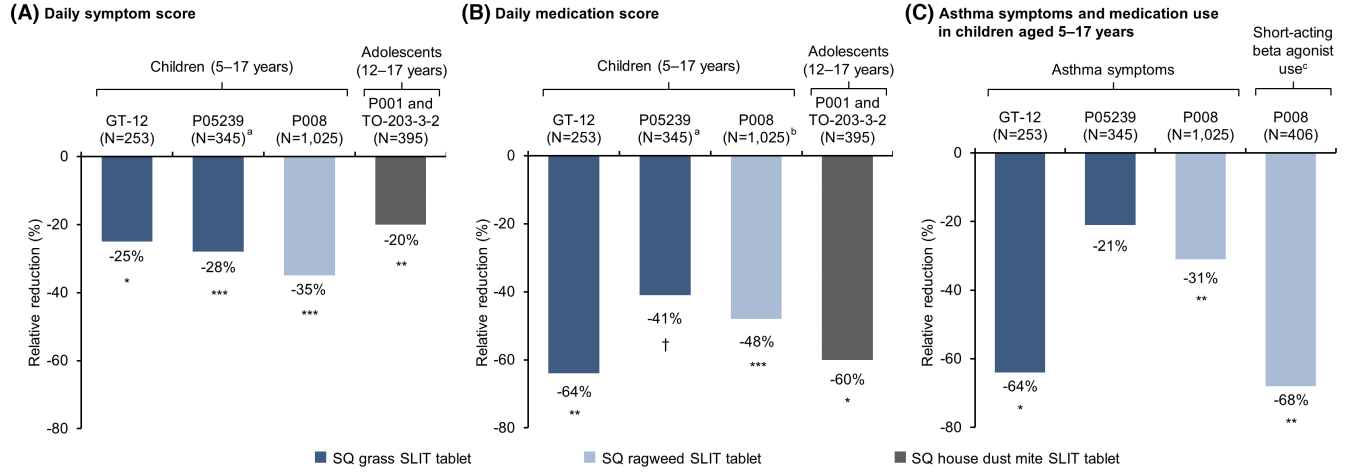

FIGURE 3 Relative reduction with SQ SLIT tablets versus placebo in (A) daily symptom score, (B) daily medication score, and in (C) asthma symptoms and medication use.[17,27,28,37] SLIT, sublingual immunotherapy. ***$p<0.001$, **$p<0.01$, *$p<0.05$, †$p=0.05$ versus placebo. *N*-values represent the number of patients randomised. [a]One patient was aged 18 years. [b]269 (58.5%) patients receiving the SQ ragweed SLIT tablet and 208 (42.7%) patients receiving placebo did not use symptom-relieving medication. Analysis for the peak season was based on the 0-inflated lognormal model. [c]Average number of daily short-acting beta agonist puffs in children with asthma. For daily symptom score and daily medication score, data for pollen trials are presented for the peak pollen season. For asthma symptoms and medication use, data are presented for the peak pollen season for P008 and the entire pollen season for GT-12 and P05239.

3.2 | Children and/or adolescent populations

Baseline demographic and clinical characteristics of the trial populations are summarised in Table 1. The mean duration of allergic rhinitis ranged from 3.4 years in the long-term grass trial (GAP trial) to 8.3 years in a house dust mite trial (P001).[14,33] Most patients were polysensitised (range 65%–89%). Of the trials that enrolled patients with asthma, the prevalence of asthma at baseline ranged from 3.5% to 44%.

3.3 | Efficacy of SLIT tablets on allergic rhinitis or rhinoconjunctivitis symptoms

SQ SLIT tablets were associated with consistent and greater reductions in total combined score versus placebo across grass, ragweed, tree and house dust mite allergies (Figure 2a, Table S2). In the trials evaluating daily symptom score and daily medication score, reductions in clinical symptoms (−20% to −35%) and the use of symptom-relieving medication (−41% to −64%) were consistently observed with SQ SLIT tablets versus placebo across the respiratory allergies (Figure 3a,b). For grass and ragweed pollen allergies, efficacy was consistent between the peak pollen season (when the pollen counts are highest) and the entire pollen season (Tables S2 and S3).

