Abstracts & Posters

ACAAI 2019 Annual Scientific Meeting
Houston, TX, United States

ALK

CONTENTS

Dear ACAAI delegate

ALK welcomes you to the ACAAI 2019 Annual Meeting in Houston, TX.

As the world leader in allergy immunotherapy (AIT), we are proud to present a total of three abstracts. One abstract reports the primary and key secondary results from the first ever large Phase 3 trial of ragweed sublingual immunotherapy tablets (SLIT-tablet) in children and adolescents. Another abstract focuses on house dust mite (HDM) allergy, specifically the proportion of super-responders to HDM SLIT-tablet treatment evaluated in an environmental chamber challenge trial. Lastly, one abstract reports the histamine skin prick test wheal size, allergen-specific skin index, and specific IgE levels at baseline by age, sex, and geographic region subgroups using data from multiple AIT trials and a population survey.

ALK is committed to sustain, develop and disseminate AIT and anaphylaxis management worldwide.

Enjoy the congress and please join us at our stand in the exhibition area to learn more about our concepts and ongoing research activities at ALK.

Hendrik Nolte, MD, PhD
Senior Vice President
Research & Development

Skin prick test and specific IgE sensitivity across demographic subgroups and geographic regions

Bernstein DI[1], Kleine-Tebbe J[2], Andersen PS[3], Nolte H[4]
[1]Division of Immunology, Allergy and Rheumatology, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [2]Allergy & Asthma Center Westend, Berlin, Germany; [3]ALK, Hørsholm, Denmark; [4]ALK, Bedminster, NJ, USA

Introduction

Regulatory authorities have expressed concern that subgroup variations in skin prick tests (SPT) and serum allergen-specific IgE (sIgE) used as eligibility criteria for allergy immunotherapy trials could lead to population variability and possible bias. This analysis assessed if clinically important differences in SPT or sIgE exist across subgroups.

Methods

SPT responses to histamine (10 mg/mL) and sIgE at screening were collected from individuals who participated in timothy grass, ragweed, and house dust mite allergy immunotherapy trials and analyzed by age, sex, and geographic region. IRB approvals were obtained.

Results

Median (Q1, Q3) histamine wheal size was 5 (4, 6) mm for the 4-17y subgroup, 6 (5, 7) for 18-29y, 30-38y, and 39-46y subgroups, and 6 (5, 7.5) for >46y. Median (Q1, Q3) wheal size was 5.5 (4.5, 7) mm for both males and females and was 6 (5, 7.5) for the US, 5 (5, 6.5) for Canada, and 5.5 (4.5, 6.5) for Europe. Median (Q1, Q3) sIgE level was 44 (14, 109) kU$_A$/L for 4-17y, 15 (4, 38) for 18-29y, 10 (3, 26) for 30-38y, 9 (3, 23) for 39-46y, and 10 (3, 27) for >46y. Median (Q1, Q3) sIgE level was 15 (5, 43) kU$_A$/L for males, 12 (4, 38) for females, 7 (3, 18) for the US, 11 (4, 29) for Canada, and 30 (10, 83) for Europe.

Conclusion

Skin reactivity was generally lower and sIgE levels higher in children/adolescents versus adults and some statistically significant differences were observed among geographic subgroups which might be linked to regional clinical practice differences.

Abstract ID: P459
Location: Halls A3 & B3 (Level 3)
Day: 11/10, Time: 12:00 - 12:15 PM, Monitor: 10

D.I. Bernstein,[1] J. Kleine-Tebbe,[2] P.S. Andersen,[3] H. Nolte[4]

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Introduction

Regulatory authorities have expressed concern that subgroup variations in skin prick tests (SPT) and serum allergen-specific IgE (sIgE) used as eligibility criteria for allergy immunotherapy trials could lead to population variability and possible bias. This analysis assessed if clinically important differences in SPT or sIgE exist across age, sex, and geographic subgroups.

