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Safety of sublingual immunotherapy Timothy grass tablet in subjects with allergic rhinitis with or without conjunctivitis and history of asthma

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Abstract

Background: Patients with asthma may be more susceptible to adverse events (AEs) with sublingual immunotherapy tablet (SLIT-tablet) treatment, such as severe systemic reactions and asthma-related events. Using data from eight trials of grass SLIT-tablet in subjects with allergic rhinitis with/without conjunctivitis (AR/C), AE frequencies were determined in adults and children with and without reported asthma.

Methods: Data from randomized, double-blind, placebo-controlled trials of Timothy grass SLIT-tablet MK-7243 (2800 BAU/75 000 SQ-T, Merck/ALK-Abelló) were pooled for *post hoc* analyses. Subjects with uncontrolled and severe asthma were excluded from the trials. Frequencies for treatment-emergent AEs (TEAEs), local allergic swelling (mouth or throat), systemic allergic reactions, and asthma-related treatment-related AEs (TRAEs) were calculated.

Results: Among adults (n = 3314) and children (n = 881), 24% and 31%, respectively, had reported asthma. No serious local allergic swellings or serious systemic allergic reactions occurred in subjects with asthma treated with SLIT-tablet. There was no evidence of increased TEAEs, systemic allergic reactions, or severe local allergic swellings in adults or children with asthma treated with grass SLIT-tablet versus subjects without asthma in or outside of pollen season. There were 6/120 asthma-related TRAEs assessed as severe with grass SLIT-tablet and 2/60 with placebo, without a consistent trend among subjects with and without asthma (5 and 3 events, respectively).

Conclusions: In the AR/C subjects with reported well-controlled mild asthma included in these studies, grass SLIT-tablet did not increase TEAE frequency, severe local allergic swelling, or systemic allergic reactions versus subjects without asthma. There was no indication that treatment led to acute asthma worsening.

Allergic rhinitis with or without conjunctivitis (AR/C) is a prevalent atopic condition, estimated to occur in more than 500 million people worldwide (1). Grass pollens are among the most prominent seasonal aeroallergens that may provoke AR/C and asthma (2, 3). Although many patients with grass pollen-induced AR/C rely on pharmacotherapy to manage their symptoms, allergen immunotherapy offers the potential for a long-term disease-modifying effect and an associated decreased reliance on medications that reduce symptoms (4, 5).

AR/C and asthma are closely associated. Concomitant asthma is estimated to occur in 10% to 40% of patients with

AR/C, and most patients with asthma have AR/C (1). In patients receiving subcutaneous allergen immunotherapy (SCIT), asthma is a risk factor for systemic reactions (6). The majority of fatal SCIT-related systemic reactions reported in the literature occurred in patients with poorly controlled asthma (7, 8), and thus, severe or uncontrolled asthma is a contraindication for the administration of allergen immunotherapy (4). Subsequently, safety evaluation of any allergen immunotherapy product in patients with asthma is of paramount importance.

A comprehensive review of clinical trials indicated a relatively benign adverse event (AE) profile for sublingual allergen immunotherapy (SLIT), consisting of primarily transient mild-to-moderate local application site reactions (9). Adverse events of particular interest with SLIT treatment are severe local allergic swellings that may result in upper airway obstruction, severe systemic reactions, and asthma-related events. Using pooled data from eight clinical trials, we investigated the incidence of AEs overall, as well as the AEs of main interest, in adult and pediatric subjects with AR/C and well-controlled asthma who received treatment with Timothy grass sublingual allergen immunotherapy tablets (SLIT-tablet).