In the five-year GAP trial, significant reductions versus placebo in allergic rhinoconjunctivitis symptoms were observed during the three-year treatment period, which were sustained throughout the two-year follow-up period (Figure 2b).[14] In the fifth year, the daily use of allergic rhinoconjunctivitis symptom-relieving medication during the grass pollen season was also significantly lower with the SQ grass SLIT tablet versus placebo.[14] These findings were supported by a statistically significant increase in grass pollen-specific immunoglobulin G, class 4 with the SQ grass SLIT tablet versus placebo after the three-year treatment period and after the two-year follow-up ($p<0.001$), indicating induction of tolerance.[14]

Similarly, significant increases in allergen-specific immunoglobulin G, class 4 versus placebo were observed in children and adolescents treated with the SQ ragweed SLIT tablet ($p<0.001$) and in adolescents treated with the SQ house dust mite SLIT tablet ($p<0.01$).[17,37]

With grass or ragweed SQ SLIT tablets, symptom reductions during the peak pollen season were driven by consistent and significant reductions in all nasal and ocular symptoms versus placebo (Figure 4).[38]

3.4 | Efficacy of SLIT tablets on asthma-related outcomes

Children and adolescents with allergic rhinitis or rhinoconjunctivitis with or without asthma at baseline experienced reductions in asthma symptoms with SQ grass or ragweed SLIT tablets versus placebo (−21% to −64%) (Figure 3c).[17,27,28] With the SQ ragweed SLIT tablet, significant reductions in the daily use of short-acting beta agonist medication versus placebo (−68%) were also observed (Figure 3c).[17]

In the GAP trial, a non-significant 10% relative reduction in the primary endpoint of time to onset of asthma was observed with SQ grass SLIT tablet versus placebo: hazard ratio (95% confidence interval) 0.9 (0.57–1.43).[14] The proportion of children experiencing asthma symptoms or using asthma medication remained lower and more stable with the SQ grass SLIT tablet versus placebo overall, during the summer, and from the third winter(Figure 5).[14]

Post hoc analysis showed that the number-needed-to-treat with SQ grass SLIT tablet to prevent one additional child