Methods

SPT responses to histamine (10 mg/mL), SPT responses to allergen, and sIgE at screening were collected from individuals who participated in 6 timothy grass, ragweed, and house dust mite sublingual immunotherapy tablet trials and in 1 cross-sectional survey conducted in 1998 (**Table 1**). Details of the trials and survey have been previously published.[1-8] Specific IgE from serum samples was measured by ImmunoCAP IgE assay (Thermo Fisher Scientific/Phadia, Uppsala, Sweden) or the ADVIA Centaur IgE antibody assay system (Siemens Healthineers, Tarrytown, NY). SPT histamine wheal size, allergen-specific skin index (SI; SPT allergen/SPT histamine, including only allergen SPT ≥3 mm), and sIgE levels were analyzed by age, sex, and geographic region subgroups. Institutional review board approvals were obtained.

Table 1. Details of data sources for SPT and sIgE subgroup analysis.

Study Identifier	Allergen for sIgE and Allergen-Specific SPT	Number of Individuals	Age Group, y	Geographic Region
Copenhagen Allergy Study 1998 (CAS 98)[1,2]	*Phleum pratense*	1216	15–41	Europe
GT-21 (Ped grass)[3]	*Phleum pratense*	758	5–12	Europe
P05238 (Adult grass)[4]	*Phleum pratense*	548		US and Canada
MT02/03 (Adult/ped HDM)	*Dermatophagoides pteronyssinus*	234		
MT02[5]			14+	Europe
MT03[6]			5–14	Europe
P05233 (Adult RW 1)[7]	*Ambrosia artemisiifolia*	566	18–50	US and Canada
P05234 (Adult RW 2)[8]	*Ambrosia artemisiifolia*	785	18–50	US, Canada, and Europe

HDM, house dust mite; RW, ragweed; sIgE, specific IgE; SPT, skin prick test.

Results

Overall, SPT histamine responses, allergen-specific SI responses, and sIgE levels were collected from 4097 children and adults; median (Q1, Q3) values for all subgroups are shown in **Table 2**. Statistically significant differences were found in the SPT histamine wheal size for children aged 4-17 years versus all other age subgroups and for individuals in the US versus Europe and Canada (all P<0.0001; **Figure 1**). No significant differences were found between males and females.

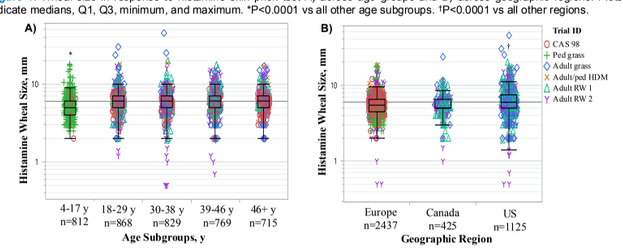
Funding: These trials were funded by ALK, Hørsholm, Denmark and Merck & Co., Inc. This analysis was funded by ALK, Hørsholm, Denmark. Medical writing and editorial assistance were funded by ALK, Hørsholm, Denmark.
Disclosure of presenting author: D.I. Bernstein has received grant support from Aimmune, ALK, Amgen, AstraZeneca, Biocryst, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Lupin, Menlo, Merck, Mylan, Novartis, Pearl, Shire, and TEVA and served as an advisor for ALK America, Gerson-Lehman, GlaxoSmith Kline, and Guidepoint Global.

Table 2. Median (Q1, Q3) SPT, allergen-specific SI, and sIgE values by subgroup.

Test	Age Group Median (Q1, Q3)					Sex Median (Q1, Q3)		Geographic Region Median (Q1, Q3)		
	4-17 y	*18-29 y*	*30-38 y*	*39-46y*	*46+ y*	*Male*	*Female*	*Europe*	*Canada*	*US*
Histamine SPT, mm	5 (4, 6)	6 (5, 7)	6 (5, 7)	6 (5, 7)	6 (5, 7.5)	5.5 (4.5, 7)	5.5 (4.5, 7)	5.5 (4.5, 6.5)	5 (5, 6.5)	6 (5, 7.5)
Allergen-specific SI	1.2 (0.9, 1.5)	1.7 (1.3, 2.2)	1.8 (1.3, 2.3)	1.7 (1.3, 2.3)	1.4 (1.1, 1.9)	1.6 (1.2, 2.1)	1.7 (1.3, 2.2)	1.2 (0.9, 1.6)	2.0 (1.6, 2.5)	1.7 (1.3, 2.3)
sIgE, kU$_A$/L	44 (14, 109)	15 (4, 38)	10 (3, 26)	9 (3, 23)	10 (3, 27)	15 (5, 43)	12 (4, 38)	30 (10, 83)	11 (4, 29)	7 (3, 18)

