# Attenuating the atopic march: Meta-analysis of the dupilumab atopic dermatitis database for incident allergic events

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#### **GRAPHICAL ABSTRACT**



Background: Atopic march refers to the sequential development of allergic diseases from infancy through adolescence, typically beginning with atopic dermatitis (AD), followed by food allergy and then airway diseases, later evolving to broader or worsened spectrum of allergic diatheses. No intervention has shown to alter its course.

Objective: We sought to determine the rate of acquisition of new or worsened allergic events for dupilumab versus placebo in patients with AD.

Methods: Allergy-associated events from 12 clinical trials were grouped into 17 allergy categories, and IgE changes from baseline were defined. A new/worsened event was considered one step of atopic march. Treatment effect was assessed by incidence rate ratios (IRRs), dupilumab versus placebo, by meta-analysis.

Results: The duration of pooled AD studies was 4 to 52 weeks (1359 patient-years; n = 2296 dupilumab, n = 1229 placebo, median age 35 years). The median age at AD onset was 2 years.

Baseline allergic disease burden was comparable between groups. Dupilumab reduced the risk of new/worsening allergies by 34% (IRR 0.66; 95% confidence interval [CI], 0.52-0.84) and new allergies by 37% (IRR 0.63; 95% CI, 0.48-0.83) versus placebo. Including IgE category shift, the IRR for combined new/ worsening allergies was reduced by 54% (IRR 0.46; 95% CI, 0.36-0.57). These treatment benefits did not reverse on treatment discontinuation in off-treatment follow-up. Conclusions: The acquisition/worsening of allergic conditions suggestive of atopic march was observed in a pooled adult/ adolescent AD study population with inadequately controlled AD. Treatment with dupilumab reduced new/worsened allergy events versus placebo; inclusion of IgE category change increased the

Key words: Atopic march, dupilumab, dermatitis, atopic, food hypersensitivity, eczema, antibodies, monoclonal, asthma, rhinitis, allergic, IgE responsiveness, atopic, meta-analysis

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Abbreviations used

- AD: Atopic dermatitis
- CI: Confidence interval
- EASI: Eczema Area and Severity Index
- IRR: Incidence rate ratio
- TEAE: Treatment-emergent adverse event

Atopic march has been defined as the serial acquisition of new and worsened allergies after a first instance of clinically important allergic diathesis.<sup>1-7</sup> Allergic immune responses are characterized by the presence of allergen-specific IgE,<sup>8</sup> T-helper cell subsets, and antigen-specific  $T_H 2$  cells<sup>9</sup> that produce a pattern of cytokines (IL-4, IL-5, and IL-13). Innate immune cells (group 2 innate lymphoid cells, or ILC2) magnify the production of cytokines (IL-4, IL-5, IL-9, and IL-13) and contribute to the generation of the allergic immune response, constituting an important contributor to type 2 inflammation.

The risk of atopic march is higher in children who produce IgE antibodies in response to environmental triggers than in those who do not. IgE-associated allergic sensitization is an important factor in atopic march, and the relationship of increasing IgE concentrations with acquisition of allergic conditions may depend on genetic and environmental factors.<sup>1,10</sup> The presence of one allergic condition is a risk factor for developing others, increasing allergic disease burden.<sup>2,11</sup>

The presence and severity of atopic dermatitis (AD) positively correlates with the risk of developing food hypersensitivities, typically present from an early age.<sup>2,12</sup> While food-specific IgE antibodies were reported in a small number of infants with AD 3 months after birth, up to 10% of infants at the age of 1 year<sup>3</sup> and almost 15% of children under 6 years of age with AD exhibited food hypersensitivities.<sup>13</sup> AD is also strongly associated with IgE responses to inhalant allergens as well as the development of asthma and allergic rhinitis.<sup>2</sup> About one third of people with AD develop asthma, while two thirds develop allergic rhinitis during their lives.<sup>1,12,14,15</sup> Multiple longitudinal studies provide evidence of atopic march between AD and subsequent allergies.<sup>1,12,16-22</sup>

The main predictors of later atopic diseases, such as asthma, are IgE sensitization and early onset and severity of AD,<sup>23,24</sup> both dependent on type 2 inflammatory signals, most critically IL-4. Modulation of IL-4 signaling<sup>25,26</sup> therefore may represent an important therapeutic approach to target the drivers of atopic march. Dupilumab, a monoclonal antibody designed to block IL-4R, has been shown to provide efficacy in the treatment of moderate-to-severe AD, allergic asthma, chronic rhinosinusitis with nasal polyposis, and eosinophilic esophagitis, all known to be driven largely by type 2 inflammation.<sup>27-30</sup>

In this analysis, we evaluated whether dupilumab would attenuate the acquisition of new allergic conditions or the worsening of existing allergic conditions for participants involved in our large AD clinical trial database compared to those treated with placebo. Using meta-analytical methodology, applied to the entire pooled AD clinical database treated for 4 to 52 weeks, we determined the progression of allergic disease after infancy in this highly atopic population of adolescents and adults.

#### METHODS Study desig

Study design

To qualify for meta-analyses of adverse events for the objectives, the studies must have been randomized, placebo-controlled, double-blind, parallel-grouped trials of dupilumab in the treatment of AD. Twelve such studies completed as of June 2019 were identified, conducted in both adolescent and adult subjects.<sup>31-42</sup> To qualify for enrollment onto the studies, all subjects had moderate-to-severe AD at baseline not adequately controlled with topical medications, an Investigator's Global Assessment severity score of at least 3 (5-point scale; graded 0-4), and generally an Eczema Area and Severity Index (EASI) score of 16 or higher (maximum of 72). The dupilumab dosing regimens in the 12 studies ranged from 100 mg every 4 weeks to 300 mg weekly, with most patients, including all dupilumab-treated patients in the larger pivotal trials, receiving 300 mg weekly or every 2 weeks. The majority of trials studied dupilumab as monotherapy, while 1 long-term study added dupilumab or placebo to topical corticosteroids. The treatment duration ranged from 4 to 52 weeks. Patients may have been treated on a rescue basis with topical corticosteroids while continuing to receive the study drug. However, if patients were rescued with systemic corticosteroids, nonsteroidal immunosuppressants, or phototherapy, study drug was discontinued. An overview of the study design of the individual trials is shown in Table E1 in this article's Online Repository at www.jacionline.org.

### **End points**

In order to track new allergic conditions or determine the impact on existing allergic diatheses, separate from the main effects on AD (which was the primary end point of these studies), we assessed allergic treatment-emergent adverse events (TEAEs). Medical Dictionary for Regulatory Activities– preferred terms from baseline medical history, a specific atopic disease questionnaire, and allergic TEAEs were pooled to identify allergic events across all studies and treatment groups. Because all subjects had AD, this term and terms that mapped to AD were not included for assessment of atopic march. All subjects had moderate-to-severe AD at study initiation; improvement would imply efficacy, while deterioration would have been considered treatment failure that led to rescue therapy.

The selected preferred terms were then assigned to allergy categories to combine terms referring to similar allergic events. The selection process and categorization were performed independently by a board-certified allergist who was unaware of the trial and treatment assignment. A list of allergy categories and associated preferred terms is provided in Table E2 in the Online Repository at www.jacionline.org.

New allergic TEAEs were defined as events not present at the time of study entry (ie, not captured in the list of current or past medical conditions), and worsened TEAEs were defined as allergic conditions that had been identified in the medical history or were present at study entry that had worsened during the course of the studies. This approach to capturing adverse events is a standard of controlled clinical trials. New and worsened IgE categories were defined on the basis of the category shifts from baseline during treatment period, as shown in Table E3 in the Online Repository at www.jacionline.org. IgE categories were analyzed by both 1- and 2-step increases. One-step increases constituted the minimal amount that might be deemed to represent an important change that was prespecified. Though these minimal changes were substantial, as a sensitivity analysis, we included a more conservative 2-step increase to assess the contribution of IgE changes to atopic march (Table E3). Each new or worsening event in a category was considered to be 1 step of atopic march. Any single term coded from a category constituted an end point. Multiple terms from 1 allergic TEAE event category (eg, different pollen reports of pollen sensitization) were deemed to represent a single change in that category (ie, allergy to plants). Thus, a subject deemed to have acquired new sensitizations, such as having grass allergy at baseline and newly reporting tree allergy, was not considered to have acquired a new allergic diathesis and was instead considered to have worsened allergy. If the allergic manifestation involved a different organ (eg, asthma), it was considered a new category of allergy.

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Characteristic	Variable	Dupilumab (n = 2296)	Placebo (n = 1229)
Age (years)	Mean (SD)	36.2 (14.5)	36.5 (14.5)
	Median (Q1, Q3)	34.0 (24.0, 46.0)	35.0 (24.0, 47.0)
Age at onset (years)	Mean (SD)	9.1 (13.8)	9.1 (14.3)
5	Median (Q1, Q3)	2.0 (1.0, 12.0)	2.0 (1.0, 10.0)
Allergic burden	Mean (SD)	3.4 (2.6)	3.4 (2.6)
	Median (Q1, Q3)	3.0 (1.0, 5.0)	3.0 (1.0, 5.0)
Sex	Male, no. (%)	1352 (58.9)	706 (57.4)
	Female, no. (%)	944 (41.1)	523 (42.6)
Region	North America, no. (%)	1017 (44.3)	561 (45.6)
	Europe, no. (%)	973 (42.4)	508 (41.3)
	Asia, no. (%)	268 (11.7)	138 (11.2)
	Oceania, no. (%)	38 (1.7)	22 (1.8)
Race	White, no. (%)	1647 (71.7)	865 (70.4)
	Asian, no. (%)	426 (18.6)	232 (18.9)
	Black, no. (%)	153 (6.7)	96 (7.8)
	Other, no. (%)	70 (3.0)	36 (2.9)

Q, Quartile; SD, standard deviation.

#### Statistical analysis

In the meta-analyses, patients were analyzed as treated in the dupilumab or placebo arms from the 12 trials. Demographic and baseline allergic burden and age at AD onset were summarized by treatment groups, dupilumab versus placebo. Mean, standard deviation, median, and interquartile range were used for continuous variables. Percentage of each level was summarized for all categorical variables. In addition, analysis of variance adjusting for study was used to assess baseline allergic burden between treatment groups. Association of baseline burden with baseline IgE was evaluated by negative binomial regression. Time to end of treatment between treatment groups was analyzed by the log-rank test, stratified by study.

Incidence rate ratio (IRR) was defined as the number of events divided by exposure (patient-years) comparing dupilumab to placebo. To account for differential treatment duration across studies and individuals due to early dropout, IRR was used as the metric to quantify the treatment effect in the meta-analyses. All dupilumab dose levels were combined in the metaanalyses, as no apparent dose-response trend with respect to rates of allergic TEAE events was observed. Both fixed-effect models (assuming homogeneity of treatment effects across studies) and random-effect models (assuming heterogeneity of treatment effects across studies) were used for the meta-analyses. Heterogeneity of treatment effects was evaluated using the  $I^2$ statistic, and an  $I^2$  value of  $\geq$ 50% was considered to indicate significant heterogeneity.43 Results of fixed-effect models were reported if no heterogeneity was present; otherwise, results of random-effect models were reported. When we pooled the treatment effects in the meta-analysis, the inverse of the variance was used to determine the weight of each study. Analyses were performed separately for the on-treatment period (from the date of first exposure to the end of treatment) and for the entire study period (from the date of first exposure to treatment to study end date-ie, both the on-treatment period and the off-treatment follow-up period) for combined new and worsening allergic TEAE events, new allergic TEAE events alone, combined new and worsening allergic TEAE events, and new and worsening IgE events.

Descriptive subgroup analyses were completed for the variables of age, age at AD onset, region, race, severity of AD, baseline IgE, presence of asthma at baseline, and baseline burden to assess level of varying treatment effects.

The analyses were all performed by R software (R Project; www.r-project. org), and the R package 'meta' was used for the meta-analyses.<sup>44</sup>

#### RESULTS

The pooled analysis data set included 3525 subjects (n = 2296, dupilumab; n = 1229, placebo). Among the placebo subgroups,

the total treatment period was 482 patient-years; the total dupilumab exposure was 877 patient-years. Patient demographics were balanced between the dupilumab and placebo groups in the combined data set (Table I; data for individual studies are presented in Table E4 in the Online Repository at www.jacionline.org). The mean age was 36 years (median, 35 years; range, 12-88 years). The median age at onset of AD was 2 years (mean, 9.1 years; range, 0-80 years), and the mean duration of AD was 27 years. Baseline allergic burden was comparable between treatment groups across studies (P = .672), and the average baseline concomitant allergic burden was 3.4 categories (excluding AD). Increased burden rate was significantly associated with increased IgE (IRR 1.17; 95% confidence interval [CI], 1.14-1.20; P < .001; see Table E5 in the Online Repository at www.jacionline.org).

Log-rank test stratified by study indicated that there was differential dropout between placebo and dupilumab, as significantly more subjects in the placebo group dropped out before the scheduled end-of-treatment period than in the dupilumab group (P < .001). In 10 of 12 trials, time on treatment with dupilumab was greater than placebo. For the pooled data set, a small imbalance in dropout rates (yielding approximately 5% less time on dupilumab vs placebo) may have led to a slightly more conservative estimate of treatment benefit for dupilumab in reducing rates of new and worsened allergy, because events in the placebo arm would have been artificially constrained by less time on randomized treatment.

As can be seen in Fig 1, among the 17 categories contributing to allergic TEAE events, asthma, pruritus, and urticaria were especially notable contributors to the overall positive treatment effect of dupilumab. There were very few IgE events that were new, likely as a result of the small number of these subjects with AD with a baseline IgE level of <30 IU/mL at study entry. However, the statistically significant reduction in IgE events (demonstrated as a 1- or 2-step increase) in dupilumab versus placebo was driven by worsening of IgE in the placebo arm, attenuated in the dupilumab arm, leading to an IRR of 0.32 (95% CI, 0.15-0.67; Fig 1, A). Further examination of allergen-specific IgE data from the largest study where this was available, R668-AD-1224, demonstrated a reduction in new as well as in new and worsened allergen-specific IgEs with treatment of dupilumab from baseline to end