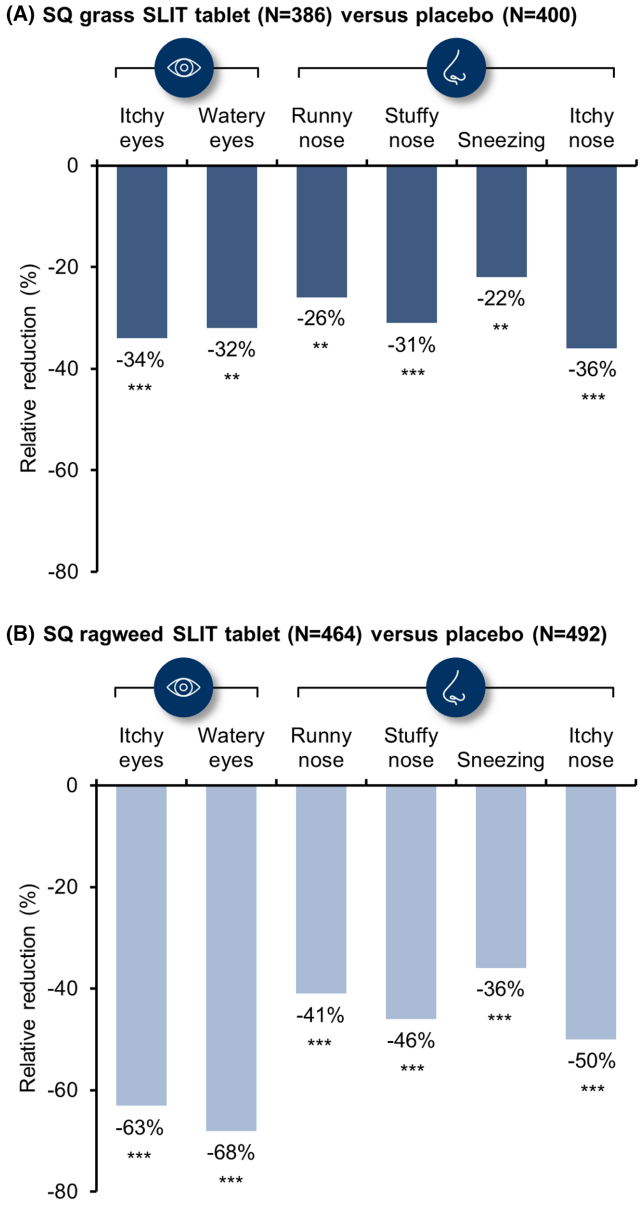

FIGURE 4 Relative reductions versus placebo in nasal and ocular symptom scores during the peak pollen season in children and adolescents (5–17 years) treated with (A) SQ grass SLIT tablet and (B) SQ ragweed SLIT tablet.[38] SLIT, sublingual immunotherapy. ***$p < 0.001$, **$p < 0.01$ versus placebo. Data for SQ grass SLIT tablet are pooled from GT-12, P05239, and P08067. Data for SQ ragweed SLIT tablet are from P008.

developing asthma symptoms and using asthma medication during the two-year follow-up increased with age.[14] The number-needed-to-treat was six in children aged five years and 20 in children aged 12 years.[14]

3.5 | Safety and tolerability of SLIT tablets

The most common treatment-related adverse events associated with SQ SLIT tablets were local application site reactions affecting the mouth, throat and ear (Table S4).[14,17,27,37] The majority of treatment-related adverse events were mild or moderate in severity, with a low incidence of severe events (1%–3%) (Figure 6).[14,27,37] In most cases, local events occurred shortly after the first administration of SQ SLIT tablets (in the first few days) and were transient, typically resolving within one to two weeks.[14,17,27,28] For local reactions that occurred on the first day of treatment, the median duration of symptoms was 10.5–25.0 min.[17] The frequency and pattern of adverse events was similar for children with grass or ragweed allergic rhinitis or rhinoconjunctivitis with and without concomitant asthma.[17,27]

In general, there was a low incidence of serious treatment-related adverse events with SQ SLIT tablets (range 0%–2%),[14,17,27,28,37] and a low incidence of discontinuation due to adverse events (range 3%–10%).[14,17,27,28,37] Of the 3631 children and/or adolescents randomised in the trials, only one event of adrenaline administration in association with a treatment-related adverse event was reported.[28] The patient experienced moderate event with SQ grass SLIT tablet comprising lip angioedema, slight dysphagia, and intermittent cough, which was not considered a systemic reaction.[28] Following adrenaline administration, the symptoms resolved and the patient recovered.[28] There were no deaths, and no cases of anaphylactic shock related to SQ SLIT tablets were reported.

4 | DISCUSSION

In light of the high prevalence of respiratory allergy in children,[1,4] paediatricians are optimally positioned to educate children and their caregivers regarding the benefits and tolerability of AIT.[39] Paediatric guidelines from EAACI and the German Society of Allergy and Clinical Immunology recommend using standardised AIT products with documented evidence of clinical efficacy and safety in paediatric populations.[2,40] Consequently, to adhere to this guidance and provide the best possible care for children with allergic rhinitis, clinicians should keep up-to-date with the latest clinical evidence. In this review, nine phase three, randomised, placebo-controlled trials involving more than 3600 children and adolescents evaluated the efficacy and safety of fast-dissolving SQ SLIT tablets.[14,17,27–30,33–35]

Across the trials, SQ SLIT tablets were associated with consistent reductions in allergic rhinitis or rhinoconjunctivitis symptoms and symptom-relieving medication versus placebo (Box 1). Since children and adolescents had free access to symptom-relieving medication, the clinical benefits with SQ SLIT tablets occurred in addition to existing pharmacotherapy. This suggests that the use of SQ SLIT tablets is instrumental in achieving long-term symptom control. Furthermore, the efficacy outcomes for all trials show at least a 20% difference with SQ SLIT tablets versus placebo, meeting the criterion for clinical relevance outlined by the World Allergy Organization.[41] The recently completed paediatric phase three trials of the SQ house dust mite SLIT tablet (NCT04145219; EudraCT 2019–000560-22) and the SQ tree SLIT tablet (NCT04878354;