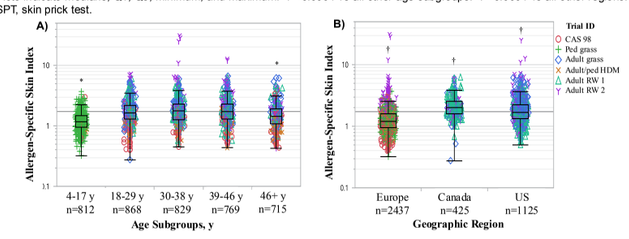
sIgE, specific IgE; SI, skin index; SPT, skin prick test.

Figure 1. Wheal size in response to histamine skin prick test A) across age groups and B) across geographic regions. Plots indicate medians, Q1, Q3, minimum, and maximum. *P<0.0001 vs all other age subgroups. †P<0.0001 vs all other regions.



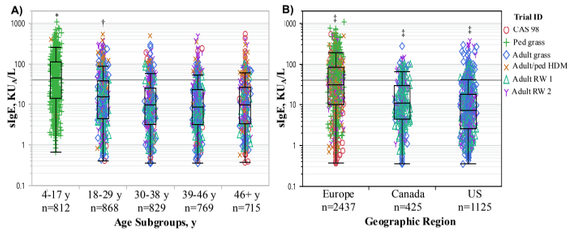
Statistically significant differences were found in the allergen-specific SI for children aged 4-17 years versus all other age subgroups, for the 46+ year subgroup versus all other age subgroups, and among all 3 geographic regions (all P<0.0001; **Figure 2**). No significant differences were found between males and females.

Figure 2. Allergen-specific skin index (SPT allergen/SPT histamine) A) across age groups and B) across geographic regions. Plots indicate medians, Q1, Q3, minimum, and maximum. *P<0.0001 vs all other age subgroups. †P<0.0001 vs all other regions. SPT, skin prick test.



Statistically significant differences were found in the sIgE levels for the 4-17 years and 18-29 years subgroups versus all other age subgroups (all P≤0.003; **Figure 3A**) and among all 3 geographic regions (all P<0.0001; **Figure 3B**). No significant differences were found between males and females.

Figure 3. sIgE levels across A) age groups and B) geographic regions. Plots indicate medians, Q1, Q3, minimum, and maximum. *P<0.0001 vs all other age subgroups. †P≤0.003 vs all other age subgroups. ‡P<0.0001 vs all other regions.



References

1. Linneberg A, et al. *Allergy.* 2000;55(8):767-772; 2. Linneberg A, et al. *J Allergy Clin Immunol.* 2000;106(2):247-252.
3. Valovirta E, et al. *J Allergy Clin Immunol.* 2018;141:529-538; 4. Nelson HS, et al. *J Allergy Clin Immunol.* 2011;127(1):72-80 e72.
5. Mosbech H, et al. *J Allergy Clin Immunol.* 2014;134(3):568-575 e567; 6. Corzo JL, et al. *J Investig Allergol Clin Immunol.* 2014;24(3):154-161; 7. Nolte H, et al. *Ann Allergy Asthma Immunol.* 2013;110(6):450-456 e454; 8. Creticos PS, et al. *J Allergy Clin Immunol.* 2013; 131(5):1342-1349 e1346.

Conclusion

Skin reactivity was marginally lower and sIgE levels higher in children/adolescents versus adults and some statistically significant differences were observed among geographic subgroups which might be linked to regional clinical practice differences in SPT methodology. Approximately one-third of the European subgroup were children, which may have skewed the results.

Super- and Low-Responders Among Subjects with Allergic Rhinoconjunctivitis Receiving House Dust Mite Sublingual Immunotherapy Tablet

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Introduction

Efficacy and safety from field trials of allergy immunotherapy products are required by the US Food and Drug Administration to obtain regulatory approval, but environmental exposure chamber (EEC) trials are useful for determining dose ranges and onset of action. The FDA considers a 20% improvement from baseline in symptom scores after allergen challenge a clinically meaningful response to allergy immunotherapy in EEC trials. The objective of this post-hoc analysis was to evaluate the proportion of super- and low-responders to house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet using data from an EEC trial.