#### Α

		Dupitutitab		Placebo	incluence Rate			
Allergy Category	Events	Patient Years	Events	Patient Years	Ratio	IRR	95%-CI	Weight
Allergy to opimal	2	076 71	2	401 74	- al	0.92	[0 14, 4 02]	1 60/
Allergy to animal	ى 1	070.71 876 71	2	401.74		- 1.65	[0.14, 4.93]	0.5%
Alleray to insects	2	876 71	1	401.74		1.05	[0.07, 40.47]	0.0%
Alleray to metals	2	876 71	1	481 74		0.18	[0.10, 12.12]	0.5%
Angioedema	4	876 71	3	481 74		0.10	[0.01; 4.00]	2.3%
Asthma	22	876 71	33	481 74		0.70	[0.10, 0.27]	17.7%
Contact dermatitis	13	876.71	8	481.74		0.89	[0.37: 2.15]	6.6%
Drug hypersensitivity (inc Penicillin)	5	876.71	1	481.74		2.75	[0.32: 23.52]	1.1%
Food allergy	9	876.71	8	481.74	<u>_</u>	0.62	[0.24; 1.60]	5.7%
Hypersenstivity unspecified	6	876.71	3	481.74	<u> </u>	1.10	[0.27; 4.39]	2.7%
IGE	11	876.71	19	481.74		0.32	[0.15; 0.67]	9.3%
Nasal polyps	1	876.71	1	481.74		0.55	[0.03; 8.78]	0.7%
Oral allergy syndrome	1	876.71	0	481.74		- 1.65	[0.07; 40.47]	0.5%
Pruritus	23	876.71	27	481.74		0.47	[0.27; 0.82]	16.6%
Rhinitis allergic	25	876.71	13	481.74		1.06	[0.54; 2.07]	11.5%
Seasonal allergy undefined	20	876.71	6	481.74	: <del>  _</del>	1.83	[0.74; 4.56]	6.2%
Urticaria	22	876.71	18	481.74		0.67	[0.36; 1.25]	13.3%
Wheezing	4	876.71	3	481.74		0.73	[0.16; 3.27]	2.3%
Overall	172		147		<b></b>	0.63	[0.50; 0.79]	100.0%
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					<b></b>	<b></b>		
					Favors dupilumab Favors pla	icebo		
В								
В		Dupilumab		Placebo	Incidence Rate			
B Allergy Category	Events	Dupilumab Patient Years	Events	Placebo Patient Years	Incidence Rate Ratio	IRR	95%-CI	Weight
B Allergy Category	Events	Dupilumab Patient Years	Events	Placebo Patient Years 481 74	Incidence Rate Ratio	<b>IRR</b>	<b>95%-CI</b>	Weight
B Allergy Category Allergy to animal Allergy to chemicals	Events 2	Dupilumab Patient Years 876.71 876.71	Events	Placebo Patient Years 481.74 481.74	Incidence Rate Ratio	<b>IRR</b> 0.55 - 1.65	<b>95%-CI</b> [0.08; 3.90] [0.07: 40.47]	<b>Weight</b> 2.0% 0.8%
B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects	Events 2 1 2	Dupilumab Patient Years 876.71 876.71 876.71	Events 2 0 1	Placebo Patient Years 481.74 481.74 481.74	Incidence Rate Ratio	IRR 0.55 - 1.65 1.10	<b>95%-CI</b> [0.08; 3.90] [0.07; 40.47] [0 10: 12 12]	<b>Weight</b> 2.0% 0.8% 1.3%
B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects Allergy to metals	<b>Events</b> 2 1 2 0	Dupilumab Patient Years 876.71 876.71 876.71 876.71	<b>Events</b> 2 0 1	Placebo Patient Years 481.74 481.74 481.74 481.74	Incidence Rate Ratio	IRR 0.55 - 1.65 1.10 0.18	<b>95%-CI</b> [0.08; 3.90] [0.07; 40.47] [0.10; 12.12] [0.01: 4.50]	Weight 2.0% 0.8% 1.3% 0.8%
B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects Allergy to metals Angioedema	<b>Events</b> 2 1 2 0 4	Dupilumab Patient Years 876.71 876.71 876.71 876.71 876.71	<b>Events</b> 2 0 1 1 3	Placebo Patient Years 481.74 481.74 481.74 481.74 481.74	Incidence Rate Ratio	0.55 - 1.65 1.10 0.18 0.73	<b>95%-CI</b> [0.08; 3.90] [0.07; 40.47] [0.10; 12.12] [0.01; 4.50] [0.16: 3.27]	Weight 2.0% 0.8% 1.3% 0.8% 3.4%
B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects Allergy to metals Angioedema Asthma	<b>Events</b> 2 1 2 0 4 7	Dupilumab Patient Years 876.71 876.71 876.71 876.71 876.71 876.71	Events 2 0 1 1 3 20	Placebo Patient Years 481.74 481.74 481.74 481.74 481.74 481.74	Incidence Rate Ratio	IRR 0.55 1.65 1.10 0.18 0.73 0.19	<b>95%-Cl</b> [0.08; 3.90] [0.07; 40.47] [0.10; 12.12] [0.01; 4.50] [0.16; 3.27] [0.08: 0.45]	Weight 2.0% 0.8% 1.3% 0.8% 3.4% 10.4%
B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects Allergy to metals Angioedema Asthma Contact dermatitis	<b>Events</b> 2 1 2 0 4 7 13	Dupilumab Patient Years 876.71 876.71 876.71 876.71 876.71 876.71 876.71	Events 2 0 1 1 3 20 8	Placebo Patient Years 481.74 481.74 481.74 481.74 481.74 481.74 481.74	Incidence Rate Ratio	IRR 0.55 1.65 1.10 0.18 0.73 0.19 0.89	<b>95%-Cl</b> [0.08; 3.90] [0.07; 40.47] [0.10; 12.12] [0.01; 4.50] [0.16; 3.27] [0.08; 0.45] [0.37; 2.15]	Weight 2.0% 0.8% 1.3% 0.8% 3.4% 10.4% 9.9%
B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects Allergy to metals Angioedema Asthma Contact dermatitis Drug hypersensitivity (inc Penicillin)	Events 2 1 2 0 4 7 13 5	Dupilumab Patient Years 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71	Events 2 0 1 1 3 20 8 1	Placebo Patient Years 481.74 481.74 481.74 481.74 481.74 481.74 481.74	Incidence Rate Ratio	IRR 0.55 1.65 1.10 0.18 0.73 0.19 0.89 2.75	<b>95%-CI</b> [0.08; 3.90] [0.07; 40.47] [0.10; 12.12] [0.01; 4.50] [0.16; 3.27] [0.08; 0.45] [0.37; 2.15] [0.32; 23.52]	Weight 2.0% 0.8% 1.3% 0.8% 3.4% 10.4% 9.9% 1.7%
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B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects Allergy to metals Angioedema Asthma Contact dermatitis Drug hypersensitivity (inc Penicillin) Food allergy Hypersenstivity unspecified IGE	Events 2 0 4 7 13 5 5 6 1	Dupilumab Patient Years 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71	<b>Events</b> 2 0 1 1 3 20 8 1 6 3 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Placebo Patient Years 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74	Incidence Rate Ratio	IRR 0.55 1.65 1.10 0.18 0.73 0.19 0.89 2.75 0.46 1.10 0.55	<b>95%-Cl</b> [0.08; 3.90] [0.07; 40.47] [0.10; 12.12] [0.01; 4.50] [0.16; 3.27] [0.08; 0.45] [0.37; 2.15] [0.32; 23.52] [0.14; 1.50] [0.27; 4.39] [0.03; 8.78]	Weight 2.0% 0.8% 1.3% 0.8% 3.4% 10.4% 9.9% 1.7% 5.5% 4.0%
B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects Allergy to insects Allergy to metals Angioedema Asthma Contact dermatitis Drug hypersensitivity (inc Penicillin) Food allergy Hypersensitivity unspecified IGE Nasal polyps	Events 2 1 2 0 4 7 13 5 5 6 1 1 0	Dupilumab Patient Years 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71	<b>Events</b> 2 0 1 1 3 20 8 1 6 3 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Placebo Patient Years 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74	Incidence Rate Ratio	IRR 0.55 1.65 1.10 0.18 0.73 0.19 0.89 2.75 0.46 1.10 0.55 0.18	<b>95%-Cl</b> [0.08; 3.90] [0.07; 40.47] [0.10; 12.12] [0.01; 4.50] [0.16; 3.27] [0.08; 0.45] [0.37; 2.15] [0.32; 23.52] [0.14; 1.50] [0.27; 4.39] [0.03; 8.78] [0.01; 4.50]	Weight 2.0% 0.8% 1.3% 0.8% 3.4% 10.4% 9.9% 1.7% 5.5% 4.0% 1.0% 0.8%
B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects Allergy to metals Angioedema Asthma Contact dermatitis Drug hypersensitivity (inc Penicillin) Food allergy Hypersenstivity unspecified IGE Nasal polyps Oral allergy syndrome	Events 2 1 2 0 4 7 13 5 5 6 1 0 0 1	Dupilumab Patient Years 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71	<b>Events</b> 2 0 1 1 3 20 8 1 6 3 1 1 0	Placebo Patient Years 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74	Incidence Rate Ratio	IRR 0.55 1.65 1.10 0.18 0.73 0.19 0.89 2.75 0.46 1.10 0.55 0.18 - 1.65	<b>95%-Cl</b> [0.08; 3.90] [0.07; 40.47] [0.10; 12.12] [0.01; 4.50] [0.16; 3.27] [0.08; 0.45] [0.37; 2.15] [0.32; 23.52] [0.14; 1.50] [0.27; 4.39] [0.03; 8.78] [0.01; 4.50] [0.07; 40.47]	Weight 2.0% 0.8% 1.3% 0.8% 3.4% 10.4% 9.9% 1.7% 5.5% 4.0% 1.0% 0.8%
B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects Allergy to insects Allergy to metals Angioedema Asthma Contact dermatitis Drug hypersensitivity (inc Penicillin) Food allergy Hypersenstivity unspecified IGE Nasal polyps Oral allergy syndrome Pruritus	Events 2 1 2 0 4 7 13 5 5 6 1 0 1 22	Dupilumab Patient Years 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71	Events 2 0 1 1 3 20 8 1 6 3 1 1 0 24	Placebo Patient Years 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74	Incidence Rate Ratio	IRR 0.55 1.65 1.10 0.18 0.73 0.19 0.89 2.75 0.46 1.10 0.55 0.18 - 1.65 0.50	<b>95%-CI</b> [0.08; 3.90] [0.07; 40.47] [0.10; 12.12] [0.01; 4.50] [0.16; 3.27] [0.32; 23.52] [0.32; 23.52] [0.14; 1.50] [0.27; 4.39] [0.03; 8.78] [0.01; 4.50] [0.07; 40.47] [0.28; 0.90]	Weight 2.0% 0.8% 1.3% 0.8% 3.4% 10.4% 9.9% 1.7% 5.5% 4.0% 1.0% 0.8% 0.8% 0.8% 0.8%
B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects Allergy to insects Allergy to metals Angioedema Asthma Contact dermatitis Drug hypersensitivity (inc Penicillin) Food allergy Hypersenstivity unspecified IGE Nasal polyps Oral allergy syndrome Pruritus Rhinitis allergic	Events 2 1 2 0 4 7 7 13 5 5 5 6 1 0 1 22 2 2 12	Dupilumab Patient Years 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71	<b>Events</b> 2 0 1 1 3 20 8 1 6 3 1 1 0 24 6 2 4 6 2 2 2 2 2 2 2 2 2 2 2 2 2 2	Placebo Patient Years 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74	Incidence Rate Ratio	IRR 0.55 1.65 1.10 0.18 0.73 0.19 0.89 2.75 0.46 1.10 0.55 0.18 - 1.65 0.50 0.50 1.10	<b>95%-Cl</b> [0.08; 3.90] [0.07; 40.47] [0.10; 12.12] [0.01; 4.50] [0.16; 3.27] [0.32; 23.52] [0.32; 23.52] [0.14; 1.50] [0.27; 4.39] [0.03; 8.78] [0.01; 4.50] [0.07; 40.47] [0.28; 0.90] [0.41; 2.93]	Weight 2.0% 0.8% 1.3% 0.8% 3.4% 10.4% 9.9% 1.7% 4.0% 1.0% 0.8% 0.8% 23.0%
B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects Allergy to insects Allergy to metals Angioedema Asthma Contact dermatitis Drug hypersensitivity (inc Penicillin) Food allergy Hypersenstivity unspecified IGE Nasal polyps Oral allergy syndrome Pruritus Rhinitis allergic Seasonal allergy undefined	Events 2 1 2 0 4 7 13 5 5 6 6 1 0 1 22 12 14	Dupilumab Patient Years 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71	<b>Events</b> 2 0 1 1 3 20 8 1 6 3 1 1 0 24 6 4	Placebo Patient Years 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74	Incidence Rate Ratio	IRR 0.55 1.65 1.10 0.18 0.73 0.19 0.89 2.75 0.46 1.10 0.55 0.18 - 1.65 0.18 - 1.65 0.10 1.10	<b>95%-CI</b> [0.08; 3.90] [0.07; 40.47] [0.10; 12.12] [0.01; 4.50] [0.16; 3.27] [0.08; 0.45] [0.32; 23.52] [0.14; 1.50] [0.27; 4.39] [0.03; 8.78] [0.01; 4.50] [0.07; 40.47] [0.28; 0.90] [0.41; 2.93] [0.63; 5.84]	Weight 2.0% 0.8% 1.3% 0.8% 3.4% 10.4% 9.9% 1.7% 5.5% 4.0% 1.0% 0.8% 0.8% 23.0% 8.0% 8.0%
B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects Allergy to metals Angioedema Asthma Contact dermatitis Drug hypersensitivity (inc Penicillin) Food allergy Hypersenstivity unspecified IGE Nasal polyps Oral allergy syndrome Pruritus Rhinitis allergic Seasonal allergy undefined Urticaria	Events 2 1 2 0 4 7 13 5 5 5 6 6 1 1 0 1 2 2 12 14 18	Dupilumab Patient Years 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71	<b>Events</b> 2 0 1 1 3 20 8 1 6 3 1 1 0 24 6 4 17	Placebo Patient Years 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74	Incidence Rate Ratio	IRR 0.55 1.65 1.10 0.18 0.73 0.19 0.89 2.75 0.46 1.10 0.55 0.48 1.10 0.55 0.18 - 1.65 0.50 1.10 0.55 0.58	<b>95%-Cl</b> [0.08; 3.90] [0.07; 40.47] [0.10; 12.12] [0.01; 4.50] [0.16; 3.27] [0.08; 0.45] [0.37; 2.15] [0.32; 23.52] [0.14; 1.50] [0.27; 4.39] [0.03; 8.78] [0.01; 4.50] [0.07; 40.47] [0.28; 0.90] [0.41; 2.93] [0.63; 5.84] [0.30; 1.13]	Weight 2.0% 0.8% 1.3% 0.8% 3.4% 10.4% 9.9% 1.7% 5.5% 4.0% 0.8% 0.8% 23.0% 8.0% 6.2% 17.5%
B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects Allergy to metals Angioedema Asthma Contact dermatitis Drug hypersensitivity (inc Penicillin) Food allergy Hypersensitivity unspecified IGE Nasal polyps Oral allergy syndrome Pruritus Rhinitis allergic Seasonal allergy undefined Urticaria Wheezing	Events 2 1 2 0 4 7 7 13 5 5 6 6 1 1 0 1 22 12 14 14 18 3 3	Dupilumab Patient Years 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71	<b>Events</b> 2 0 1 1 3 20 8 1 6 3 1 1 0 24 6 4 17 3	Placebo Patient Years 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74	Incidence Rate Ratio	IRR 0.55 1.65 1.10 0.18 0.73 0.19 0.89 2.75 0.46 1.10 0.55 0.18 - 1.65 0.50 1.10 1.92 0.55 0.58 0.55	<b>95%-Cl</b> [0.08; 3.90] [0.07; 40.47] [0.10; 12.12] [0.01; 4.50] [0.16; 3.27] [0.08; 0.45] [0.37; 2.15] [0.37; 2.15] [0.27; 4.39] [0.02; 4.39] [0.01; 4.50] [0.07; 40.47] [0.28; 0.90] [0.41; 2.93] [0.63; 5.84] [0.30; 1.13] [0.11; 2.72]	Weight 2.0% 0.8% 1.3% 0.8% 3.4% 10.4% 9.9% 1.7% 5.5% 4.0% 0.8% 0.8% 23.0% 8.0% 6.2% 17.5% 3.0%
B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects Allergy to metals Angioedema Asthma Contact dermatitis Drug hypersensitivity (inc Penicillin) Food allergy Hypersenstivity unspecified IGE Nasal polyps Oral allergy syndrome Pruritus Rhinitis allergic Seasonal allergy undefined Urticaria Wheezing	Events 2 0 4 7 13 5 5 6 6 1 1 0 1 22 12 14 18 3	Dupilumab Patient Years 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71	<b>Events</b> 2 0 1 1 3 20 8 1 6 3 1 1 0 24 6 4 17 3	Placebo Patient Years 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74	Incidence Rate Ratio	IRR 0.55 1.65 1.10 0.18 0.73 0.19 0.89 2.75 0.46 1.10 0.55 0.18 - 1.65 0.50 1.10 1.92 0.55 0.55	<b>95%-Cl</b> [0.08; 3.90] [0.07; 40.47] [0.10; 12.12] [0.01; 4.50] [0.16; 3.27] [0.08; 0.45] [0.37; 2.15] [0.37; 2.15] [0.37; 2.15] [0.27; 4.39] [0.02; 4.39] [0.01; 4.50] [0.07; 40.47] [0.28; 0.90] [0.41; 2.93] [0.63; 5.84] [0.30; 1.13] [0.11; 2.72]	Weight 2.0% 0.8% 1.3% 0.8% 3.4% 10.4% 9.9% 1.7% 5.5% 4.0% 1.0% 0.8% 23.0% 8.0% 6.2% 17.5% 3.0%
B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects Allergy to insects Allergy to metals Angioedema Asthma Contact dermatitis Drug hypersensitivity (inc Penicillin) Food allergy Hypersenstivity unspecified IGE Nasal polyps Oral allergy syndrome Pruritus Rhinitis allergic Seasonal allergy undefined Urticaria Wheezing	<b>Events</b> 2 1 2 0 4 7 13 5 6 1 0 1 22 12 14 18 3 116	Dupilumab Patient Years 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71	<b>Events</b> 2 0 1 1 1 3 20 8 1 1 6 3 1 1 0 24 6 4 17 3 101	Placebo Patient Years 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74	Incidence Rate Ratio	IRR 0.55 1.65 1.10 0.18 0.73 0.19 0.89 2.75 0.46 1.10 0.55 0.18 1.65 0.50 1.10 1.92 0.55 0.55 0.55	95%-Cl [0.08; 3.90] [0.07; 40.47] [0.10; 12.12] [0.01; 4.50] [0.03; 0.45] [0.37; 2.15] [0.32; 23.52] [0.14; 1.50] [0.27; 4.39] [0.03; 8.78] [0.01; 4.50] [0.07; 40.47] [0.28; 0.90] [0.41; 2.93] [0.63; 5.84] [0.30; 1.13] [0.11; 2.72] [0.47; 0.82]	Weight 2.0% 0.8% 1.3% 0.8% 3.4% 10.4% 9.9% 1.7% 5.5% 4.0% 1.0% 0.8% 0.8% 23.0% 8.0% 6.2% 17.5% 3.0% <b>100.0%</b>
B Allergy Category Allergy to animal Allergy to chemicals Allergy to insects Allergy to insects Allergy to metals Angioedema Asthma Contact dermatitis Drug hypersensitivity (inc Penicillin) Food allergy Hypersenstivity unspecified IGE Nasal polyps Oral allergy syndrome Pruritus Rhinitis allergic Seasonal allergy undefined Urticaria Wheezing	<b>Events</b> 2 2 1 2 0 4 7 1 3 5 5 6 1 1 0 1 2 2 1 2 1 4 1 8 3 1 1 6	Dupilumab Patient Years 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71 876.71	<b>Events</b> 2 0 1 1 1 3 20 8 1 6 3 1 1 0 24 6 4 17 3 101	Placebo Patient Years 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74 481.74	Incidence Rate Ratio	IRR 0.55 1.65 1.10 0.18 0.73 0.19 0.89 2.75 0.46 1.10 0.55 0.18 1.65 0.50 1.10 1.92 0.58 0.55 0.55 0.62	95%-Cl [0.08; 3.90] [0.07; 40.47] [0.10; 12.12] [0.01; 4.50] [0.16; 3.27] [0.08; 0.45] [0.32; 23.52] [0.14; 1.50] [0.27; 4.39] [0.03; 8.78] [0.01; 4.50] [0.07; 40.47] [0.28; 0.90] [0.41; 2.93] [0.63; 5.84] [0.30; 1.13] [0.11; 2.72] [0.47; 0.82]	Weight 2.0% 0.8% 1.3% 0.8% 3.4% 10.4% 9.9% 1.7% 5.5% 4.0% 1.0% 0.8% 0.8% 23.0% 8.0% 6.2% 17.5% 3.0% <b>100.0%</b>