Methods

Description of trials in *post hoc* pooled analyses

Data from eight trials of Timothy grass SLIT-tablet MK-7243 (2800 BAU/75,000 SQ-T *Phleum pratense p* 5, Merck & Co., Whitehouse Station, NJ, USA/ALK-Abelló, Hørsholm, Denmark) were used in this *post hoc* pooled analysis. The trials were all randomized, multicentered, double-blind, parallel group, and placebo-controlled (GT-02, GT-07, GT-08, GT-12, GT-14, P05238, P05239, and P08067). Details of study design, patient characteristics, and primary outcomes have been published previously for each study (10–17). Six of the trials were registered on clinicaltrials.gov (GT-02 and GT-07 were conducted before the availability of the public registry); identifiers were NCT00227279, NCT00408616, NCT00421655, NCT00562159, NCT00550550, and NCT01385371 for GT-08, GT-12, GT-14, P05238, P05239, and P08067, respectively. Subjects were randomized 1:1 (or 2:1 in GT-07) to receive once-daily Timothy grass SLIT-tablet or placebo before the grass pollen season and throughout the season. Study GT-02 also included doses 93 BAU and 933 BAU, which were determined not to be of clinical efficacy (14) and were excluded from the present analysis. All trials were of approximately 24 weeks' treatment duration with the exception of GT-08, which included 3 years of treatment and 2 years of post-treatment follow-up. For the present analysis, only safety data from the entire year 1 of GT-08 are included for consistency in duration with the other studies. The protocols for all studies were approved by institutional review boards from each center. All subjects or their guardians gave written informed consent.

Subjects in all trials were required to have a clinical history of physician-diagnosed grass pollen-induced AR/C with or without controlled asthma. It was a requirement that subjects had a history of medication use to treat symptoms of AR/C during the previous pollen season, forced expiratory volume in 1 s (FEV_1) ≥ 70% of predicted (FEV_1 ≥ 80% in GT-12), a positive skin prick test for *Phleum pratense* (wheal diameter ≥5 mm in North American trials or ≥3 mm larger than saline control in European trials), and a positive serum-specific IgE against *Phleum pratense* (≥0.7 kU/L). GT-07 required subjects to have a clinical history of mild-to-moderate grass pollen-induced asthma that required medication to control asthma symptoms during the last two grass pollen seasons. Subjects with severe asthma, those who required inhaled corticosteroids for asthma outside of the pollen season, those with symptomatic AR/C and/or asthma caused by an allergen(s) other than grass during the grass pollen season, or those who had a history of significant perennial AR/C and/or asthma to an allergen requiring regular medication to which the subject was regularly exposed, were excluded from all trials.

Predefined, open-label asthma rescue medications were provided for use in a stepwise manner during pollen season if prespecified asthma symptom thresholds were met. As a precaution, each subject in the three North American trials (P05238, P05239, and P08067) was supplied with self-injectable epinephrine to be used in the event of an acute severe systemic reaction.

Asthma assessments

An asthma-related AE was defined as any asthma symptom reported as an AE (asthma, dyspnea, wheezing, cough, chest tightness/discomfort). FEV_1 was assessed at preseason, peak season, and postseason in each study, except GT-12.

Safety assessments

Safety assessments included AEs summarized by treatment group and by subgroups of subjects with and without asthma. Adverse events were characterized by the investigators evaluating the subjects as mild, moderate, or severe in intensity. Causality was assessed by the investigators as probably related, possibly related, or unlikely related; treatment-related AEs (TRAEs) included those assessed as probably or possibly treatment related. AEs that were assessed as not related to treatment were designated treatment-emergent AEs (TEAEs). Any of the asthma-related AEs (defined above) that were assessed as related to treatment were designated asthma-related TRAEs. A serious AE (SAE) was any AE that met at least one of the regulatory criteria of seriousness, namely, an AE that resulted in death or was life threatening, that required prolonged hospitalization, that resulted in persistent or significant disability or incapacity, that was a congenital anomaly or birth defect in offspring of a study subject, or that consisted of any other medically important event as determined by the investigator.

Local allergic swelling was defined as any swelling in or around the throat or mouth and was compiled from reported AEs of mouth edema, oropharyngeal swelling, palatal edema,

pharyngeal edema, tongue edema, swollen tongue, throat tightness, and laryngeal edema as reported by the physician based on history or observation of the subject.