Methods

A randomized, double-blind, EEC trial (clinicaltrials.gov identifier: NCT01644617) was conducted in adults with HDM-induced allergic rhinitis with or without conjunctivitis. IRB approval was obtained. Details and primary results from the trial have been previously published.[1] Subjects were randomized to daily doses of 12 SQ-HDM (n=42), 6 SQ-HDM (n=41), or placebo (n=41) for 24 weeks. Exposure challenges (6-hours) were conducted at screening and week 24 for the primary endpoint. The nasal symptoms runny nose, blocked nose, sneezing, and itchy nose were scored during the exposure challenges every 15 minutes on a scale of 0 to 3. The primary endpoint was the total nasal symptom score (TNSS; max=12). A post-hoc exploratory responder analysis was conducted in subjects who completed the trial (n=106). Response subgroups were defined by the percentage improvement in TNSS relative to baseline at week 24 using subjective thresholds and the FDA definition of a clinically meaningful response for EEC trials:

- ≥50% = super responder
- ≥20%-<50% = responder
- <20% = low responder (per FDA definition for EEC trials)

Odds ratios of being a super responder with active treatment versus placebo were calculated by Fisher's exact test.

Funding: This trial was funded by Merck & Co., Inc., Kenilworth, NJ, USA. The analysis was funded by ALK, Hørsholm, Denmark. Medical writing and editorial assistance were funded by ALK, Hørsholm, Denmark.
Disclosure of presenting author: Dr. Nelson serves on the Data Safety Monitoring Board for AstraZeneca.

Results

In the overall study population, the percentage improvement in TNSS relative to placebo at week 24 was 48.6% (95% CI, 35.3%, 60.2%) with 12 SQ-HDM and 26.6% (95% CI, 11.2%, 39.6%) with 6 SQ-HDM (**Figure 1**). In the responder analysis, the proportion of super responders at week 24 with 12 SQ-HDM, 6 SQ-HDM, and placebo was 61%, 36%, and 3%, respectively; the proportion of responders was 17%, 22%, and 35%, and the proportion of low responders was 22%, 42%, and 62% (**Figure 2**). The odds ratio of being a super responder was 51.9 for subjects receiving 12 SQ-HDM and 18.7 for subjects receiving 6 SQ-HDM compared with placebo.

Figure 1. Average total nasal symptom score (TNSS) during exposure challenge with house dust mite (HDM) sublingual immunotherapy tablet (12 SQ-HDM and 6 SQ-HDM doses) or placebo at week 24.

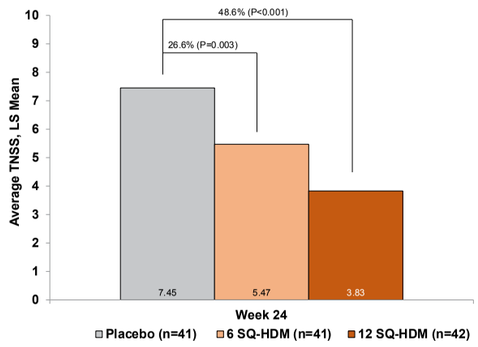
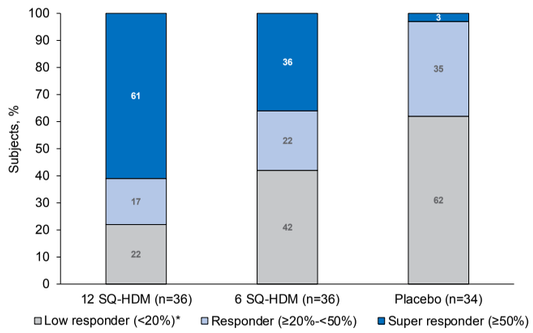


Figure 2. Responders to house dust mite (HDM) sublingual immunotherapy tablet (12 SQ-HDM and 6 SQ-HDM doses) or placebo at week 24. *Per FDA definition of clinically meaningful response in EEC trials.



Reference

1. Nolte H, et al. *J Allergy Clin Immunol.* 2015;135(6):1494-1501 e1496.

Conclusion

After 24 weeks of treatment, the majority of subjects receiving either dose of HDM SLIT-tablet were responders or super-responders.