Favors dupilumab Favors placebo

**FIG 1.** Forest plots **(A)** by allergy category for new and worsened events during the on-treatment period, and **(B)** by allergy category for new events during the on-treatment period.

of study compared to subjects treated with placebo, suggesting attenuation of acquisition of allergenic sensitivity in those treated with dupilumab versus those receiving placebo (Fig 2).

The treatment effect across all studies indicates an overall IRR favoring dupilumab (Fig 3). During the treatment period, dupilumab reduced the risk of new or worsened allergies by 34% (IRR 0.66; 95% CI, 0.52-0.84, Fig 3, A) and new allergies by 37% (IRR 0.63; 95% CI, 0.48-0.83, Fig 3, B), respectively, versus placebo. When IgE category shift (1-step increase) was taken into consideration, a greater reduction in IRR for combined new/worsening

allergic TEAEs of 54% (IRR 0.46; 95% CI, 0.37-0.56, Fig 3, *C*) was observed. Applying the more conservative 2-step definition of IgE change resulted in an IRR reduction of new or worsened allergies of 39% (IRR 0.61; 95% CI, 0.49-0.76, Fig 3, *D*). The longest and most data-dense study (R668-AD-1224) alone showed a statistically significant reduction in allergic TEAE events by dupilumab treatment (IRR 0.59; 95% CI, 0.41-0.85, Fig 3, *A*) for new and worsened allergies during the ontreatment period. A sensitivity analysis that excluded all skin events demonstrated results consistent with the primary analytic