Systemic allergic reaction was defined as an allergic event that included signs or symptoms distant from the mouth and/or throat and included investigator-reported AEs of anaphylaxis, anaphylactic reaction, anaphylactic shock, drug hypersensitivity, and hypersensitivity reaction.

Data analysis

Three data pools were generated as follows: a total pool including adult and pediatric subjects from all eight studies; an adult pool of studies GT-02, GT-07, GT-08 (first year), GT-14, P05238, and the adult subjects in P08067; and a pediatric pool of studies GT-12, P05239, and the pediatric subjects in P08067. All randomized subjects were in the pooled analyses. The number and percentage of TEAEs, systemic reactions, local allergic swellings, and asthma-related TRAEs were determined for the total pool and/or the adult and pediatric data pools. FEV_1 data are only available for the adult pool because one of the pediatric studies, GT-12, did not assess lung function during the pollen season.

Results

Subjects

A total of 4195 subjects were in the pooled population; 3314 subjects were in the adult pooled analysis, and 881 subjects were in the pediatric pooled analysis. Baseline characteristics in pooled populations are shown in Table 1. The majority of subjects were white, and treatment groups were generally well balanced for gender. In the adult pool, 25% of grass SLIT-tablet subjects and 23% of placebo subjects had a reported history of asthma at baseline; in the pediatric pool, 31% of subjects in both grass SLIT-tablet and placebo groups had reported history of asthma. Based on inclusion/exclusion criteria, the majority of subjects with reported asthma were considered to have intermittent or mild perennial or seasonal asthma.

Treatment-emergent adverse events

For subjects receiving grass SLIT-tablet, the frequency of TEAEs was numerically higher in adult subjects with reported asthma than subjects without asthma (Fig. 1A). Pediatric subjects had the same frequency (82.1%) of TEAEs regardless of whether they had concomitant asthma (Fig. 1A). No meaningful conclusions from analyses of TEAEs in other subgroups (gender, age, and race) could be made because there were few events of concern.

Local allergic swelling and systemic allergic reactions

No serious systemic allergic reactions occurred in any subject with or without asthma treated with grass SLIT-tablet. A total of nine systemic allergic reactions were reported in eight subjects receiving grass SLIT-tablet. Of these events, all were assessed as mild or moderate and occurred on day 1 or day 2 of treatment, with the exception of 1 event assessed as moderate that occurred on day 42. The event rate was similar in subjects with and without asthma.

No serious local allergic swelling or swellings that compromised the airway occurred in any subject with or without asthma treated with grass SLIT-tablet. Because there were no serious local swellings in the clinical program, those local swellings assessed by the investigators as severe in intensity were examined. A total of 16 severe local allergic swelling events were reported in 16 subjects receiving grass SLIT-tablet. Of these events, all began within 23 days of treatment initiation, with the exception of 1 event that began on day 74. Although the number of subjects was limited, the number of systemic allergic reactions or severe local allergic swellings was not higher in subjects with asthma treated with grass SLIT-tablet compared with subjects without asthma in either the adult or pediatric pooled populations (Table 2).

Table 1 Baseline demographics and characteristics of all randomized subjects in the pooled populations

	Adult pool		Pediatric pool	
	Placebo (n = 1645)	Grass SLIT-tablet (n = 1669)	Placebo (n = 435)	Grass SLIT-tablet (n = 446)
Age, mean years (range)	36 (18–65)	36 (18–65)	12 (5–18)	12 (5–17)
<12 years, n (%)	—	—	190 (44)	207 (46)
Female, n (%)	735 (45)	801 (48)	156 (36)	151 (34)
Race, n (%)				
White	1450 (88)	1464 (88)	394 (91)	384 (86)
Black	116 (7)	109 (7)	20 (5)	30 (7)
Other	80 (5)	94 (6)	21 (5)	20 (4)
Asthma*, n (%)	383 (23)	415 (25)	136 (31)	140 (31)
Duration of AR/C, mean years (SD)	20 (12)	19 (12)	5 (4)	5 (3)

AR/C, allergic rhinitis with or without conjunctivitis; SD, standard deviation; SLIT-tablet, sublingual allergen immunotherapy tablet.
*Based on patient history.