HOUSE DUST MITE SLIT-TABLET

Abstract ID: P451
Location: Halls A3 & B3 (Level 3)
Day: 11/09, Time: 11:45 - 12:00 PM, Monitor: 10

Efficacy and Safety of Ragweed SLIT-Tablet from a Large Trial in Children with Allergic Rhinoconjunctivitis

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Introduction

Ragweed sublingual immunotherapy (SLIT)-tablet improves symptoms and decreases rescue medication use in adults with allergic rhinitis with or without conjunctivitis (AR/C) but has not been evaluated in children.[1,2] This large, international, double-blind, placebo-controlled trial evaluated the efficacy and safety of ragweed SLIT-tablet in North American and European children with AR/C.

Methods

Children aged 5 to 17 years with ragweed AR/C with or without asthma (FEV_1 ≥80% predicted) were randomized 1:1 to daily ragweed SLIT-tablet (ALK, Hørsholm, Denmark) or placebo approximately 12 to 20 weeks before the ragweed season (clinicaltrials.gov identifier: NCT02478398). Treatment continued throughout the ragweed season (approximately 8 weeks). The ragweed SLIT-tablet dose evaluated was the same as the dose approved for adults (12 Amb a 1-Unit). Institutional review board approval was obtained.

The start of the ragweed pollen season (RPS) for each study site was defined as the first day of 3 consecutive recorded days with a pollen count of ≥10 grains/m^3, and the end of the RPS was defined as the last day of the last 3 consecutive recorded days with a pollen count ≥10 grains/m^3. Peak RPS for each study site was defined as the 15 consecutive recorded days within the RPS with the highest 15-day moving average pollen count.

Participants (or parents/guardians) recorded allergy symptoms, rescue medication use, and asthma symptoms in an e-diary once-daily. Six rhinoconjunctivitis symptoms and 3 asthma symptoms were measured on a scale of 0 to 3. The primary endpoint was the average total combined score (TCS; sum of rhinoconjunctivitis daily symptom score [DSS] and rhinoconjunctivitis daily medication score [DMS]) over the peak RPS. Key secondary endpoints were the average TCS during the entire RPS, and DSS and DMS during the peak RPS. Exploratory endpoints were the average asthma DSS in all participants, average daily short-acting beta-agonist (SABA) use in participants with asthma at baseline, and average weekly number of nights with nocturnal awakenings because of asthma requiring SABA use in participants with asthma at baseline during both the peak and entire RPS. Adverse events (AEs) were monitored by questioning of the participant at each study visit and by participant recording on a SLIT Report Card during the first 28 days of treatment.[3]

Results

In all, 1025 children were randomized, 1022 received treatment, and 952 completed the trial. Baseline characteristics were well balanced between treatment groups. The majority of participants were male (62.9%) and white (93.0%); the mean age was 12.1 years and 59.9% were aged 12 to 17 years. A history of asthma was reported in 42.7% of participants and 77.7% were polysensitized.

Relative improvements in TCS with ragweed SLIT-tablet compared with placebo were −38.3% (95% CI, −46.0%, −29.7%; least square [LS] mean difference=2.73; P<0.001) during peak RPS and −32.4% (95% CI, −40.7%, −23.3%; LS mean difference=1.86; P<0.001) during the entire RPS (**Figure 1**). DSS and DMS were improved with ragweed SLIT-tablet compared with placebo by −35.4% (95% CI, −43.2%, −26.1%; LS mean difference=1.40; P<0.001) and −47.7% (95% CI, −59.8, −32.5%; LS mean difference=1.84; P<0.001), respectively, during peak RPS (**Figure 2**).

Figure 1. Total combined score (TCS) during the peak and entire ragweed pollen season (RPS) (FAS population). FAS, full analysis set; SLIT, sublingual immunotherapy.