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Α	Dupil	umab	PI	acebo			
Antigen–specific IgE	Events	N	Events	N	Odds Ratio	OR	95%-CI
Alder Grey t2 IgE (kU/L)	3	218	17	142		0.10	[0.03; 0.36]
Alternar Ten/Alter, IgE (kU/L)	3	335	14	220		0.13	[0.04; 0.47]
Asperg. fumig. m3 IgE (kU/L)	0	71	5	50		0.06	[0.00; 1.07]
Bermuda Grass g2 IgE (kU/L)	3	260	11	166		0.16	[0.05; 0.60]
C. Silver Birch t3 IgE (kU/L)	4	333	21	216		0.11	[0.04; 0.33]
Cat Dander IgE (kU/L)	2	327	11	212		0.11	[0.02; 0.51]
Cladosporium IgE (kU/L)	0	259	9	167		0.03	[0.00; 0.56]
Cockroach German IgE (kU/L)	1	256	14	159		0.04	[0.01; 0.31]
Com Sting Nettle w20 IgE (kU/L)	0	37	2	25		0.13	[0.01; 2.73]
Cult. Oat g14 lgE (kU/L)	0	84	5	61		0.06	[0.00: 1.12]
Cypressit Fun t23 laF (kU/L)	0	121	6	81		0.05	[0 00 0 86]
) farianae (mite) IdE (kl l/l )	2	274	12	181		0.00	[0.02: 0.47]
D oter (mite) IgE (kU/L)	1	77	12	47		0.10	[0.02, 0.47]
Dog Dondor IgE (kU/L)	2	220	16	214		0.14	[0.02, 1.01]
	2	126	10	214		0.11	[0.03, 0.40]
English Plantain w0 lgE (kl l/l.)	2	100	0	01		0.15	[0.04, 0.93]
	0	125	0	00		0.04	[0.00, 0.02]
Eucalyptus t18 IgE (KU/L)	0	96	2	68		0.14	[0.01; 2.92]
Japanese Cedar ti / IgE (KU/L)	0	72	6	51		0.05	[0.00; 0.88]
Johnson Grass g10 IgE (kU/L)	2	147	5	93		0.24	[0.05; 1.28]
Vlelaleuca/Bottleb, IgE (kU/L)	0	23	0	17			
Oak White t7 IgE (kU/L)	2	159	4	92		0.28	[0.05; 1.56]
Orchard Grass g3 IgE (kU/L)	0	87	6	62		0.05	[0.00; 0.90]
Oriental Cockroach IgE (kU/L)	0	71	5	49		0.06	[0.00; 1.05]
Ox-eye/Marguerite, IgE (kU/L)	0	23	0	15			
Peren. Rye Grass g5 IgE (kU/L)	0	37	2	27		0.14	[0.01; 2.95]
Raqweed Short/Com IgE (kU/L)	1	187	6	120		0.10	[0.01: 0.86]
Sage, Mugwort w6 lgE (kU/L)	1	286	10	187		0.06	[0.01: 0.49]
Staph Enterotoxin A loE (kU/L)	2	380	21	255		0.06	[0 01: 0 25]
Staph Enterotoxin B lgE (kU/L)	3	380	11	255		0.00	[0.05: 0.64]
	0	72	1	52		0.10	[0.03, 0.04]
Sw. Venial Glass grige (k0/L)	0	225	16	147		0.23	[0.01, 5.05]
	3	420	10	147		0.11	[0.03, 0.39]
Vall Pellitory w 19 IgE (KU/L)	0	138	8	94		0.04	[0.00; 0.64]
/vnite Ash t15 IgE (KU/L)	1	118	4	71		0.14	[0.02; 1.31]
					0.01 0.1 1 10 100		
					$\longleftarrow \longrightarrow$		
					Favors dupilumab Favors placebo		
R							
n	Dumil	umah	DI	aaaba			
0	Dupi	umab		acebo			
Antigen–specific IgE	Events	N	Events	N	Odds Ratio	OR	95%-CI
Antigen–specific IgE	Events	N	Events	N	Odds Ratio	OR	95%-CI
Antigen–specific IgE Alder Grey t2 IgE (kU/L)	Events	N 218	Events	N 142	Odds Ratio	<b>OR</b> 0.13	<b>95%-CI</b> [0.01; 1.09]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L)	Events 1 z3	218 335	Events 5 7	142 220	Odds Ratio	<b>OR</b> 0.13 0.27	<b>95%-Cl</b> [0.01; 1.09] [0.07; 1.07]
Antigen-specific IgE Alder Grey t2 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L)	Events 1 z3 0	218 335 71	Events 5 7 1	142 220 50	Odds Ratio	OR 0.13 0.27 0.23	<b>95%-Cl</b> [0.01; 1.09] [0.07; 1.07] [0.01; 5.78]
Antigen-specific IgE Alder Grey t2 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Sermuda Grass g2 IgE (kU/L)	Events 1 z3 0 1	N 218 335 71 260	5 7 1	142 220 50 166	Odds Ratio	OR 0.13 0.27 0.23 0.64	<b>95%-Cl</b> [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26]
Antigen-specific IgE Alder Grey t2 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Sermuda Grass g2 IgE (kU/L) C. Silver Birch t3 IgE (kU/L)	23 0 1 3	N 218 335 71 260 333	5 7 1 2	142 220 50 166 216	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97	<b>95%-Cl</b> [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.16; 5.87]
Antigen-specific IgE Alder Grey t2 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Bermuda Grass g2 IgE (kU/L) C. Silver Birch t3 IgE (kU/L) Cat Dander IgE (kU/L)	Events 1 23 0 1 3 1	N 218 335 71 260 333 327	Events 5 7 1 1 2 2	142 220 50 166 216 212	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.32	<b>95%-Cl</b> [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.16; 5.87] [0.03; 3.57]
Antigen-specific IgE Alder Grey t2 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Bermuda Grass g2 IgE (kU/L) C. Silver Birch t3 IgE (kU/L) Cat Dander IgE (kU/L) Cladosporium IgE (kU/L)	Events 1 z3 0 1 3 1 0	N 218 335 71 260 333 327 259	Events 5 7 1 2 2 4	142 220 50 166 216 212 167	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.32 0.07	<b>95%-Cl</b> [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.16; 5.87] [0.03; 3.57] [0.00; 1.31]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Bermuda Grass g2 IgE (kU/L) C. Silver Birch 13 IgE (kU/L) Cat Dander IgE (kU/L) Cladosporium IgE (kU/L) Cockroach German IdE (kU/L)	Events 1 23 0 1 3 1 0 1 1	N 218 335 71 260 333 327 259 256	Events 5 7 1 1 2 2 4 3	N 142 220 50 166 216 212 167 159	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.32 0.07 0.20	<b>95%-Cl</b> [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.16; 5.87] [0.03; 3.57] [0.00; 1.31] [0.02; 1.98]
Antigen-specific IgE Alder Grey t2 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) 3ermuda Grass g2 IgE (kU/L) C. Silver Birch t3 IgE (kU/L) Cat Dander IgE (kU/L) Cladosporium IgE (kU/L) Cockroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L)	Events 1 23 0 1 3 1 0 1 0	N 218 335 71 260 333 327 259 256 37	Events 5 7 1 2 2 4 3 3 1	N 142 220 50 166 216 212 167 159 25	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.32 0.07 0.20 0.22	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.16; 5.87] [0.00; 1.31] [0.02; 1.98] [0.01; 5.57]
Antigen-specific IgE Alder Grey t2 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Bermuda Grass g2 IgE (kU/L) C. Silver Birch t3 IgE (kU/L) Cat Dander IgE (kU/L) Cadosporium IgE (kU/L) Cockroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Cuit Dat at 4 IeE (kI/L)	Events 1 23 0 1 3 1 0 1 0 1 0 0	N 218 335 71 260 333 327 259 256 37 84	Events 5 7 1 1 2 2 4 3 1 2	N 142 220 50 166 216 212 167 159 25 61	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.32 0.07 0.20 0.22 0.14	95%-CI [0.01; 1.09] [0.07; 1.07] [0.04; 10.26] [0.04; 10.26] [0.03; 3.57] [0.00; 1.31] [0.02; 1.98] [0.01; 5.57] [0.01; 2.99]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) C. Silver Birch 13 IgE (kU/L) Cat Dander IgE (kU/L) Cladosporium IgE (kU/L) Cockroach German IgE (kU/L) Coros Sting Nettle w20 IgE (kU/L) CurresstI: Fun. 123 IdE (kU/L) CorresstI: Fun. 123 IdE (kU/L)	Events 1 23 0 1 3 1 0 1 0 1 0 0 0 0	N 218 335 71 260 333 327 259 256 37 84 121	Events 5 7 1 1 2 2 4 3 1 2 3	N 142 220 50 166 216 216 212 167 159 25 61 81	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.32 0.07 0.20 0.22 0.14 0.09	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.16; 5.87] [0.00; 1.31] [0.02; 1.98] [0.01; 5.57] [0.01; 2.99] [0.01; 2.91]
Antigen-specific IgE Alder Grey t2 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) C. Silver Birch t3 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cackroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Cult. Oat g14 IgE (kU/L) Cypressit. Fun. 123 IgE (kU/L) Cypressit. Fun. 23 IgE (kU/L)	Events 1 23 0 1 3 1 0 1 0 1 0 0 0 0 0	N 218 335 71 260 333 327 259 256 37 84 121 274	Events 5 7 1 2 2 4 3 1 2 3 2 3	N 142 220 50 166 216 212 167 159 25 61 81 181	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.32 0.07 0.20 0.22 0.14 0.09 0.13	<b>95%-Cl</b> [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.03; 3.57] [0.00; 1.31] [0.02; 1.98] [0.01; 5.57] [0.01; 2.99] [0.00; 1.81] [0.01; 2.74]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Bermuda Grass g2 IgE (kU/L) C. Silver Birch 13 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Catorach German IgE (kU/L) Cockroach German IgE (kU/L) Couth Cat g14 IgE (kU/L) Cypressit. Fun. 123 IgE (kU/L) D. farianae (mite) IgE (kU/L) D. ter (mite) IgE (kU/L)	Events 1 23 0 1 3 1 0 1 0 0 0 0 0 0	N 218 335 71 260 333 327 259 256 37 84 121 274 77	Events 5 7 1 1 2 2 4 3 1 2 3 2 0	N 142 220 50 166 216 212 167 159 25 61 81 181 47	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.32 0.07 0.20 0.22 0.14 0.09 0.13	95%-Cl [0.01; 1.09] [0.07; 10.7] [0.01; 5.78] [0.04; 10.26] [0.03; 3.57] [0.00; 1.31] [0.02; 1.98] [0.01; 5.57] [0.01; 2.99] [0.00; 1.81] [0.01; 2.74]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg, fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) C. Silver Birch 13 IgE (kU/L) Cat Dander IgE (kU/L) Cadosporium IgE (kU/L) Cockroach German IgE (kU/L) Cockroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Cut. Oat g14 IgE (kU/L) Cypressit. Fun. 123 IgE (kU/L) O. farianae (mite) IgE (kU/L) D. pter (mite) IgE (kU/L) Dan Dander IgE (kU/L)	Events 1 23 0 1 3 1 0 1 0 0 0 0 0 0 0	N 218 335 71 260 333 327 259 256 37 84 121 274 274 777 220	Events 5 7 1 2 2 4 3 1 2 3 2 0 0 0 2	N 142 220 50 166 216 212 167 159 25 61 81 181 181 47 214	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.327 0.20 0.22 0.14 0.09 0.13	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.16; 5.87] [0.03; 3.57] [0.02; 1.98] [0.01; 5.57] [0.01; 2.99] [0.00; 1.81] [0.01; 2.74]
Antigen-specific IgE Alder Grey t2 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) C. Silver Birch t3 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cackroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Cult. Oat g14 IgE (kU/L) C. farianae (mite) IgE (kU/L) O. farienae (IgE (kU/L) Dog Dander IgE (kU/L) Com Sting KU/L)	Events 1 23 0 1 1 3 1 0 1 0 0 0 0 0 0 0 0 0 1 1	N 218 335 71 260 333 327 259 256 37 84 121 274 77 329 126	Events 5 7 1 1 2 2 4 3 1 2 3 2 0 2 2 0 2 2	N 142 220 50 166 216 212 167 159 25 61 81 181 47 214	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.32 0.07 0.20 0.22 0.12 0.13 0.32 0.32	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.16; 5.87] [0.00; 1.31] [0.02; 1.98] [0.01; 5.57] [0.01; 2.99] [0.01; 2.74] [0.03; 3.59] [0.02; 3.29]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Bermuda Grass g2 IgE (kU/L) Bermuda Grass g2 IgE (kU/L) Common Stander IgE (kU/L) Cat Dander IgE (kU/L) Catosporium IgE (kU/L) Cockroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Do farianae (mite) IgE (kU/L) Do g Dander IgE (kU/L) Emitie IgE (kU/L)	Events 1 23 1 1 3 1 1 0 1 0 0 0 0 0 0 0 0 1 1	N 218 335 71 260 333 327 259 256 37 84 121 274 77 329 136	Events 5 7 1 2 2 4 3 1 2 3 2 2 0 0 2 2 2 2	N 142 220 50 166 216 212 167 159 25 61 81 181 47 214 81	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.32 0.07 0.20 0.22 0.14 0.09 0.13 0.32 0.22	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.16; 5.87] [0.02; 1.98] [0.02; 1.98] [0.01; 5.57] [0.01; 5.57] [0.02; 1.98] [0.02; 1.98] [0.02; 1.98] [0.02; 1.98] [0.03; 3.57] [0.03; 3.59] [0.03; 3.59] [0.03; 3.28]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg, fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cockroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Con Sting Nettle (kU/L) Con Sting Nettle (kU/L) Con farianae (mite) IgE (kU/L) D. farianae (mite) IgE (kU/L) Do g Dander IgE (kU/L) Em 18 IgE (kU/L) English Plantain w9 IgE (kU/L)	Events 1 2 1 3 0 1 3 1 0 1 0 0 0 0 0 0 1 1 0 0 0 0 0 1 1 0 0 1 0 1 0 0 1 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 0 1 0 0 0 1 0 0 0 1 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	N 218 335 71 260 333 327 259 256 37 84 121 274 77 329 136 125 256	Events 5 7 1 2 2 4 3 1 2 3 3 2 0 0 2 2 2 2 2	N 142 220 50 166 216 212 167 159 25 61 81 181 47 214 81 83 33	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.32 0.07 0.22 0.14 0.09 0.13 0.32 0.29 0.13	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.16; 5.87] [0.02; 1.98] [0.02; 1.98] [0.01; 5.57] [0.01; 2.98] [0.01; 2.74] [0.03; 3.59] [0.03; 3.28] [0.01; 2.74]
Antigen-specific IgE Alder Grey t2 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Bermuda Grass g2 IgE (kU/L) C. Silver Birch t3 IgE (kU/L) Cat Dander IgE (kU/L) Catoasporium IgE (kU/L) Cockroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Cult. Oat g14 IgE (kU/L) Cypressit. Fun. 123 IgE (kU/L) O. farianae (mite) IgE (kU/L) O. farienae (IgE (kU/L) Dog Dander IgE (kU/L) Einit 8 IgE (kU/L) Eucalyptus t18 IgE (kU/L)	Events 1 2 3 1 0 1 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	N 218 335 71 260 333 327 259 256 37 84 121 274 77 329 136 125 96	Events 5 7 1 2 2 4 3 1 2 3 3 2 0 2 2 2 2 2 0 0 2 2 2 0 0 0 2 0 0 0 0 0 0	N 142 220 50 166 216 212 167 159 25 61 81 181 47 214 81 83 68	Odds Ratio	OR 0.13 0.23 0.64 0.97 0.32 0.07 0.20 0.22 0.14 0.09 0.13 0.32 0.29 0.13	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.16; 5.87] [0.00; 1.31] [0.02; 1.98] [0.01; 5.57] [0.01; 2.99] [0.01; 2.74] [0.03; 3.59] [0.03; 3.28] [0.01; 2.74]
Antigen–specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Bermuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Catosporium IgE (kU/L) Cockroach German IgE (kU/L) Cockroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Con Sting Nettle w20 IgE (kU/L) Corresting Nettle w20 IgE (kU/L) D. farianae (mite) IgE (kU/L) D. gp Dander IgE (kU/L) Dog Dander IgE (kU/L) Em It8 IgE (kU/L) English Plantain w9 IgE (kU/L) Japanese Cedar 117 IgE (kU/L)	Events 1 23 0 1 3 1 0 1 0 0 0 0 0 0 0 0 0 1 1 0 0 0 0	N 218 335 71 260 333 327 259 256 37 84 121 274 77 329 136 125 96 72	Events 5 7 1 2 2 4 3 1 2 3 3 1 2 2 0 0 2 2 2 0 0 0 0 0 0 0	N 142 220 50 166 216 212 167 159 25 61 81 181 47 214 81 83 68 51	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.32 0.07 0.20 0.22 0.14 0.09 0.13 0.32 0.29 0.13	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.16; 5.87] [0.02; 1.98] [0.02; 1.98] [0.01; 5.57] [0.01; 2.99] [0.02; 1.81] [0.01; 2.74] [0.03; 3.59] [0.03; 3.28] [0.01; 2.74]
Antigen–specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg, fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cackroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Com Sting Nettle (kU/L) Com Sting Nettle (kU/L) Com Sting Nettle (kU/L) D. farianae (mite) IgE (kU/L) D. farianae (mite) IgE (kU/L) D. farianae (kU/L) D. farianae (kU/L) Eint 81 IgE (kU/L) Eint 81 IgE (kU/L) Eint 81 IgE (kU/L) Eindish Plantain w9 IgE (kU/L) Japanese Cedar 117 IgE (kU/L) Johnson Grass g10 IgE (kU/L)	Events 1 23 0 1 3 1 0 1 0 0 0 0 0 0 0 0 0 1 1 0 0 0 0 0 0 1 1 0 1 1 0 1 1 0 1 1 0 1 1 0 1 1 0 1 1 0 1 1 0 1 1 0 1 1 0 1 0 1 1 0 1 0 1 0 1 0 1 0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	N 218 335 71 260 333 327 259 256 37 84 121 274 77 329 136 125 96 72 147	Events 5 7 1 2 2 4 3 1 2 3 3 2 3 2 0 0 2 2 2 0 0 2 2 0 0 0 2 2 2 0 0 0 2 2	N 142 220 50 166 216 212 167 159 25 61 181 47 214 81 83 68 51 93	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.20 0.20 0.22 0.14 0.09 0.13 0.32 0.29 0.13	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.03; 3.57] [0.02; 1.98] [0.02; 1.98] [0.02; 5.57] [0.01; 2.74] [0.03; 3.59] [0.03; 3.28] [0.01; 2.74] [0.03; 3.49]