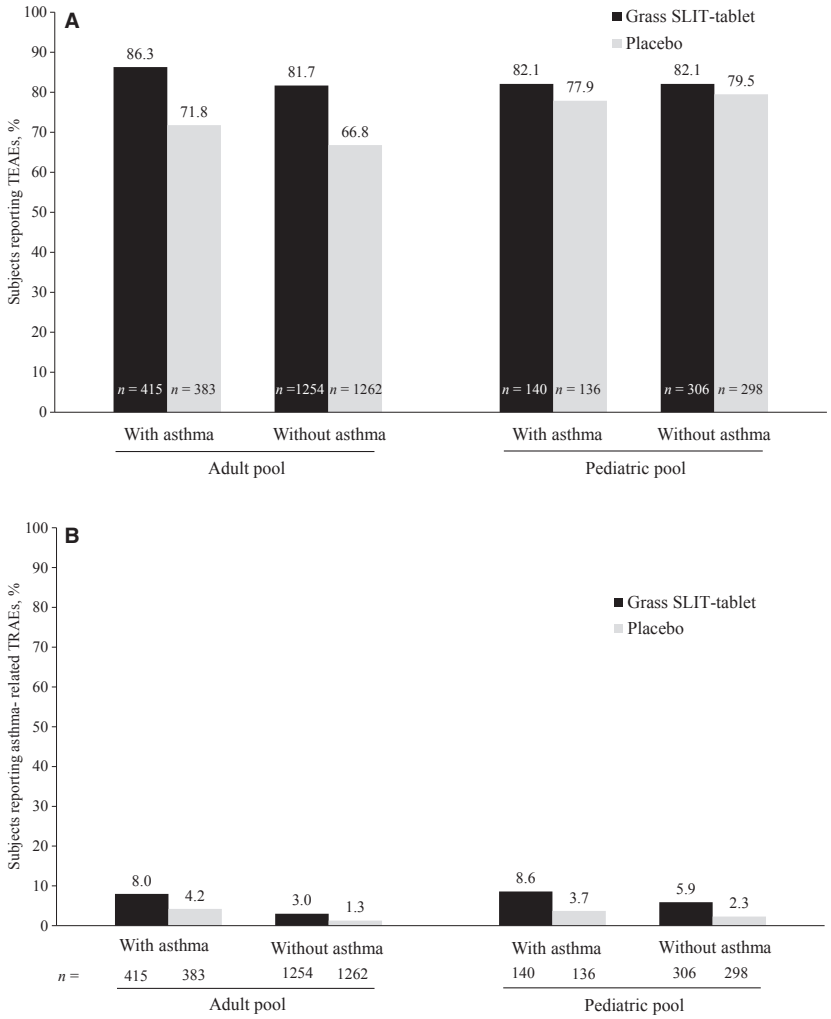

Figure 1 Frequency of (A) TEAEs and (B) asthma-related TRAEs in subjects with AR/C and controlled asthma or without asthma. AR/C, allergic rhinitis with or without conjunctivitis; SLIT-tablet, sublingual allergen immunotherapy tablet; TEAE, treatment-emergent adverse events; TRAE, treatment-related adverse events.

Asthma-related treatment-related adverse events

In the adult pool, the percentage of subjects with asthma-related TRAEs was 8.0% in the grass SLIT-tablet group and 4.2% in the placebo group; in the pediatric pool, the percentages were 8.6% and 3.7%, respectively. Although the frequency of asthma-related TRAEs (asthma, dyspnea, wheezing, cough, chest tightness/discomfort) was slightly higher in subjects with asthma compared with subjects without asthma in both the grass SLIT-tablet and placebo groups (Fig. 1B), there were no instances of acute asthma exacerbation or asthma attacks.