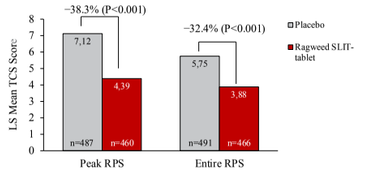
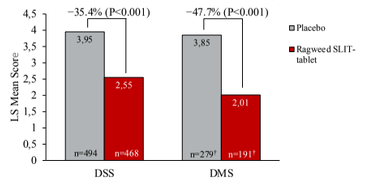
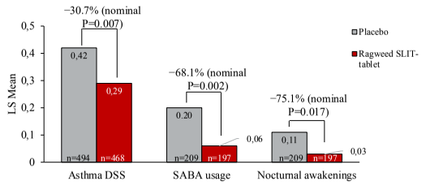


Figure 2. Daily symptom score (DSS) and daily medication score (DMS) during the peak ragweed pollen season (FAS population). †269 participants on ragweed SLIT-tablet and 208 participants on placebo had no rescue medication use. DMS analysis is based on the zero-inflated log-normal model. FAS, full analysis set; SLIT, sublingual immunotherapy.



Relative improvement in asthma DSS with ragweed SLIT-tablets compared with placebo during peak RPS was −30.7% (95% CI, −46.9%, −9.6%; LS mean difference, 0.13; nominal P=0.007). SABA use and nocturnal awakenings were improved with ragweed SLIT-tablets compared with placebo by −68.1% (95% CI, −87.6%, −39.0%; LS mean difference, 0.14; nominal P=0.002) and −75.1% (95% CI, −99.3, −35.2%; LS mean difference, 0.08; nominal P=0.017), respectively (**Figure 3**).

Figure 3. Asthma DSS (FAS population), number of daily SABA puffs (SABA usage; asthma population), and number of nocturnal awakenings because of asthma requiring SABA use (asthma population) during the peak ragweed pollen season. DSS, daily symptom score; FAS, full analysis set; SABA, short-acting beta-agonist; SLIT, sublingual immunotherapy.



Treatment was well tolerated. No deaths or events of anaphylaxis, severe ragweed SLIT-tablet-related local swellings of the mouth and/or throat, or severe ragweed SLIT-tablet-related asthma events were reported. The most common AEs related to ragweed SLIT-tablet were throat irritation, oral pruritus, and ear pruritus (**Table 1**). Discontinuation rates due to AEs were 3.9% with ragweed SLIT-tablet and 1% with placebo. Two systemic allergic reactions related to ragweed SLIT-tablet were reported (non-serious, mild skin pruritus and redness beginning on day 6 and serious moderate hypersensitivity [urticaria] on day 26). One additional participant experienced a serious AE related to ragweed SLIT-tablet (severe laryngitis on day 126 that resolved in 2 days). No participants treated with ragweed SLIT-tablet received intramuscular epinephrine.

Table 1. Treatment-related AEs reported by ≥5% of participants in either treatment group (all subjects as treated).

Treatment-related AEs, n (%)	Ragweed SLIT-Tablet (n=513)	Placebo (n=509)
Throat irritation	249 (48.5)	92 (18.1)
Oral pruritus	244 (47.6)	59 (11.6)
Ear pruritus	174 (33.9)	32 (6.3)
Lip swelling	64 (12.5)	6 (1.2)
Glossodynia	63 (12.3)	12 (2.4)
Nausea	60 (11.7)	18 (3.5)
Oral pain	60 (11.7)	16 (3.1)
Pharyngeal edema	56 (10.9)	8 (1.6)
Swollen tongue	55 (10.7)	4 (0.8)
Upper abdominal pain	48 (9.4)	22 (4.3)
Stomatitis	33 (6.4)	5 (1.0)
Enlarged uvula	32 (6.2)	2 (0.4)

AE, adverse event; SLIT, sublingual immunotherapy.

References

1. Creticos PS, et al. *J Allergy Clin Immunol.* 2013;131(5):1342-1349 e1346.
2. Nolte H, et al. *Ann Allergy Asthma Immunol.* 2013;110(6):450-456 e454.
3. Norquist J, et al. *Patient.* 2017.

Funding: This trial was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Medical writing and editorial assistance were funded by ALK, Hørsholm, Denmark.
Disclosure of presenting author: H. Nolte is an employee of ALK.

Conclusion

This is the largest allergy immunotherapy trial in children with ragweed AR/C demonstrating that ragweed SLIT-tablet significantly improves AR/C symptoms and decreases rescue medication use. Relative improvements in asthma outcomes compared with placebo were also observed. Treatment was well tolerated.

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