Antigen–specific IgE Alder Grey t2 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) C. Silver Birch t3 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cackroach German IgE (kU/L) Con Sting Nettle w20 IgE (kU/L) Con Sting Nettle w20 IgE (kU/L) Con Gring nettle w20 IgE (kU/L) O. farianae (mite) IgE (kU/L) O. farianae (mite) IgE (kU/L) D. farianae (IgE (kU/L) D. farianae (IgE (kU/L) Dog Dander IgE (kU/L) Eint 8 IgE (kU/L) Einglish Plantain w9 IgE (kU/L) Japanese Cedar 117 IgE (kU/L) Johnson Grass g10 IgE (kU/L) Melaleuca/Bottleb, IgE (kU/L)	Events 1 2 3 1 0 1 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	N 218 335 71 260 333 327 259 256 37 259 256 37 121 274 77 329 136 125 96 72 147 23	Events 5 7 1 1 2 2 4 3 1 2 3 3 2 0 2 2 2 2 0 0 0 2 0 2 0 0 0 0 0	N 142 220 50 166 216 216 159 25 61 181 47 214 81 83 68 51 93 17	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.22 0.07 0.22 0.14 0.09 0.13 0.32 0.29 0.13	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.16; 5.87] [0.00; 1.31] [0.02; 1.98] [0.01; 5.57] [0.01; 2.99] [0.01; 2.74] [0.03; 3.59] [0.03; 3.28] [0.01; 2.74] [0.03; 3.49]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cockroach German IgE (kU/L) Cockroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Cortarianae (mite) IgE (kU/L) D. farianae (mite) IgE (kU/L) Dog Dander IgE (kU/L) Dog Dander IgE (kU/L) Eint 8 IgE (kU/L) Eint 8 IgE (kU/L) Eint 8 IgE (kU/L) Japanese Cedar 117 IgE (kU/L) Johnson Grass g10 IgE (kU/L) Melaleuca/Bottleb, IgE (kU/L) Dak White 17 IgE (kU/L)	Events 1 23 0 1 3 1 0 1 0 0 0 0 0 0 0 0 1 1 0 0 1 1 0 0 1 1 0 0 1 1 0 0 1 1 0 0 1 1 0 0 1 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	N 218 335 71 260 333 327 259 256 37 84 121 274 121 274 329 136 125 96 72 147 23 159	Events 5 7 1 2 2 4 3 1 2 3 3 1 2 2 0 0 2 2 2 0 0 2 2 0 0 2 0 0 2 0 1	N 142 220 50 166 216 212 167 159 25 61 81 181 181 47 214 81 83 68 51 93 17 92	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.32 0.07 0.20 0.22 0.14 0.09 0.13 0.32 0.13 0.32 0.31 0.58	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.16; 5.87] [0.02; 1.98] [0.01; 5.57] [0.01; 2.98] [0.01; 2.74] [0.03; 3.59] [0.03; 3.28] [0.01; 2.74] [0.03; 3.49] [0.03; 3.49] [0.04; 9.32]
Antigen–specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg, fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Catockroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Com Sting Nettle (kU/L) Com Sting Nettle (kU/L) Com Sting Nettle (kU/L) D. farianae (mite) IgE (kU/L) D. farianae (mite) IgE (kU/L) D. farianae (mite) IgE (kU/L) D. farianae (mite) IgE (kU/L) Dander IgE (kU/L) Eint 81 IgE (kU/L) Eint 81 IgE (kU/L) Eint 81 IgE (kU/L) Japanese Cedar 117 IgE (kU/L) Johnson Grass g10 IgE (kU/L) Dak White 77 IgE (kU/L) Drchard Grass g3 IgE (kU/L)	Events 1 2 1 3 1 1 3 1 0 1 0 0 0 0 0 0 0 0 0 0 1 1 0 0 0 0 0 0 0 1 1 0 1 0 1 0 0 1 1 0 0 1 1 0 0 1 0 0 1 0 0 1 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	N 218 335 71 260 333 2259 256 37 259 256 37 259 256 37 259 256 37 259 256 37 259 256 37 259 256 37 121 274 121 274 121 274 125 96 125 96 125 96 125 96 329 259 259 259 259 259 259 259 259 259 2	Events 5 7 1 2 2 4 3 1 2 3 3 2 3 2 0 0 2 2 2 0 0 2 2 0 0 1 1	N 142 220 50 166 212 167 159 25 61 81 181 47 214 83 68 51 93 17 92 62	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.20 0.22 0.14 0.09 0.13 0.32 0.29 0.13 0.31 0.58 0.23	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.06; 5.87] [0.00; 1.31] [0.02; 1.98] [0.01; 5.57] [0.01; 2.98] [0.01; 2.74] [0.03; 3.29] [0.01; 2.74] [0.03; 3.28] [0.01; 2.74] [0.03; 3.49] [0.04; 9.32] [0.04; 5.85]
Antigen–specific IgE Alder Grey t2 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) C. Silver Birch t3 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Catorach German IgE (kU/L) Con Sting Nettle w20 IgE (kU/L) Con Sting Nettle w20 IgE (kU/L) Cult. Oat g14 IgE (kU/L) Cult. Oat g14 IgE (kU/L) C. farianae (mite) IgE (kU/L) O. farianae (IgE (kU/L) D. farianae (IgE (kU/L) Dander IgE (kU/L) Eint 8 IgE (kU/L) Einglish Plantain w9 IgE (kU/L) Jahnson Grass g10 IgE (kU/L) Jahnson Grass g10 IgE (kU/L) Dak White t7 IgE (kU/L) Drchard Grass g3 IgE (kU/L) Driental Cockroach IgE (kU/L)	Events 1 2 3 0 1 3 1 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	N 218 335 71 260 333 327 259 256 37 84 121 274 77 329 136 72 125 96 72 147 23 159 87 71	Events 5 7 1 1 2 2 4 3 1 2 3 3 2 0 2 2 2 2 0 0 0 2 2 2 0 0 1 1 1 1 0	N 142 220 50 166 216 212 167 159 25 61 81 181 47 214 83 68 51 93 17 92 62 49	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.20 0.22 0.14 0.09 0.13 0.32 0.29 0.13 0.32 0.29 0.13 0.31 0.58 0.23	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.04; 5.87] [0.03; 3.57] [0.02; 1.98] [0.01; 5.57] [0.01; 2.99] [0.02; 1.81] [0.01; 2.74] [0.03; 3.59] [0.03; 3.59] [0.03; 3.49] [0.04; 9.32] [0.01; 5.85]
Antigen-specific IgE Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cockroach German IgE (kU/L) Cockroach German IgE (kU/L) Corkorach German IgE (kU/L) Dong Dander IgE (kU/L) Dong Dander IgE (kU/L) Dong Dander IgE (kU/L) Eint 8 IgE (kU/L) Eint 8 IgE (kU/L) Danson Grass g10 IgE (kU/L) Dak White 17 IgE (kU/L) Drehard Grass g3 IgE (kU/L) Drehard Grass g3 IgE (kU/L) Drehard IceKorach IgE (kU/L) Coresper/Marguerite, IgE (kU/L)	Events  1 23 0 1 3 3 1 0 1 3 0 0 1 1 0 0 0 0 0 1 1 0 0 0 1 1 0 0 0 1 1 0	N 218 335 71 260 333 327 259 337 327 259 37 84 121 274 77 329 136 125 96 72 147 239 59 6 72 147 23	Events 5 7 1 2 2 4 3 1 2 2 4 3 1 2 2 2 0 0 2 2 2 0 0 2 2 0 0 2 1 1 1 0 0 0 2 0 0 0 2 0 0 0 0	N 142 220 50 166 212 167 159 25 61 181 47 214 81 83 68 51 93 17 92 62 49 15	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.22 0.14 0.09 0.13 0.32 0.13 0.32 0.13 0.32 0.31 0.58 0.23	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.03; 3.57] [0.02; 1.98] [0.01; 5.57] [0.01; 2.98] [0.01; 2.74] [0.03; 3.59] [0.01; 2.74] [0.03; 3.49] [0.03; 3.49] [0.04; 9.32] [0.01; 5.85]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg, fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Catockroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Com Sting Nettle (kU/L) Com Sting Nettle (kU/L) Com Sting Nettle (kU/L) D. farianae (mite) IgE (kU/L) D. farianae (mite) IgE (kU/L) Do g Dander IgE (kU/L) Eint 81 IgE (kU/L) Eint 81 IgE (kU/L) Eint 81 IgE (kU/L) Japanese Cedar 117 IgE (kU/L) Japanese Cedar 117 IgE (kU/L) Dak White 17 IgE (kU/L) Drichard Grass g3 IgE (kU/L) Drichard Grass g3 IgE (kU/L) Drichard Grass g3 IgE (kU/L) Paren. Rye Grass g5 IgE (kU/L)	Events Events 1 2 3 1 1 3 1 0 1 0 0 0 0 0 0 0 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0	N 218 335 71 260 333 327 259 256 337 84 121 121 274 77 329 96 125 96 125 96 125 96 125 57 2 147 23 37 59 57 2 59 37 37 57 57 57 57 57 57 57 57 57 57 57 57 57	Events 5 7 1 2 2 4 3 1 2 3 3 2 2 0 0 2 2 2 0 0 2 2 0 0 1 1 0 0 0 0 0	N 142 220 50 166 212 167 159 25 61 81 181 47 214 83 68 51 93 17 92 62 49 15 27	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.20 0.22 0.14 0.09 0.13 0.32 0.29 0.13 0.31 0.58 0.23	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.03; 3.57] [0.02; 1.98] [0.02; 1.98] [0.01; 5.57] [0.01; 2.74] [0.03; 3.29] [0.03; 3.28] [0.01; 2.74] [0.03; 3.49] [0.04; 9.32] [0.01; 5.85]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg, fumig. m3 IgE (kU/L) Bermuda Grass g2 IgE (kU/L) Common Stand Stand Stand Solver Birch 13 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cockroach German IgE (kU/L) Corkorach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Dog Dander IgE (kU/L) Dog Dander IgE (kU/L) English Plantain w9 IgE (kU/L) Japanese Cedar 117 IgE (kU/L) Dahnson Grass g10 IgE (kU/L) Dak White t7 IgE (kU/L) Driental Cockroach IgE (kU/L) Driental Gockroach IgE (kU/L) Driental Gockroach IgE (kU/L) Driental Gockroach IgE (kU/L) Paren. Rye Grass g5 IgE (kU/L) Paren Rye Grass g5 IgE (kU/L)	Events  1 23 0 1 3 0 1 0 0 0 0 0 0 0 0 1 1 0 0 0 0	N 218 335 711 260 333 327 259 333 327 259 337 259 337 125 96 72 147 72 329 136 72 125 96 72 147 73 37 159 87 71 83 71 84 71 87 187	Events 5 7 1 2 2 3 3 1 2 3 3 1 2 2 3 2 2 2 2 0 0 2 2 2 0 0 2 2 0 0 1 1 1 0 0 0 1 1	N 142 220 50 166 212 167 212 167 25 61 181 181 47 214 81 83 51 93 68 51 93 17 92 62 49 15 27 27 27 27 27 27 27 27 27 27	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.32 0.07 0.20 0.22 0.14 0.99 0.13 0.32 0.29 0.13 0.31 0.58 0.23	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.05; 5.87] [0.02; 1.98] [0.01; 5.57] [0.02; 1.98] [0.01; 5.57] [0.01; 2.74] [0.03; 3.59] [0.03; 3.59] [0.03; 3.28] [0.01; 2.74] [0.03; 3.49] [0.04; 9.32] [0.04; 10.33]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander German IgE (kU/L) Cockroach German IgE (kU/L) Cockroach German IgE (kU/L) Cors Sting Nettle w20 IgE (kU/L) Corpander IgE (kU/L) Dog Dander IgE (kU/L) Eint 8 IgE (kU/L) Eint 8 IgE (kU/L) Eint 8 IgE (kU/L) Eucalyptus 118 IgE (kU/L) Johnson Grass g10 IgE (kU/L) Drichard Grass g3 IgE (kU/L) Drichard Grass g3 IgE (kU/L) Prenen. Rye Grass g5 IgE (kU/L) Page, Muawort w6 IaE (kU/L) Sage, Muawort w6 IaE (kU/L)	Events  1 2 3 0 1 3 1 0 1 0 0 0 0 0 0 1 1 0 0 0 0 1 1 0 0 0 0 1 1 0 0 0 0 1 1 1 0 0 0 1 1 1 0 0 0 1 1 1 0 0 0 1 1 1 0 0 0 1 1 1 0 0 0 1 1 1 0 0 0 1 1 1 0 0 0 1 1 1 0 0 0 1 1 1 0 0 0 1 1 1 0 0 0 0 1 1 1 0 0 0 0 1 1 1 0 0 0 0 1 1 1 0 0 0 0 1 1 1 0 0 0 0 0 1 1 1 0 0 0 0 0 1 1 1 0 0 0 0 0 0 1 1 1 0 0 0 0 0 0 1 1 1 0 0 0 0 0 0 0 1 1 1 0	N 218 335 711 260 333 327 259 333 327 259 337 84 121 274 77 329 136 125 96 72 136 125 96 72 147 23 37 159 87 71 23 37 37 187 72 23 84 23 22 23 22 23 23 25 25 25 25 25 25 25 25 25 25 25 25 25	Events 5 7 1 2 2 4 3 1 2 2 4 3 3 2 2 0 0 2 2 2 0 0 2 2 0 0 2 2 0 0 1 1 1 0 0 0 1 1 1 2 2 3 3 3 1 2 0 0 2 2 0 0 1 2 2 1 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 3 1 2 2 4 3 3 3 2 2 4 3 1 2 2 4 3 3 3 2 2 4 4 3 3 3 2 2 4 3 3 2 2 4 4 3 3 2 2 4 4 3 3 2 2 4 4 3 3 2 2 4 4 3 3 2 2 4 4 3 3 2 2 4 4 3 3 2 2 4 4 3 3 3 2 2 2 4 3 3 2 2 2 4 3 3 2 2 2 2	N 142 220 50 166 212 167 159 25 61 181 47 214 81 83 68 51 93 17 92 62 49 15 27 120 16 187 15 16 187 15 16 16 16 16 16 16 16 16 16 16	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.20 0.22 0.14 0.09 0.13 0.32 0.32 0.13 0.32 0.31 0.58 0.23	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.05; 5.87] [0.02; 1.98] [0.02; 1.98] [0.01; 5.57] [0.01; 2.99] [0.02; 1.98] [0.01; 2.74] [0.03; 3.59] [0.03; 3.59] [0.03; 3.59] [0.03; 3.49] [0.04; 9.32] [0.04; 5.85] [0.04; 10.33] [0.03; 3.60]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg, fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Catockroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Com Sting Nettle (kU/L) Com Sting Nettle (kU/L) D. farianae (mite) IgE (kU/L) D. farianae (mite) IgE (kU/L) D. farianae (mite) IgE (kU/L) Eint 81 IgE (kU/L) Eint 81 IgE (kU/L) Eint 81 IgE (kU/L) Dapanese Cedar 117 IgE (kU/L) Japanese Cedar 117 IgE (kU/L) Dack White 77 IgE (kU/L) Drichard Grass g3 IgE (kU/L) Drichard Grass g3 IgE (kU/L) Drichard Grass g3 IgE (kU/L) Drichard Grass g3 IgE (kU/L) Paren. Rye Grass g5 IgE (kU/L) Ragweed Short/Com IgE (kU/L) Stape Enterotoxin A InF (kU/L)	Events Events 1 2 3 1 1 3 1 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	N 218 335 71 260 333 327 259 256 37 329 256 37 37 84 121 121 274 77 329 136 125 96 125 96 72 147 235 57 218 37 37 329 37 329 37 329 37 327 259 37 37 329 259 37 37 37 37 37 37 37 37 37 37 37 37 37	Events 5 7 1 1 2 2 4 3 1 2 3 3 2 3 3 2 2 0 0 2 2 2 0 0 2 2 2 0 0 1 1 0 0 1 1 2 2 8 8	N 142 220 50 166 212 167 159 25 61 81 83 68 51 93 17 92 62 49 15 62 49 15 27 120 187 25 50 167 197 25 50 106 212 25 25 25 25 25 25 25 25 25 2	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.20 0.22 0.14 0.09 0.13 0.32 0.29 0.13 0.31 0.58 0.23 0.64 0.32 0.44 0.32 0.44 0.97 0.32 0.44 0.97 0.20 0.20 0.22 0.14 0.97 0.20 0.13 0.44 0.97 0.20 0.22 0.14 0.97 0.20 0.13 0.44 0.97 0.20 0.22 0.14 0.93 0.13 0.13 0.22 0.14 0.13 0.13 0.29 0.13 0.13 0.20 0.22 0.14 0.13 0.29 0.13 0.29 0.13 0.32 0.13 0.32 0.14 0.32 0.13 0.29 0.13 0.32 0.32 0.32 0.44 0.97 0.20 0.13 0.32 0.32 0.32 0.44 0.97 0.32 0.14 0.97 0.20 0.13 0.32 0.32 0.32 0.31 0.58 0.23 0.44 0.97 0.32 0.32 0.32 0.34 0.32 0.32 0.32 0.34 0.32 0.32 0.34 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.44 0.32 0.32 0.32 0.44 0.58 0.23 0.44 0.43 0.58 0.44 0.	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.03; 3.57] [0.02; 1.38] [0.01; 5.57] [0.01; 5.57] [0.01; 2.74] [0.03; 3.59] [0.03; 3.28] [0.01; 2.74] [0.03; 3.49] [0.04; 9.32] [0.04; 9.32] [0.04; 10.33] [0.03; 3.60]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Bermuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Corkroach German IgE (kU/L) Do g Dander IgE (kU/L) Do g Dander IgE (kU/L) Dog Dander IgE (kU/L) Dog Dander IgE (kU/L) Em 18 IgE (kU/L) Em 18 IgE (kU/L) Japanese Cedar 117 IgE (kU/L) Johnson Grass g10 IgE (kU/L) Dak White 17 IgE (kU/L) Driental Cockroach IgE (kU/L) Driental Gockroach IgE (kU/L) Driental Gockroach IgE (kU/L) Peren. Rye Grass g5 IgE (kU/L) Sagwed Short/Com IgE (kU/L) Staph Enterotoxin A IgE (kU/L)	Events  1 23 0 1 3 3 1 0 1 3 1 0 0 0 0 0 0 0 0 1 1 0 0 0 0	N 218 335 71 260 333 327 259 333 327 259 337 84 121 274 77 121 274 77 122 96 72 136 125 96 72 337 159 87 123 37 123 337 123 337 337 337 337 337 337 337 337 337 3	Events 5 7 1 2 2 4 3 1 2 2 3 3 1 2 2 2 2 2 0 0 2 2 2 0 0 2 2 0 0 1 1 1 0 0 0 1 1 2 8 4 4 3 3 1 2 2 3 3 1 1 2 2 4 4 3 3 1 1 2 2 4 4 3 3 1 1 2 2 4 4 3 3 1 1 2 2 4 4 3 3 1 1 2 2 4 4 3 3 1 1 2 2 4 4 3 3 1 1 2 2 4 4 3 3 1 1 2 2 4 4 3 3 1 1 2 2 4 4 3 3 1 1 2 2 4 4 3 3 1 1 2 2 4 4 3 3 1 1 2 2 4 4 3 3 3 2 2 2 4 4 3 3 3 2 2 2 4 4 3 3 3 2 2 2 2	N 142 220 50 166 212 167 255 61 181 181 477 214 81 83 86 51 93 77 92 62 49 155 277 120 187 255 50 187 255 275 275 275 275 275 275 27	Odds Ratio	OR 0.13 0.27 0.23 0.64 0.97 0.32 0.07 0.22 0.14 0.97 0.22 0.13 0.32 0.31 0.58 0.23 0.64 0.32 0.64 0.75 0.	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.06; 5.87] [0.02; 1.98] [0.01; 5.57] [0.02; 1.98] [0.01; 5.57] [0.01; 2.99] [0.01; 2.74] [0.03; 3.59] [0.03; 3.28] [0.01; 2.74] [0.03; 3.49] [0.04; 9.32] [0.04; 9.32] [0.04; 10.33] [0.03; 3.60] [0.00; 0.67] [0.02; 14.9]