There were no serious asthma-related TRAEs in any of the pooled analyses; therefore, the number of asthma-related TRAEs assessed as severe in intensity by the investigator was examined in the overall pooled population and reviewed for a relationship with asthma status. Across the entire pooled population of 2116 subjects treated with grass SLIT-tablet, there were very few asthma-related TRAEs assessed as severe (six severe events with grass SLIT-tablet and two severe events with placebo; Table 3); these severe events did not consistently occur in subjects with asthma (Table 4). The events assessed as severe in intensity either resolved without asthma medications or were treated with albuterol (two subjects).

Timing of asthma events

In general, there were few subjects who experienced asthma-related TRAEs during the grass pollen season. Events typically occurred in the preseason period, and the percentage of subjects experiencing each of the events was generally similar when comparing the subjects treated with grass SLIT-tablet with those in the placebo arm.

Table 2 Frequency of adverse events of interest in subjects treated with grass SLIT-tablet

	Adult Pool		Pediatric Pool	
	Grass SLIT-tablet (N = 1669) n (%)		Grass SLIT-tablet (N = 446) n (%)	
	With asthma (n = 415)	Without asthma (n = 1254)	With asthma (n = 140)	Without asthma (n = 306)
Any AE of systemic allergic reaction* (all mild and moderate)	1 (0.2)	6 (0.5)	0	1 (0.3)
Any serious AE of systemic allergic reaction	0	0	0	0
Treatment-related severe local allergic swellings†	3 (0.7)	12 (1.0)	1 (0.7)	0
Serious AE of local allergic swelling†	0	0	0	0

AE, adverse event; SLIT-tablet, sublingual allergen immunotherapy tablet.
*Systemic allergic reaction comprised reported AEs of anaphylaxis, anaphylactic reaction, hypersensitivity, drug hypersensitivity, and anaphylactic shock.
†Local allergic swellings comprised reported AEs of mouth edema, oropharyngeal swelling, palatal edema, pharyngeal edema, tongue edema, swollen tongue, throat tightness, and laryngeal edema.

Table 3 Asthma-related TRAEs by severity in the total pooled population

	Asthma-related TRAEs					
Treatment group	Chest discomfort	Asthma	Dyspnea	Wheezing	Cough	Total*
Grass SLIT-tablet, (N = 2116), n	**35**	**10**	**28**	**5**	**42**	**120**
Severity, n (%)						
Mild	24 (68.6)	4 (40.0)	15 (53.6)	3 (60.0)	28 (66.7)	74 (61.7)
Moderate	11 (31.4)	6 (60.0)	10 (35.7)	1 (20.0)	12 (28.6)	40 (33.3)
Severe	0	0	3 (10.7)	1 (20.0)	2 (4.8)	6 (5.0)
Placebo, (N = 2079), n	**11**	**8**	**9**	**9**	**23**	**60**
Severity, n (%)						
Mild	9 (81.8)	3 (37.5)	6 (66.7)	8 (88.9)	15 (65.2)	41 (68.3)
Moderate	1 (9.1)	4 (50.0)	3 (33.3)	1 (11.1)	8 (34.8)	17 (28.3)
Severe	1 (9.1)	1 (12.5)	0	0	0	2 (3.3)

SLIT-tablet, sublingual allergen immunotherapy tablet; TRAE, treatment-related adverse event.
*Subjects may have had more than 1 event and therefore may have been counted more than once.

Table 4 Severe asthma-related treatment-related adverse events in subjects with and without controlled asthma in the total pooled population

	With asthma		Without asthma	
Asthma-related TRAE	Grass SLIT-tablet (n = 555) n (%)	Placebo (n = 519) n (%)	Grass SLIT-tablet (n = 1561) n (%)	Placebo (n = 1560) n (%)
Chest discomfort	0	0	0	1 (0.06)
Asthma	0	1 (0.2)	0	0
Dyspnea	1 (0.2)	0	2 (0.1)	0
Wheezing	1 (0.2)	0	0	0
Cough	2 (0.4)	0	0	0

SLIT-tablet, sublingual allergen immunotherapy tablet; TRAE, treatment-related adverse event.