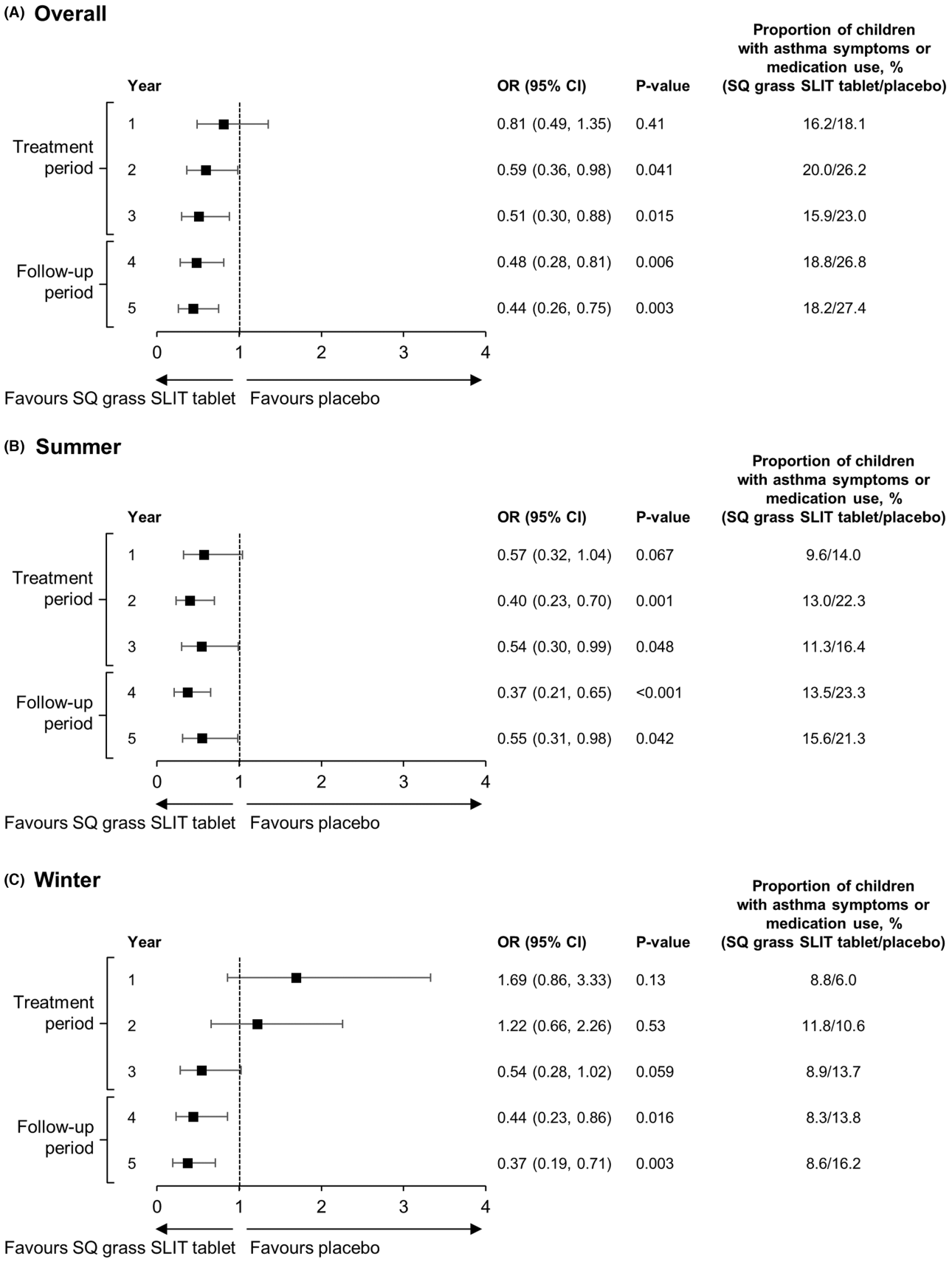

FIGURE 5 Likelihood of experiencing asthma symptoms or using asthma medication in children treated with SQ grass SLIT tablet versus placebo during the five-year GAP trial (A) overall, (B) in the summer and (C) in the winter.[14] CI, confidence interval; OR, odds ratio; SLIT, sublingual immunotherapy. Includes data from Valovirta et al.[14] SQ grass SLIT-tablet, $N = 398$; placebo, $N = 414$.