Antigen-specific IgE Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg, fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander German IgE (kU/L) Cockroach German IgE (kU/L) Corkorach German IgE (kU/L) Cors Sting Nettle w20 IgE (kU/L) Cors Sting Nettle w20 IgE (kU/L) Cor Sting Nettle w20 IgE (kU/L) Cor Sting Nettle w20 IgE (kU/L) Cor Sting Nettle w20 IgE (kU/L) D. farianae (mite) IgE (kU/L) D. farianae (mite) IgE (kU/L) Dog Dander IgE (kU/L) Eucalyptus 118 IgE (kU/L) Eucalyptus 118 IgE (kU/L) Japanese Cedar 117 IgE (kU/L) Datw Vhite 17 IgE (kU/L) Drichard Grass g3 IgE (kU/L) Driental Cockroach IgE (kU/L) Peren. Rye Grass g5 IgE (kU/L) Page. Mugwort w6 IgE (kU/L) Staph Enterotoxin A IgE (kU/L) Staph Enterotoxin B IgE (kU/L)	Events	N 218 335 71 260 333 327 259 333 327 259 337 259 329 127 47 77 329 96 125 427 47 72 329 96 125 427 47 72 329 587 72 159 87 71 23 37 187 71 23 337 327 259 329 20 327 259 329 327 259 329 327 259 329 20 327 20 329 327 20 329 20 327 20 327 20 327 20 327 20 327 20 327 20 327 20 327 20 327 20 327 20 327 20 327 20 327 20 327 20 327 20 327 20 327 20 327 20 327 20 20 37 20 37 20 37 20 37 20 37 20 37 20 37 20 37 20 37 20 37 20 20 20 20 20 20 20 20 20 20 20 20 20	Events 5 7 1 2 2 4 3 3 1 2 2 4 3 3 2 2 0 0 2 2 2 0 0 2 2 0 0 2 2 0 0 1 1 1 0 0 0 1 1 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 4 3 1 2 2 4 4 3 1 2 2 4 4 3 1 2 2 4 4 3 1 2 2 4 4 3 1 2 2 4 4 3 1 2 2 2 4 4 3 2 2 2 4 3 3 2 2 2 2 2 2 2 2	N 142 220 50 166 212 167 159 25 61 181 47 214 81 81 83 68 51 93 17 92 62 49 51 92 62 49 51 25 25 51 25 25 25 25 25 25 25 25 25 25	Odds Ratio	OR           0.13           0.27           0.23           0.64           0.97           0.32           0.77           0.20           0.14           0.99           0.13           0.32           0.13           0.32           0.13           0.32           0.13           0.32           0.13           0.32           0.31           0.58           0.23           0.64           0.32           0.04           0.17	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.03; 3.57] [0.02; 1.98] [0.01; 5.57] [0.01; 2.99] [0.01; 2.74] [0.03; 3.59] [0.01; 2.74] [0.03; 3.59] [0.01; 2.74] [0.03; 3.49] [0.04; 9.32] [0.04; 5.85] [0.04; 10.33] [0.03; 3.60] [0.02; 1.49]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg, fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Catockroach German IgE (kU/L) Cockroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Con Sting Nettle w20 IgE (kU/L) Con Sting Nettle w20 IgE (kU/L) Con Sting Nettle w20 IgE (kU/L) D. farianae (mite) IgE (kU/L) D. farianae (mite) IgE (kU/L) D. farianae (kU/L) Eint 81 IgE (kU/L) Eint 81 IgE (kU/L) Eint 81 IgE (kU/L) Dop Dander IgE (kU/L) Dapanese Cedar 117 IgE (kU/L) Johnson Grass g10 IgE (kU/L) Drchard Grass g3 IgE (kU/L) Drchard Grass g3 IgE (kU/L) Paren. Rye Grass g5 IgE (kU/L) Ragweed Short/Com IgE (kU/L) Staph Enterotoxin A IgE (kU/L) Staph Enterotoxin A IgE (kU/L) Sw. Vernal Grass g1 IgE (kU/L) Sw. Vernal Grass g1 IgE (kU/L)	Events 1 3 0 1 3 3 1 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	N 218 335 711 260 3327 259 256 37 329 256 37 329 256 37 329 121 121 125 96 72 1125 96 72 1125 96 72 1125 96 72 1125 96 37 37 37 37 37 37 37 37 37 37 37 37 37	Events 5 7 1 1 2 2 4 3 1 2 3 3 2 3 2 0 0 2 2 2 0 0 2 2 2 0 0 1 1 0 0 0 1 1 2 8 4 0 0 0 0 1 2 2 2 0 0 0 0 0 1 1 1 2 2 4 4 3 2 2 2 4 3 2 2 2 4 4 3 2 2 2 4 4 3 2 2 2 4 3 2 2 2 4 4 3 2 2 2 4 4 3 2 2 2 4 4 3 2 2 2 4 4 3 2 2 2 4 4 3 2 2 2 4 4 3 2 2 2 2	N 142 220 50 166 212 167 159 25 61 81 47 214 83 68 51 83 17 93 17 92 62 49 15 62 49 15 52 52 52 52 52 52 52 52 52 5	Odds Ratio	OR           0.13           0.27           0.23           0.64           0.32           0.07           0.20           0.14           0.09           0.13           0.32           0.14           0.09           0.13           0.32           0.13           0.31           0.58           0.23           0.64           0.32           0.64           0.32           0.64           0.32           0.64           0.32           0.64           0.32	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 5.87] [0.02; 1.98] [0.02; 1.98] [0.01; 5.57] [0.01; 2.74] [0.01; 2.74] [0.03; 3.29] [0.03; 3.28] [0.01; 2.74] [0.03; 3.49] [0.04; 9.32] [0.01; 5.85] [0.04; 10.33] [0.03; 3.60] [0.00; 0.67] [0.02; 2.50]
Antigen-specific IgE Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cockroach German IgE (kU/L) Corkorach German IgE (kU/L) Corkorach German IgE (kU/L) Corkorach German IgE (kU/L) Corkorach German IgE (kU/L) Cor Sting Nettle w20 IgE (kU/L) Cor Sting Nettle w20 IgE (kU/L) Dog Dander IgE (kU/L) Dog Dander IgE (kU/L) Dog Dander IgE (kU/L) Dag Dander IgE (kU/L) End Is IgE (kU/L) End Is IgE (kU/L) Iapanese Cedar 117 IgE (kU/L) Dak White 17 IgE (kU/L) Dacatyptus 118 IgE (kU/L) Dachard Grass g3 IgE (kU/L) Dachard Grass g5 IgE (kU/L) Peren. Rye Grass g5 IgE (kU/L) Staph Enterotoxin A IgE (kU/L) Staph Enterotoxin A IgE (kU/L) Staph Enterotoxin A IgE (kU/L) Staph Enterotoxin A IgE (kU/L) Staph Enterotoxin B IgE (kU/L) Staph Enterotoxin B IgE (kU/L) Staph Enterotoxin B IgE (kU/L) Firmothy (Phleump.) IgE (kU/L)	Events  1 23 0 1 3 3 1 0 1 1 0 0 0 0 0 0 0 1 1 0 0 0 0	N 218 335 711 260 333 327 259 333 327 259 337 84 121 274 77 125 329 125 96 72 136 125 96 72 136 125 96 72 1427 23 37 187 2286 380 380 73 2225	Events 5 7 1 2 2 4 3 1 2 2 4 3 1 2 2 2 2 2 0 0 2 2 2 0 0 2 2 0 0 0 2 0 0 0 2 0 0 0 2 0 0 0 2 0 0 0 2 0 0 0 1 1 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 4 4 3 3 1 2 2 4 4 3 3 1 2 2 4 4 3 3 1 2 2 4 4 3 3 1 2 2 4 4 3 3 1 2 2 4 4 3 3 1 2 2 4 4 3 3 1 2 2 4 4 3 3 2 2 4 4 3 3 1 2 2 4 4 3 3 2 2 4 4 3 3 2 2 0 2 0 2 0 2 0 2 0 2 0 2 0 2 0 2	N 142 220 50 166 212 167 159 25 61 181 47 214 81 83 68 51 93 17 92 62 49 37 192 62 49 15 27 159 25 61 181 47 25 61 181 47 25 61 181 47 25 61 181 47 25 61 181 47 25 61 181 47 25 61 181 47 25 61 181 47 25 61 181 47 25 61 181 47 25 61 181 47 25 61 181 47 25 61 181 47 25 61 181 47 25 62 181 181 47 25 62 182 17 25 61 181 47 25 62 193 27 27 25 61 181 47 27 25 62 49 17 92 62 49 15 52 52 16 27 27 16 93 17 92 62 49 15 52 52 16 27 15 93 17 92 62 49 15 27 15 27 15 27 15 27 15 27 15 27 15 27 15 27 15 27 15 27 15 27 15 27 15 27 15 27 15 27 15 25 25 27 12 27 12 25 25 25 25 25 25 25 25 25 2	Odds Ratio	OR           0.13           0.27           0.23           0.64           0.32           0.13	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.06; 5.87] [0.02; 1.98] [0.01; 5.57] [0.02; 1.98] [0.01; 5.57] [0.01; 2.74] [0.03; 3.59] [0.03; 3.59] [0.03; 3.28] [0.01; 2.74] [0.03; 3.49] [0.04; 9.32] [0.04; 9.32] [0.04; 9.32] [0.04; 10.33] [0.03; 3.60] [0.00; 6.67] [0.02; 1.49] [0.03; 3.60] [0.02; 1.49]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg, fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Catosporium IgE (kU/L) Cockroach German IgE (kU/L) Corkroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Com Sting Nettle (kU/L) Com Sting Nettle (kU/L) Com Sting Nettle (kU/L) Com Sting Nettle (kU/L) Dander IgE (kU/L) Do pter (mite) IgE (kU/L) Eunt 81 gE (kU/L) Eunt 81 gE (kU/L) Ibnson Grass g10 IgE (kU/L) Johnson Grass g10 IgE (kU/L) Orchard Grass g3 IgE (kU/L) Driental Cockroach IgE (kU/L) Peren. Rye Grass g5 IgE (kU/L) Page. Mugwort w6 IgE (kU/L) Staph Enterotoxin A IgE (kU/L) Staph Enterotoxin A IgE (kU/L) Staph Enterotoxin B IgE (kU/L) Staph Enterot	Events 1 2 3 0 1 3 1 0 1 0 0 0 0 0 0 0 0 0 1 1 0 0 0 0 0 0 1 1 0 0 0 0 0 0 0 1 1 3 1 0 1 0 1 0 1 0 0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	N 218 335 71 260 333 327 259 256 337 84 121 121 259 6 125 96 125 96 125 96 125 96 125 136 135 1387 337 187 71 23 337 37 187 71 23 37 37 125 96 380 387 37 37 25 96 37 37 32 57 32 58 37 37 37 37 37 37 37 37 37 37 37 37 37	Events 5 7 1 1 2 2 4 3 3 1 2 2 4 3 3 1 2 2 2 0 0 2 2 2 0 0 2 2 0 0 2 2 0 0 1 1 1 0 0 0 2 2 2 3 3 0 0 2 2 3 3 0 0 2 2 3 3 0 0 2 2 3 3 0 0 2 2 3 3 0 0 1 1 1 2 2 3 3 1 1 2 2 3 3 1 1 2 2 3 3 1 1 2 2 3 3 1 1 2 2 3 3 1 1 2 2 3 3 1 1 2 2 3 3 1 1 2 2 3 3 1 1 2 2 3 3 1 1 2 2 3 3 1 1 2 2 3 3 1 1 2 2 3 3 1 1 2 2 3 3 1 1 2 2 2 3 3 1 1 2 2 2 3 3 1 2 2 2 3 3 1 1 2 2 2 3 1 1 2 2 2 2	N 142 220 50 166 212 167 159 25 61 81 81 81 47 214 83 68 51 93 17 92 62 49 15 25 62 49 15 25 51 27 159 25 50 167 181 181 47 25 51 25 25 51 25 51 25 25 25 51 27 25 55 27 25 55 27 27 25 55 27 27 25 55 27 27 25 55 27 27 25 55 27 27 25 55 27 27 25 55 25 52 27 27 25 55 25 52 27 27 25 55 27 27 25 55 27 27 25 55 27 27 27 25 55 27 27 27 27 27 27 27 27 27 27		OR           0.13           0.27           0.23           0.64           0.97           0.22           0.14           0.99           0.13           0.32           0.13           0.32           0.13           0.32           0.13           0.32           0.13           0.32           0.31           0.58           0.23           0.64           0.32           0.04           0.17           0.32           0.92	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.03; 3.57] [0.02; 1.98] [0.01; 5.57] [0.01; 2.99] [0.00; 1.81] [0.01; 2.74] [0.03; 3.59] [0.01; 2.74] [0.03; 3.59] [0.03; 3.28] [0.01; 2.74] [0.03; 3.49] [0.04; 9.32] [0.04; 5.85] [0.04; 10.33] [0.03; 3.60] [0.00; 1.85] [0.00; 1.85]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg, fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Catockroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Cutt. Oat g14 IgE (kU/L) Cutt. Oat g14 IgE (kU/L) D. farianae (mite) IgE (kU/L) D. farianae (mite) IgE (kU/L) D. farianae (kU/L) Eint 81 IgE (kU/L) Eint 81 IgE (kU/L) Dapanese Cedar 117 IgE (kU/L) Johnson Grass g10 IgE (kU/L) Orchard Grass g3 IgE (kU/L) Drehard Grass g3 IgE (kU/L) Drehard Grass g3 IgE (kU/L) Paren. Rye Grass g5 IgE (kU/L) Staph Enterotoxin A IgE (kU/L) Staph Enterotoxin A IgE (kU/L) Sw. Vernal Grass g1	Events  1 1 23 0 1 3 1 0 1 1 0 0 0 0 0 0 0 0 0 0 0 0	N 218 335 711 260 333 327 259 333 327 259 37 121 274 77 329 136 72 125 96 72 23 159 87 71 233 37 71 260 37 225 96 72 147 77 286 76 77 295 96 77 205 77 205 96 77 205 71 205 71 205 71 205 71 205 71 205 71 205 71 205 71 205 71 205 71 205 71 205 71 205 71 205 71 205 71 205 71 205 87 71 205 71 71 205 71 71 71 71 71 71 71 71 71 71	Events 5 7 1 2 2 4 3 1 2 2 3 3 1 2 2 2 0 0 2 2 2 0 0 0 2 2 0 0 0 2 2 0 0 0 1 1 1 0 0 0 0	N 142 220 50 166 212 167 25 61 159 25 61 181 181 47 214 81 83 17 92 62 147 25 61 181 181 181 181 181 187 255 255 255 255 255 255 255 25		OR           0.13           0.27           0.23           0.64           0.32           0.07           0.22           0.14           0.09           0.13           0.32           0.13           0.32           0.13           0.31           0.58           0.64           0.32           0.64           0.32           0.64           0.32           0.64           0.32           0.64           0.32           0.64           0.32           0.617           0.32           0.99           0.12	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.05; 5.87] [0.02; 1.98] [0.01; 5.57] [0.02; 1.98] [0.01; 5.57] [0.01; 2.99] [0.03; 3.59] [0.03; 3.59] [0.03; 3.59] [0.01; 2.74] [0.03; 3.49] [0.04; 9.32] [0.04; 9.32] [0.04; 10.33] [0.02; 1.49] [0.02; 1.49] [0.02; 1.49] [0.02; 1.49] [0.02; 1.49] [0.02; 1.49]
Antigen-specific IgE Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg. fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cockroach German IgE (kU/L) Corkroach German IgE (kU/L) Corkroach German IgE (kU/L) Cor Sting Nettle w20 IgE (kU/L) Cor Sting Nettle w20 IgE (kU/L) Cor Sting Nettle w20 IgE (kU/L) Do g Dander IgE (kU/L) Do g Dander IgE (kU/L) Dog Dander IgE (kU/L) End Is IgE (kU/L) End Is IgE (kU/L) Hantain w9 IgE (kU/L) Japanese Cedar 117 IgE (kU/L) Johnson Grass g10 IgE (kU/L) Dak White I7 IgE (kU/L) Drehard Grass g3 IgE (kU/L) Drehard Grass g3 IgE (kU/L) Drehard Grass g5 IgE (kU/L) Paren. Rye Grass g5 IgE (kU/L) Staph Enterotoxin A IgE (kU/L) Mail Qellitory w19 IgE (kU/L) Wite Ash 15 IgE (kU/L)	Events  1 23 0 1 3 3 0 1 0 0 0 0 0 0 0 0 0 0 0 1 1 0 0 0 0	N 218 335 71 260 333 327 259 337 84 121 274 77 329 136 125 96 72 147 73 299 136 125 96 72 137 87 125 96 72 136 135 87 73 37 226 87 73 37 226 96 72 147 23 37 72 239 84 121 239 37 229 239 37 229 239 37 229 239 37 229 37 37 229 37 37 229 37 37 229 37 37 229 37 37 229 37 229 37 37 229 37 229 37 229 37 229 37 229 37 229 37 229 37 229 37 229 37 37 229 37 229 37 229 37 229 37 229 229 37 229 37 229 37 229 37 229 37 229 37 229 37 229 37 229 37 229 37 229 37 229 37 229 37 229 37 229 37 229 37 229 37 229 220 229 229 220 229 220 220 220 220	Events 5 7 1 2 2 4 3 1 2 2 4 3 1 2 2 2 2 2 0 0 2 2 2 2 0 0 2 2 0 0 0 2 2 0 0 0 2 0 0 1 1 1 0 0 0 0	N 142 220 50 166 212 167 159 25 61 181 181 47 214 81 83 68 51 93 17 92 62 49 93 17 92 62 49 155 255 255 275 166 214 81 81 81 81 81 81 81 81 81 81		OR           0.13           0.27           0.23           0.64           0.32           0.13           0.32           0.07           0.22           0.14           0.09           0.13           0.32           0.31           0.58           0.23           0.64           0.32           0.04           0.17           0.32           0.09           0.12	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.05; 5.87] [0.02; 1.98] [0.01; 5.57] [0.01; 2.98] [0.01; 2.74] [0.03; 3.59] [0.03; 3.59] [0.03; 3.28] [0.01; 2.74] [0.03; 3.49] [0.04; 9.32] [0.04; 9.32] [0.04; 9.32] [0.02; 1.49] [0.02; 1.49] [0.02; 1.49] [0.03; 3.60] [0.00; 1.85] [0.01; 2.48]
Antigen-specific IgE Alder Grey 12 IgE (kU/L) Alternar Ten/Alter, IgE (kU/L) Asperg, fumig. m3 IgE (kU/L) Barmuda Grass g2 IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cat Dander IgE (kU/L) Cockroach German IgE (kU/L) Corkroach German IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Com Sting Nettle w20 IgE (kU/L) Com Sting Nettle (kU/L) Com Sting Nettle (kU/L) Com Sting Nettle (kU/L) Dander IgE (kU/L) Dander IgE (kU/L) Eint 8 IgE (kU/L) Eint 8 IgE (kU/L) Eint 8 IgE (kU/L) Japanese Cedar 117 IgE (kU/L) Johnson Grass g10 IgE (kU/L) Drichard Grass g3 IgE (kU/L) Drichard Grass g3 IgE (kU/L) Peren. Rye Grass g5 IgE (kU/L) Sape. Mugwort w6 IgE (kU/L) Staph Enterotoxin A IgE (kU/L) Staph Enterotoxin A IgE (kU/L) Staph Enterotoxin B IgE (kU/L) Staph Enterotoxin B IgE (kU/L) Staph Enterotoxin B IgE (kU/L) Mail Pellitory w19 IgE (kU/L) Mail Pellitory w19 IgE (kU/L) Main Ash t15 IgE (kU/L)	Events 1 2 3 0 1 3 1 0 0 0 0 0 0 0 0 0 0 0 0 0	N 218 335 71 260 333 327 259 333 327 259 256 37 84 121 227 47 77 329 136 125 96 125 96 125 96 125 136 136 159 87 71 23 37 187 187 136 159 159 87 112 159 87 125 136 136 136 136 137 125 136 137 125 137 136 135 137 137 137 136 135 137 137 137 137 137 137 137 137 137 137	<b>Events</b> 5 7 1 1 2 2 4 3 3 1 2 2 3 3 2 0 0 2 2 2 0 0 2 2 0 0 2 2 0 0 1 1 1 0 0 0 1 1 2 2 3 3 2 0 0 2 2 3 3 2 0 0 2 2 3 3 2 0 0 2 2 3 3 2 2 3 3 2 2 3 3 2 2 3 3 3 2 2 3 3 3 3 3 3 2 2 3	N 142 220 50 166 212 167 159 25 61 81 181 47 214 83 68 51 93 17 29 62 49 15 25 62 49 15 25 51 27 159 25 61 81 81 81 81 81 83 65 16 21 27 159 25 61 81 81 81 81 81 83 65 16 21 25 61 81 81 81 81 81 81 81 81 81 8	Odds Ratio	OR           0.13           0.27           0.23           0.64           0.97           0.22           0.14           0.99           0.13           0.32           0.13           0.32           0.13           0.31           0.58           0.23           0.64           0.32           0.64           0.32           0.417           0.32           0.12	95%-Cl [0.01; 1.09] [0.07; 1.07] [0.01; 5.78] [0.04; 10.26] [0.03; 3.57] [0.02; 1.98] [0.01; 5.57] [0.01; 2.99] [0.00; 1.81] [0.01; 2.74] [0.03; 3.59] [0.03; 3.59] [0.01; 2.74] [0.03; 3.49] [0.04; 9.32] [0.01; 5.85] [0.04; 10.33] [0.02; 1.49] [0.02; 1.49] [0.02; 1.49] [0.02; 1.49] [0.02; 1.49] [0.01; 2.74]