Lung function

In subjects with asthma in the adult pool, the mean (SD) percent predicted FEV_1 was 93.2% (12.1%) and 94.5% (12.0%) during the preseason visit in the grass SLIT-tablet and placebo groups, respectively. At peak season, mean (SD) percentages were 92.2% (13.5%) and 92.1% (13.0%), respectively, and at the postseason visit, percentages were 94.4% (13.1%) and 94.2% (19.0%). Lung function was only assessed in one of the pediatric studies, and therefore, no pooled pediatric FEV_1 data are available. In the pediatric study with available data, no clinically relevant changes in FEV_1 were observed.

Discussion

Asthma and AR/C are often comorbid conditions. Asthma is a risk factor for systemic reactions with allergen immunotherapy. The safety profile of any allergen immunotherapy product should be characterized in patients with asthma. In the grass SLIT-tablet clinical development program, the pooled analysis of 4195 adult and pediatric subjects treated with grass SLIT-tablet or placebo revealed that there was no increase in systemic allergic reactions or severe local allergic swellings in the 1074 subjects with reported well-controlled, mild asthma. Additionally, there was no indication from the pooled population that treatment with grass SLIT-tablet resulted in acute worsening of asthma, acute asthma attacks, or exacerbations in the subjects with reported controlled asthma.

The results of this pooled analysis are in agreement with the individual results from one of the studies included in the pool, GT-07, which specifically investigated the safety of Timothy grass SLIT-tablet in 114 subjects with mild-to-moderate grass pollen-induced asthma (13). In GT-07, subjects were required to have an $FEV_1 \geq 70\%$ of predicted and were excluded if they required continuous year-round inhaled corticosteroid treatment. The results demonstrated that grass SLIT-tablet was well tolerated in subjects with mild-to-moderate controlled asthma. No SAEs were reported in the trial. Asthma-related AEs (regardless of causality) in the grass SLIT-tablet groups were primarily mild to moderate in intensity, and there was no increase in asthma-related TRAEs in subjects receiving active treatment compared with placebo. The results of the current analysis confirm the GT-07 results, with the strength of evidence from a much larger data pool.

In the current analysis, subjects with asthma had more asthma events than subjects without asthma, as would be expected. Additionally, there was a trend toward a slightly higher frequency of asthma-related TRAEs in subjects receiving active treatment compared with placebo. However, none of the asthma-related TRAEs were serious and the few severe events did not consistently occur in subjects with asthma. Thus, there is no indication that patients with well-controlled mild asthma are at increased risk of serious or severe asthma-related events in response to Timothy grass SLIT-tablet. Interestingly, two of the individual studies included in this pooled analysis reported a significant reduction in asthma symptoms during the grass pollen season for the active treatment group versus placebo (11, 17). This further indicates that grass SLIT-tablet is more associated with improvement of symptoms than with increasing the risk of asthma during pollen season. However, no conclusions regarding improvements in asthma symptoms can be made from the current analysis, and future trials specifically addressing this issue are needed.

No serious systemic allergic reactions or serious local allergic swellings were reported in this pooled analysis that focused on Timothy grass SLIT-tablet. These results are in agreement with those of a meta-analysis of 16 trials that assessed the general safety (asthma-related AEs were not specifically assessed) of SLIT in subjects with allergic asthma treated for house dust mite or various pollen allergies (18). Systemic reactions were found to occur; however, serious systemic reactions were rare. Thus, the authors concluded that SLIT was generally safe and well tolerated in patients with asthma.