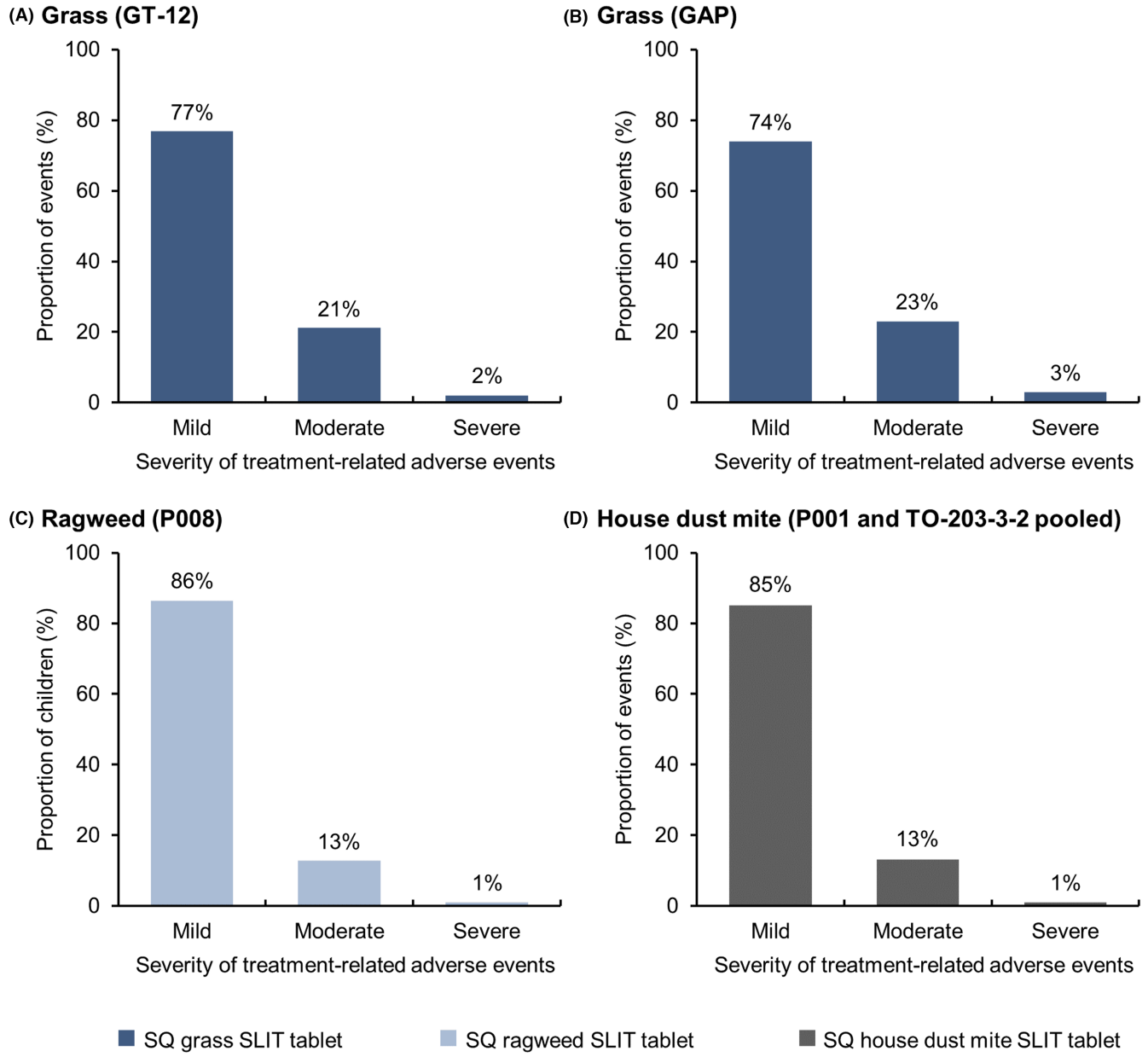

FIGURE 6 Severity of treatment-related adverse events with SQ SLIT tablets across clinical trials in (A, B) grass and (C) ragweed allergic rhinoconjunctivitis (children aged 5–17 years) and (D) in house dust mite allergic rhinitis (adolescents aged 12–17 years).[14,17,27,37] The severity of treatment-related adverse events with SQ SLIT tablets is presented as a proportion of events for GT-12, GAP, and P001 and TO-203-3-2 pooled, and as a proportion of children with ≥1 event for P008. GAP, Grazax Asthma Prevention; SLIT, sublingual immunotherapy.

EudraCT 2020–004372-17) further strengthen the evidence base in this population.[42,43]

In addition to benefits in the first year of treatment, the five-year GAP trial demonstrated the long-term, disease-modifying effects of the SQ grass SLIT tablet in children.[14] Significant reductions in allergic rhinoconjunctivitis symptoms extending beyond the three-year treatment period were documented and, in the fifth year, medication use was significantly lower with SQ grass SLIT tablet versus placebo.[14]

SQ SLIT tablets may have additional clinical benefits for children with well-controlled asthma. Exploratory outcomes showed that children experienced fewer asthma symptoms and a reduction in asthma medication use.[17,27] However, as with other forms of AIT, SLIT tablets are contraindicated in children with a recent history of severe and/or uncontrolled asthma.[2] Further research is needed in this area, including trials specifically designed to evaluate asthma outcomes.[2,40]

Data from the GAP trial suggest that initiating AIT earlier in the course of disease may be clinically relevant. The number-needed-to-treat with the SQ grass SLIT tablet to prevent one additional child developing asthma symptoms or requiring asthma medication was lowest in younger children, indicating a higher chance of preventing asthma symptoms and use of asthma medication when treatment is initiated earlier.[14] These clinical benefits are cited in EAACI guidelines.[2]