Favors dupilumab Favors placebo

**FIG 2.** Forest plot by antigen-specific IgE for study R668-AD-1224. For 1-step analysis, for each antigen, new event was defined as below lower limit of quantification (LLOQ) at baseline and above LLOQ at week 52; worsened event was defined as above LLOQ at baseline and increases by at least 1-fold at week 52. For 2-step analysis, for each antigen, new event was defined as below LLOQ at baseline and at least 2 times as large as LLOQ at week 52; worsened event was defined as above LLOQ at baseline and increases by at least 2 times as large as LLOQ at week 52; worsened event was defined as above LLOQ at baseline and increases by at least 2 times as large as LLOQ at week 52; worsened event was defined as above LLOQ at baseline and increases by at least 2-fold at week 52; MOR-step analysis for new and worsened allergic events. **(B)** One-step analysis for new allergic events only. **(C)** Two-step analysis for new and worsened allergic events. **(D)** Two-step analysis for new allergic events only. Antigen-specific IgE were tested by region-specific allergen panels; not all patients were tested for all antigens, which led to different sample sizes for different antigens. Percentage of missing (not shown) data was comparable between treatment groups for all antigens. *OR*, Odds ratio.

### **ARTICLE IN PRESS**

C	Dupi	umab	Pla	acebo			
Antigen-specific IgE	Events	Ν	Events	Ν	Odds Ratio	OR	95%-CI
Alder Grey t2 IgE (kU/L)	1	218	8	142		0.08	[0.01; 0.62]
Alternar Ten/Alter, IgE (kU/L)	0	335	5	220		0.06	[0.00; 1.06]
Asperg. fumig. m3 IgE (kU/L)	0	71	1	50		0.23	[0.01; 5.78]
Bermuda Grass g2 IgE (kU/L)	1	260	3	166		0.21	[0.02; 2.03]
C. Silver Birch t3 IgE (kU/L)	2	333	8	216		0.16	[0.03; 0.75]
Cat Dander IgE (kU/L)	0	327	3	212		0.09	[0.00; 1.78]
Cladosporium IgE (kU/L)	0	259	3	167		0.09	[0.00; 1.76]
Cockroach German IgE (kU/L)	0	256	6	159		0.05	[0.00; 0.82]
Com Sting Nettle w20 IgE (kU/L)	0	37	1	25		0.22	[0.01; 5.57]
Cult. Oat g14 IgE (kU/L)	0	84	1	61		0.24	[0.01; 5.96]
Cypresslt. Fun. t23 IgE (kU/L)	0	121	2	81		0.13	[0.01; 2.76]
D. farianae (mite) IgE (kU/L)	1	274	5	181		0.13	[0.01; 1.11]
D. pter (mite) IgE (kU/L)	1	77	0	47		1.86	[0.07; 46.67]
Dog Dander IgE (kU/L)	2	329	6	214		0.21	[0.04; 1.06]
Elm t8 IgE (kU/L)	1	136	3	81		0.19	[0.02; 1.88]
English Plantain w9 IgE (kU/L)	0	125	3	83		0.09	[0.00; 1.80]
Eucalyptus t18 IgE (kU/L)	0	96	0	68			
Japanese Cedar t17 IgE (kU/L)	0	72	2	51		0.14	[0.01; 2.91]
Johnson Grass g10 IgE (kU/L)	2	147	1	93		1.27	[0.11; 14.19]
Melaleuca/Bottleb, IgE (kU/L)	0	23	0	17			
Oak White t7 IgE (kU/L)	1	159	2	92		0.28	[0.03; 3.18]
Orchard Grass g3 IgE (kU/L)	0	87	2	62		0.14	[0.01; 2.93]
Oriental Cockroach IgE (kU/L)	0	71	3	49		0.09	[0.00; 1.84]
Ox-eye/Marguerite, IgE (kU/L)	0	23	0	15			
Peren. Rye Grass g5 IgE (kU/L)	0	37	2	27		0.14	[0.01; 2.95]
Ragweed Short/Com IgE (kU/L)	0	187	1	120		0.21	[0.01; 5.26]
Sage. Mugwort w6 IgE (kU/L)	0	286	4	187		0.07	[0.00; 1.33]
Staph Enterotoxin A IgE (kU/L)	1	380	7	255		0.09	[0.01; 0.76]
Staph Enterotoxin B IgE (kU/L)	2	380	5	255		0.26	[0.05; 1.37]
Sw. Vernal Grass g1 IgE (kU/L)	0	73	0	52			
Timothy (Phleump.) IgE (kU/L)	1	225	5	147		0.13	[0.01; 1.10]
Wall Pellitory w19 IgE (kU/L)	0	138	4	94		0.07	[0.00; 1.36]
White Ash t15 IgE (kU/L)	1	118	3	71		0.19	[0.02; 1.90]
					0.01 0.1 1 10 100		

Favors dupilumab Favors placebo

Favors dupilumab Favors placebo

D	Dupil	umab	Pla	acebo			
Antigen-specific IgE	Events	N	Events	N	Odds Ratio	OR	95%-CI
Alder Grey t2 IgE (kU/L)	0	218	2	142		0.13	[0.01; 2.70]
Alternar Ten/Alter, IgE (kU/L)	0	335	3	220		0.09	[0.00; 1.80]
Asperg. fumig. m3 IgE (kU/L)	0	71	0	50			
Bermuda Grass g2 lgE (kU/L)	0	260	0	166			
C. Silver Birch t3 IgE (kU/L)	2	333	2	216		0.65	[0.09; 4.62]
Cat Dander IgE (kU/L)	0	327	0	212			
Cladosporium IgE (kU/L)	0	259	1	167		0.21	[0.01; 5.28]
Cockroach German IgE (kU/L)	0	256	1	159		0.21	[0.01; 5.09]
Com Sting Nettle w20 IgE (kU/L)	0	37	0	25			
Cult. Oat g14 IgE (kU/L)	0	84	1	61		0.24	[0.01; 5.96]
Cypresslt. Fun. t23 IgE (kU/L)	0	121	1	81		0.22	[0.01; 5.49]
D. farianae (mite) IgE (kU/L)	0	274	1	181		0.22	[0.01; 5.41]
D. pter (mite) IgE (kU/L)	0	77	0	47			
Dog Dander IgE (kU/L)	1	329	1	214		0.65	[0.04; 10.44]
Elm t8 IgE (kU/L)	0	136	1	81		0.20	[0.01; 4.88]
English Plantain w9 IgE (kU/L)	0	125	1	83		0.22	[0.01; 5.44]
Eucalyptus t18 IgE (kU/L)	0	96	0	68			
Japanese Cedar t17 IgE (kU/L)	0	72	0	51			
Johnson Grass g10 IgE (kU/L)	1	147	0	93		1.91	[0.08; 47.50]
Melaleuca/Bottleb, IgE (kU/L)	0	23	0	17			
Oak White t7 IgE (kU/L)	0	159	0	92			
Orchard Grass g3 IgE (kU/L)	0	87	1	62		0.23	[0.01; 5.85]
Oriental Cockroach IgE (kU/L)	0	71	0	49			
Ox-eye/Marguerite, IgE (kU/L)	0	23	0	15			
Peren. Rye Grass g5 IgE (kU/L)	0	37	0	27			
Ragweed Short/Com IgE (kU/L)	0	187	0	120			
Sage. Mugwort w6 IgE (kU/L)	0	286	2	187		0.13	[0.01; 2.71]
Staph Enterotoxin A IgE (kU/L)	0	380	2	255		0.13	[0.01; 2.79]
Staph Enterotoxin B IgE (kU/L)	0	380	1	255		0.22	[0.01; 5.49]
Sw. Vernal Grass g1 IgE (kU/L)	0	73	0	52			
Timothy (Phleump.) IgE (kU/L)	0	225	1	147		0.22	[0.01; 5.35]
Wall Pellitory w19 IgE (kU/L)	0	138	1	94		0.23	[0.01; 5.58]
White Ash t15 lgE (kU/L)	0	118	1	71		0.20	[0.01; 4.93]
,							
					0.01 0.1 1 10 100		

FIG 2. (Continued).

approach and a maintained reduction in the incidence rate of new and worsened allergic events in those treated with dupilumab. Additionally, the treatment effects were consistent across all studies after removing the clinical trials that included topical corticosteroids (see Fig E1 in the Online Repository at www. jacionline.org).

When analyzed over the entire study period (including both ontreatment and off-treatment follow-up periods), the treatment effect В

Α		Dupilumab		Placebo	Incidence	Rate			Weight	Weight
Study	Events	Patient Years	Events	Patient Years	Ratio	)	IRR	95%-CI	(fixed)	(random)
R668-AD-0914	1	1.43	2	0.36 —			0.13	[0.01; 1.40]	1.0%	1.0%
R668-AD-1021	20	84.00	6	14.26			0.57	[0.23; 1.41]	6.8%	6.8%
R668-AD-1026	1	1.57	1	0.43			0.27	[0.02; 4.37]	0.7%	0.7%
R668-AD-1117	5	10.81	4	7.79		_	0.90	[0.24; 3.36]	3.3%	3.3%
R668-AD-1121	0	1.26	0	0.56 —			0.44	[0.01; 22.35]	0.4%	0.4%
R668-AD-1224	56	382.11	63	255.15			0.59	[0.41; 0.85]	43.4%	43.4%
R668-AD-1307	1	7.05	1	5.01			0.71	[0.04; 11.37]	0.7%	0.7%
R668-AD-1314	5	27.18	7	27.68		-	0.73	[0.23; 2.29]	4.3%	4.3%
R668-AD-1334	22	123.08	13	57.65			0.79	[0.40; 1.57]	12.0%	12.0%
R668-AD-1416	17	132.42	11	60.70			0.71	[0.33; 1.51]	9.8%	9.8%
R668-AD-1424	22	62.64	10	30.56		-	1.07	[0.51; 2.27]	10.1%	10.1%
R668-AD-1526	11	43.22	10	21.62			0.55	[0.23; 1.30]	7.7%	7.7%
Fixed effect model	161		128		4		0.66	[0.52; 0.84]	100.0%	
Random effects model				_	\$		0.66	[0.52; 0.84]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0	.93		I	1 1		I			
				0.01	0.1 1	10	100			
				4						

Favors dupilumab Favors placebo

Study	Events	Dupilumab Patient Years	Events I	Placebo Patient Years	Incidence Ra Ratio	ite IRR	95%-CI	Weight (fixed)	Weight (random)
R668-AD-0914	1	1.43	1	0.36 —		0.25	[0.02; 4.05]	1.0%	1.0%
R668-AD-1021	14	84.00	3	14.26		0.79	[0.23; 2.76]	4.9%	4.9%
R668-AD-1026	1	1.57	1	0.43 -		0.27	[0.02; 4.37]	1.0%	1.0%
R668-AD-1117	2	10.81	4	7.79		0.36	[0.07; 1.97]	2.6%	2.6%
R668-AD-1121	0	1.26	0	0.56 —		0.44	[0.01; 22.35]	0.5%	0.5%
R668-AD-1224	55	382.11	61	255.15		0.60	[0.42; 0.87]	57.0%	57.0%
R668-AD-1307	0	7.05	1	5.01 —		- 0.24	[0.01; 5.82]	0.7%	0.7%
R668-AD-1314	3	27.18	4	27.68		0.76	[0.17; 3.41]	3.4%	3.4%
R668-AD-1334	13	123.08	7	57.65	<u> </u>	0.87	[0.35; 2.18]	9.0%	9.0%
R668-AD-1416	11	132.42	5	60.70		1.01	[0.35; 2.90]	6.8%	6.8%
R668-AD-1424	10	62.64	6	30.56	<u> </u>	0.81	[0.30; 2.24]	7.4%	7.4%
R668-AD-1526	5	43.22	7	21.62		0.36	[0.11; 1.13]	5.8%	5.8%
Fixed effect model	115		100		-	0.63	[0.48; 0.83]	100.0%	
Random effects model					$\diamond$	0.63	[0.48; 0.83]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0	.96							
				0.01	0.1 1	10 100			
				←					

Favors dupilumab Favors placebo

FIG 3. Forest plots (A) by study for new and worsened allergic events during the on-treatment period, (B) by study for new allergic events during the on-treatment period, (C) by study for new and worsened allergic events (includes IgE 1-step increases) during the on-treatment period, and (D) by study for new and worsened allergic events (includes IgE 2-step increases) during the on-treatment period.

of dupilumab was moderated (new + worsened: IRR 0.72; 95% CI, 0.58-0.90, Fig E2, *A*, in the Online Repository at www.jacionline. org; new: IRR 0.69; 95% CI, 0.54-0.88, Fig E2, *B*) due to diminished treatment effect during the off-treatment period. However, although the treatment effects of dupilumab on further preventing atopic march were moderated during the off-treatment period, they were not reversed (see Fig E3 in the Online Repository).

A difference in effect according to age at onset of AD (with earlier life emergence and consequent greater amount of time to develop additional allergic diatheses over a lifetime), the severity of AD on study entry (perhaps indicating enhanced type 2 disease), and the coexistence of asthma (suggesting that a second step in atopic march had already been observed) were assessed. In addition, the role of demographic features (age, gender, race, ethnicity) and environment (geography), as well as the relationship to baseline IgE and baseline allergic burden, were examined.

As shown in Fig E4 in the Online Repository at www. jacionline.org, on the basis of shifts in point estimates across these subgroup analyses, treatment benefit seemed to be greater for younger patients (age <18 years), those with early onset of AD (before age 2 years), those with more severe AD at baseline, and those with baseline asthma versus no asthma. Sensitivity analyses suggested that treatment benefits were continuously observed from later age at AD onset up through onset as late as 12 years of age (data not shown). Patients in North America and Europe had a greater number of allergic conditions at baseline and demonstrated stronger treatment benefits versus those from Asia/Oceania. This difference across geographies carried through in part to the analysis across ethnicities, where a greater effect of treatment was seen in White versus Asian participants. In addition, patients with baseline IgE levels between 375 and 2000 IU/mL seemed to benefit more than others. Treatment effect analyzed by baseline IgE quartiles and baseline EASI quartiles are shown in Fig E5 in the Online Repository. Also, treatment benefit seemed to be greater for patients with greater allergic burden at baseline ( $\geq 2$  concomitant allergic conditions).