Clinicians may be dissuaded from administering immunotherapy to patients with asthma, as the majority of fatal allergen immunotherapy-related systemic reactions (all with SCIT) reported in the literature occurred in this group (7). The results of these pooled analyses indicate that Timothy grass SLIT-tablet is safe to administer to adults and children with mild, controlled asthma. Asthma events typically occurred in the first weeks of treatment, and exacerbations of asthma did not occur during the grass pollen season. The temporal pattern highlights the importance of the recommendation that the first dose of the tablet be administered in a supervised setting by a physician with experience in the treatment and management of allergic disease. Patients with severe or uncontrolled asthma, those receiving inhaled corticosteroids for asthma outside the pollen season or those with significant perennial allergen-related asthma, were excluded from the clinical development program, and no extrapolations should be made to this population. Furthermore, severe systemic side effects or deaths from allergen immunotherapy are rare (8); thus, a large number of patients are needed to provide definitive safety conclusions. As such, large-scale postmarketing surveillance will be necessary to provide more conclusive evidence of the safety of grass SLIT-tablet in patients with asthma. Additional limitations of this analysis include the fact that subjects were assessed as having current asthma based on clinical history and not by diagnostic testing.

Conclusions

Pooled results from a total of eight randomized placebo-controlled trials indicate that in subjects with AR/C and reported concomitant well-controlled mild asthma, treatment with Timothy grass SLIT-tablet did not result in an increase in the frequency of TEAEs, severe local allergic swelling, or systemic allergic reactions versus subjects without asthma. Furthermore, there was no indication that treatment led to acute worsening of asthma or asthma exacerbations in or outside of the grass pollen season.

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Author contributions

Each author has contributed substantially to this paper. Drs. Durham, Skoner, Dahl, Bufe, Bernstein, Murphy, Waserman, Berman, and White were each principal investigators on at least one of the studies included in this analysis and were responsible for the acquisition of data. Drs. Maloney and Nolte contributed to the study design, data collection, and analyses and were responsible for the conduct of several of the studies. Dr. Kaur provided oversight in the conduct of statistical analyses. All authors participated in the data interpretation and contributed to the concept and review of the manuscript for intellectual content.

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Conflicts of interests

Dr. Maloney is an employee of Merck & Co., Inc. Dr. Durham has received research support from ALK-Abelló, Merck & Co., Inc. and Stallergenes, has received consultancy fees from ALK-Abelló, Biomay, Circassia, and Stallergenes, and has provided expert testimony for Merck & Co., Inc. Dr. Skoner reports advisory board membership and speaker's bureau participation for, is a consultant for, and has received grants from Merck & Co., Inc. Dr. Dahl is a consultant for ALK-Abelló, Boehringer Ingelheim, Cipla, Cytos, Meda, Novartis, and Vectura, has provided expert testimony for Teva, and has given lectures for ALK-Abelló, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Novartis, and Teva. Dr. Bufe reports advisory board membership and has served as a consultant for ALK-Abelló. Dr. Bernstein is on the American Board of Allergy and Immunology, is a speaker/consultant for and has received research support from Merck & Co., Inc., has provided expert testimony for Porter Wright Morris & Author, and has received grants for the Bernstein Clinical Research Center. Dr. Murphy reports speaker's bureau participation and is a consultant for Merck & Co., Inc., AstraZeneca, Genentech, Greer, Meda, Mylan, Novartis, and Teva. Dr. Waserman has served on advisory boards for Merck Frost, GlaxoSmithKline, and Takeda Canada, is a speaker/consultant for Novartis Canada, Sanofi Canada, Shire Pharmaceuticals, CSL Behring, and Paladin Laboratories Inc, and has received honoraria from Merck Frost, Pfizer Canada, Sanofi Canada, Takeda Canada, CSL Behring, and Paladin Laboratories Inc. Dr. Berman reports no conflict of interest. Dr. White has served as an investigator for, received grant money from, and is a speaker/consultant for Merck & Co., Inc. Dr. Kaur and Dr. Nolte are employees of and hold stock in Merck & Co., Inc.

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