BOX 1 Key messages

- Evidence from phase three, randomised, placebo-controlled trials supports the use of fast-dissolving SQ SLIT tablets in clinical practice for children and adolescents with grass and ragweed allergic rhinitis or rhinoconjunctivitis and for adolescents with house dust mite allergic rhinitis.
- The GAP trial demonstrated long-term, disease-modifying benefits of SQ grass SLIT tablet in children, with reductions in allergic rhinoconjunctivitis symptoms, and in asthma symptoms and medication use, extending beyond the three-year treatment period.
- Initiating AIT earlier in the course of allergic rhinitis may be clinically relevant. In the GAP trial, fewer younger children needed to be treated with SQ grass SLIT tablet to prevent one additional child developing asthma symptoms compared with older children.
- SQ SLIT tablets are generally well tolerated by children and adolescents with allergic rhinitis or rhinoconjunctivitis, with or without asthma. Local application site reactions are most common and are, typically, transient.

Moreover, earlier initiation of AIT may have economic benefits, with lower healthcare costs anticipated with earlier than later initiation.[44] Long-term data have also been generated for SQ grass and tree pollen SCIT in children,[13] and for the Japanese cedar SLIT tablet,[18] supporting the disease-modifying role of AIT in children. However, despite its reported benefits in children with allergic rhinitis that is poorly controlled by symptom-relieving medication,[45] AIT is underutilised in the paediatric population.[11] AIT is often initiated only when the allergic disease has progressed and comorbidities, such as asthma, have developed.[11] To ensure optimal management and reduce the burden of allergic disease, physicians could consider initiating AIT earlier in the disease course in eligible children.[11,12]

Overall, SQ SLIT tablets were well tolerated by children and adolescents with allergic rhinitis or rhinoconjunctivitis, with and without concomitant asthma, and similar safety profiles were observed across the trials. These findings are consistent with the results of a recent, open-label safety trial in 253 adolescents with house dust mite allergic rhinitis or rhinoconjunctivitis treated with SQ house dust mite SLIT tablet.[46] Furthermore, as suggested by previous safety analyses, the safety profiles of SQ SLIT tablets are comparable in children, adolescents, and adults.[47,48] According to the European Medicines Agency, orodispersible dosage forms are a preferred route of administration in children.[49] Studies have also demonstrated a significant preference for SLIT tablets versus SCIT among caregivers of children with allergic rhinitis.[15,16] These findings are supported by a recent systematic review and meta-analysis of SLIT drops and tablets versus SCIT in children with allergic rhinitis.[50] Whilst acknowledging the limited availability of head-to-head studies of SLIT and SCIT and the heterogeneous evidence base, the analysis suggested that SLIT may be superior to SCIT in terms of treatment-related adverse events, potentially making it a more favourable choice in paediatric populations.[50]

In the present review, the most common treatment-related adverse events were local reactions, such as oral pruritus and throat irritation, which are an expected consequence of administering the SLIT tablet under the tongue in a sensitised individual.[47,51] Crucially, the trials found that local reactions tended to occur soon after SQ SLIT tablet administration, were mostly mild to moderate in severity and were of short duration. These findings are in line with observations from a small number of trials of non-SQ SLIT tablets that included children and/or adolescents with allergic rhinitis.[52–54] To optimise adherence to AIT, it is important to communicate the features of local reactions, as well as the potential benefits of treatment, to the caregiver and the child or adolescent.[55] In clinical practice, administering an antihistamine tablet prior to SLIT tablet administration may be considered to mitigate potential local allergic reactions.[56]

5 | CONCLUSION

Existing data support the efficacy and tolerability of fast-dissolving SQ SLIT tablets in children and adolescents with grass and ragweed allergic rhinitis or rhinoconjunctivitis and in adolescents with house dust mite allergic rhinitis, in line with paediatric guidelines.[2,40]

AUTHOR CONTRIBUTIONS

Peter Csonka: Conceptualization; writing – review and editing. **Eckard Hamelmann:** Conceptualization; writing – review and editing. **Mirjana Turkalj:** Conceptualization; writing – review and editing. **Graham Roberts:** Conceptualization; writing – review and editing. **Douglas P. Mack:** Conceptualization; writing – review and editing.

ACKNOWLEDGEMENTS

Professional medical writing and editorial support was provided by Laura Upstone and her colleagues at Cambridge – a division of Prime, Knutsford, UK – funded by ALK-Abelló according to Good Publication Practice guidelines.

FUNDING INFORMATION

This review was funded by ALK-Abelló. The sponsor reviewed the article for scientific accuracy. However, the ultimate responsibility for the opinions, conclusions, and data interpretation lies with the authors.

CONFLICT OF INTEREST STATEMENT

Péter Csonka reports consultation fees from ALK-Abelló, Thermo Fisher Scientific, Orion Pharma, Sanofi, Nutricia, and GSK. Eckard Hamelmann is Vice President of the German Allergy Society (DGAKI), President of the German Asthma Net

(GAN e.V.), has received grants from the German Ministry of Education and Research (BMBF), Network University Medicine (NUM), Ministry of Health and Social Affairs of Nordrhein-Westfalen (MAGS), and Federal Joint Committee (G-BA), and has received fees for lectures and consulting activities from Abbvie, AImmune, ALK-Abelló, Allergopharma, AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, DBV, GSK, Leti Pharma, Novartis, Nutricia, nutrimmun, Sanofi, and Stallergenes. Mirjana Turkalj reports consultation fees from ALK-Abelló. Graham Roberts was chair of the EAACI rhinoconjunctivitis immunotherapy guidelines and advisory board for ALK-Abelló. Douglas P. Mack reports consultation fees from ALK-Abelló, has spoken for ALK-Abelló, and Medexus, and is an investigator for ALK-Abelló, DBV and AstraZeneca.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Csonka P, Hamelmann E, Turkalj M, Roberts G, Mack DP. SQ sublingual immunotherapy tablets for children with allergic rhinitis: A review of phase three trials. Acta Paediatr. 2024;00:1–12. https://doi.org/10.1111/apa.17221