A higher allergic burden was observed in patients with higher IgE levels and more severe AD assessed by EASI scores at

C		Dupilumab		Placebo	Incidence Rat	te		Weight	Weight
Study	Events	Patient Years	Events	Patient Years	Ratio	IRR	95%-CI	(fixed)	(random)
R668-AD-0914	1	1.43	2	0.36 —		0.13	[0.01; 1.40]	0.7%	0.9%
R668-AD-1021	27	84.00	7	14.26		0.65	[0.29; 1.50]	6.2%	7.0%
R668-AD-1026	1	1.57	1	0.43 —		0.27	[0.02; 4.37]	0.6%	0.7%
R668-AD-1117	7	10.81	8	7.79	<u></u>	0.63	[0.23; 1.74]	4.2%	4.8%
R668-AD-1121	0	1.26	0	0.56	- i	0.44	[0.01; 22.35]	0.3%	0.3%
R668-AD-1224	59	382.11	78	255.15	÷	0.51	[0.36; 0.71]	37.6%	32.4%
R668-AD-1307	1	7.05	2	5.01		0.36	[0.03; 3.92]	0.7%	0.9%
R668-AD-1314	5	27.18	12	27.68		0.42	[0.15; 1.20]	4.0%	4.6%
R668-AD-1334	25	123.08	33	57.65		0.35	[0.21; 0.60]	15.9%	16.4%
R668-AD-1416	20	132.42	33	60.70		0.28	[0.16; 0.48]	14.0%	14.6%
R668-AD-1424	22	62.64	10	30.56	<u> </u>	1.07	[0.51; 2.27]	7.7%	8.6%
R668-AD-1526	13	43.22	16	21.62		0.41	[0.20; 0.84]	8.0%	8.9%
Fixed effect model	181		202		4	0.46	[0.37; 0.56]	100.0%	
Random effects model					$\diamond$	0.46	[0.36; 0.57]		100.0%
Heterogeneity: $I^2 = 7\%$ , $\tau^2$	= 0.0119,	p = 0.38							
				0.01	0.1 1	10 100			
				←					
				Fave	ors dupilumab Favo	ors placebo			

D		Dupilumab		Placebo	Incidence Rate	•		Weight	Weight
Study	Events	Patient Years	Events	Patient Years	Ratio	IRR	95%-CI	(fixed)	(random)
R668-AD-0914	1	1.43	2	0.36 —		0.13	[0.01; 1.40]	0.9%	0.9%
R668-AD-1021	22	84.00	7	14.26		0.53	[0.23; 1.25]	7.0%	7.0%
R668-AD-1026	1	1.57	1	0.43 -		0.27	[0.02; 4.37]	0.7%	0.7%
R668-AD-1117	6	10.81	5	7.79		0.87	[0.26; 2.84]	3.6%	3.6%
R668-AD-1121	0	1.26	0	0.56 —	+	- 0.44	[0.01; 22.35]	0.3%	0.3%
R668-AD-1224	58	382.11	71	255.15		0.55	[0.39; 0.77]	42.3%	42.3%
R668-AD-1307	1	7.05	1	5.01		- 0.71	[0.04; 11.37]	0.7%	0.7%
R668-AD-1314	5	27.18	8	27.68		0.64	[0.21; 1.95]	4.1%	4.1%
R668-AD-1334	25	123.08	14	57.65		0.84	[0.43; 1.61]	11.9%	11.9%
R668-AD-1416	19	132.42	16	60.70	-	0.54	[0.28; 1.06]	11.5%	11.5%
R668-AD-1424	22	62.64	10	30.56	<u>+</u>	1.07	[0.51; 2.27]	9.1%	9.1%
R668-AD-1526	12	43.22	12	21.62		0.50	[0.22; 1.11]	7.9%	7.9%
Fixed effect model	172		147		\$	0.61	[0.49; 0.76]	100.0%	
Random effects model					\$	0.61	[0.49; 0.76]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0.	.85							
				0.01	0.1 1 1	0 100			
				Fav	ors dupilumab Favors	s placebo			



baseline (Table E5). Dupilumab substantially reduced IgE levels and EASI scores over the course of treatment across all levels of IgE and EASI scores (see Table E6 in the Online Repository at www.jacionline.org). The changes in IgE levels and EASI scores from end-of-treatment to end-of-study across trials are shown in Table E7 in the Online Repository. Although higher allergic burden provides a greater opportunity to demonstrate treatment benefit, the clear-cut, though moderated, effect on atopic march at the highest levels of IgE suggests the possibility that reaching threshold reductions of IgE as a reflection of blockade of IL-4/IL-13 biologic activity plays a role in the degree of its attenuation. It follows that those individuals with the highest IgE levels at baseline may require longer duration of treatment to obtain the IgE threshold that would maximally attenuate atopic march.

### DISCUSSION

Individuals with AD demonstrate an increased propensity for the development of other allergic diseases, with the existence of atopic march supported by cross-sectional and longitudinal research, as well as experimental evidence from animal models.<sup>20,21,45-48</sup> The typical type and pattern of sequential development of allergic disease suggests an underlying progressive atopic diathesis, as opposed to a simple, chance manifestation of single allergic conditions occurring throughout life.<sup>1,22,23</sup> The classical sequence observed in atopic march presents first in the skin as AD, followed by the gastrointestinal tract as food allergy, and can then progress to the upper and lower airways as allergic rhinitis and asthma, respectively, in modestly variable sequence.<sup>2,23</sup> Many argue that AD is not a causal factor for atopic march but mostly represents the first clinical manifestation of the IgE atopic response.<sup>1</sup> Other analyses of the AD and asthma dupilumab clinical trial databases showed a markedly greater number of concomitant allergies in those with AD versus those with asthma, suggesting that AD may reflect stronger type 2 immune influences promoting atopic disease compared to other allergic conditions (in preparation).

It has been conventionally thought that atopic march is a process that begins in early infancy and extends into childhood. However, it has been more recently noted that sensitization to allergens as well as first presentation of AD, and new aeroallergen and food hypersensitivities can develop in late adolescence and adulthood.<sup>3,13,17,22,49</sup> New manifestations of allergy, such as asthma, urticaria/angioedema, allergic sinusitis, and sensitivity to a variety of chemicals and drugs on exposure of the skin and mucosal surfaces may be acquired progressively over the course of time, from childhood into adulthood.<sup>2,6,17,22,50,51</sup>

The current analyses were performed on the largest and most comprehensive clinical trial database of moderate-to-severe AD. We believe that we have shown for the first time, in a large pooled study population of mostly adults (mean age, 36 years; median age, 35 years; range, 12-88 years) and generally consistent across the individual component studies, evidence of atopic march in adults, separated in time from their most active period of allergy acquisition in childhood. This was uncovered despite the relatively short follow-up period (mean, 0.390 years; median, 0.290 years; range, 0.003-1.018 years). Furthermore, this analysis showed that dupilumab can interfere with atopic march. Dupilumab reduced both the incidence of new allergies and worsening of preexisting allergic conditions compared to controls treated with standard of care.

Shifts in point estimates across subgroup analyses revealed that the treatment benefit of dupilumab appeared greater for younger patients (<18 years), those with early onset of AD (<2 years), those with more severe AD at baseline, and those with baseline asthma versus no asthma (Fig E4). Greater treatment benefit was also observed in the atopic White population compared with the Asian population. This is likely due to the larger number of allergies at baseline in the White group, providing a greater potential for worsening, and therefore a greater opportunity to demonstrate a treatment benefit. Of note, previous studies have shown differences in the number and severity of allergic conditions between ethnic groups.<sup>52-57</sup>

A persistent, albeit attenuated, effect was observed with discontinuing dupilumab therapy in off-treatment periods; however, no rebound in allergic events was noted after dupilumab treatment had been discontinued, as evidenced by continued treatment benefits observed in follow-up periods after discontinuation of therapy. Thus, although larger and longer trials will be needed to further confirm these findings, dupilumab treatment may provide some prolonged disease modification, at least over the follow-up duration of these studies (beyond 5 dupilumab halflives). An even longer follow-up will be required to assess the durability of this potential effect on atopic march. In addition, longer duration of dupilumab treatment will be needed to assess the full impact in those with the highest IgE levels and the greatest allergic burden. Finally, further study of patients who have less severe AD and who are younger would provide insight into the generalizability of dupilumab's effects on atopic march in newly developed or milder AD.

Dupilumab treatment showed significant improvement in disease severity, with remarkable reduction in serum total IgE levels. Interestingly, a nonmonotonic relationship was observed for treatment effect and baseline serum IgE levels (Fig E4). Although dupilumab treatment effects were demonstrated with improvement in disease severity irrespective of IgE level at baseline, the greatest treatment effect was observed in patients whose baseline IgE levels were between 375 and 2000 IU/mL, defined empirically and prospectively as thresholds. When baseline IgE was analyzed by quantiles, the data showed a similar trend (Fig E5). Whether this occurred by chance or reflects a difference in intensity of type 2 inflammation, with low- or intermediate-grade intensities more easily quenched than very severe type 2 inflammatory responses, or whether the relationship of dupilumab to IgE in those with highest IgE levels might demonstrate greater effects with longer duration of dupilumab exposure, is not known. The effects of dupilumab were more pronounced for those with more active atopic march irrespective of IgE, marked by other indicators of degree of allergy sensitization, such as earlier age at onset or greater severity of AD, presence of asthma, and higher allergic burden at study start, while the nonmonotonic relationship between IRR and IgE by quantile also extended to EASI scores at baseline (Fig E5). Because EASI and IgE are highly correlated, this may also reflect differences in exposure response, whereby the strongest type 2 inflammatory signals may require longer exposure to dupilumab to optimally demonstrate benefit. Larger and longer clinical trials focused on this question may be required to confirm this result.

Other agents have unsuccessfully been used to attempt to modify allergic disease progression in atopic march. Pimecrolimus, a calcineurin inhibitor that downregulates IL-2–induced T-cell activation and inhibits cytokine activation pathways, including production of IL-4 and IL-10 by  $T_H^2$  cells,<sup>58</sup> was assessed in a study designed to evaluate effects on atopic march by administration at first manifestation of AD in infancy to assess effect on asthma incidence by 6 years of age.<sup>21</sup> An unexpectedly high discontinuation rate (48%) reduced the power of the study, which was also confounded by the use of emollients and the topical corticosteroid fluticasone, and the asthma end point could not be tested because the study was stopped at year 3.<sup>21</sup> Other trials have used prophylactic antihistamines, pre- and postnatal probiotics, and ceramide-dominant emollients to attempt to abrogate atopic march, without success.<sup>59,60</sup>

This analysis across the entire adolescent and adult AD clinical database determined that dupilumab reduced the acquisition of new or the worsening of preexisting allergic conditions in a large AD clinical trial database in a highly atopic population. This provided important evidence that dupilumab may be effective in reducing allergic burden in these individuals over the course of time, reflecting a potential for disease modification in slowing the atopic march. Specifically designed larger trials of longer duration across an even broader spectrum of age and disease severity will be required to confirm whether dupilumab can completely and durably exert these effects correcting the underlying immune skew towards type 2 inflammation, which underlies the atopic march.

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Clinical implications: Atopic march is associated with progressive allergic disease burden, and there are no disease-modifying treatments. Dupilumab was associated with fewer new/worsening allergies in AD and may attenuate atopic march.

#### REFERENCES

 Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. Allergy 2014;69:17-27.

- 2. Hill DA, Spergel JM. The atopic march: critical evidence and clinical relevance. Ann Allergy Asthma Immunol 2018;120:131-7.
- Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. J Allergy Clin Immunol 1999;103:1173-9.
- 4. Gustafsson D, Sjoberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis—a prospective follow-up to 7 years of age. Allergy 2000;55:240-5.
- Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. BMJ 1996;312:1195-9.
- **6**. Belgrave DCM, Granell R, Simpson A, Guiver J, Bishop C, Buchan I, et al. Developmental profiles of eczema, wheeze, and rhinitis: two population-based birth cohort studies. PLoS Med 2014;11:e1001748.
- Paternoster L, Savenije OEM, Heron J, Evans DM, Vonk JM, Brunekreef B, et al. Identification of atopic dermatitis subgroups in children from 2 longitudinal birth cohorts. J Allergy Clinical Immunol 2018;141:964-71.
- Ishizaka K, Ishizaka T, Hornbrook MM. Physico-chemical properties of human reaginic antibody. IV. Presence of a unique immunoglobulin as a carrier of reaginic activity. J Immunol 1966;97:75-85.
- Springer TA, Davignon D, Ho MK, Kürzinger K, Martz E, Sanchez-Madrid F. LFA-1 and Lyt-2,3, molecules associated with T lymphocyte–mediated killing; and Mac-1, an LFA-1 homologue associated with complement receptor function. Immunol Rev 1982;68:171-95.
- Holguin F. The atopic march: IgE is not the only road. Lancet Respir Med 2014;2: 88-90.
- Hill DA, Grundmeier RW, Ram G, Spergel JM. The epidemiologic characteristics of healthcare provider-diagnosed eczema, asthma, allergic rhinitis, and food allergy in children: a retrospective cohort study. BMC Pediatr 2016;16:133.
- Somanunt S, Chinratanapisit S, Pacharn P, Visitsunthorn N, Jirapongsananuruk O. The natural history of atopic dermatitis and its association with atopic march. Asian Pac J Allergy Immunol 2017;35:137-43.
- Eller E, Kjaer HF, Høst A, Andersen KE, Bindslev-Jensen C. Food allergy and food sensitization in early childhood: results from the DARC cohort. Allergy 2009;64: 1023-9.
- van der Hulst AE, Klip H, Brand PLP. Risk of developing asthma in young children with atopic eczema: a systematic review. J Allergy Clin Immunol 2007;120:565-9.
- **15.** Ricci G, Patrizi A, Baldi E, Menna G, Tabanelli M, Masi M. Long-term follow-up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. J Am Acad Dermatol 2006;55:765-71.
- 16. von Kobyletzki LB, Bornehag CG, Hasselgren M, Larsson M, Lindström CB, Svensson Å. Eczema in early childhood is strongly associated with the development of asthma and rhinitis in a prospective cohort. BMC Dermatol 2012; 12:11.
- Burgess JA, Walters EH, Byrnes GB, Matheson MC, Jenkins MA, Wharton CL, et al. Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. J Allergy Clin Immunol 2007;120:863-9.
- Leynaert B, Neukirch C, Kony S, Guénégou A, Bousquet J, Aubier M, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. J Allergy Clin Immunol 2004;113:86-93.
- Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, et al. Rhinitis and onset of asthma: a longitudinal population-based study. Lancet 2008;372: 1049-57.
- Saunes M, Øien T, Dotterud CK, Romundstad PR, Storrø O, Holmen TL, et al. Early eczema and the risk of childhood asthma: a prospective, population-based study. BMC Pediatr 2012;12:168.
- Schneider L, Hanifin J, Boguniewicz M, Eichenfield LF, Spergel JM, Dakovic R, et al. Study of the atopic march: development of atopic comorbidities. Pediatr Dermatol 2016;33:388-98.
- 22. Burgess JA, Dharmage SC, Byrnes GB, Matheson MC, Gurrin LC, Wharton CL, et al. Childhood eczema and asthma incidence and persistence: a cohort study from childhood to middle age. J Allergy Clin Immunol 2008;122:280-5.
- Bantz SK, Zhu Z, Zheng T. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. J Clin Cell Immunol 2014;5:202.
- 24. Chiricozzi A, Maurelli M, Peris K, Girolomoni G. Targeting IL-4 for the treatment of atopic dermatitis. Immunotargets Ther 2020;9:151-6.
- Nelms K, Keegan AD, Zamorano J, Ryan JJ, Paul WE. The IL-4 receptor: signaling mechanisms and biologic functions. Annu Rev Immunol 1999;17:701-38.
- Luzina IG, Keegan AD, Heller NM, Rook GA, Shea-Donohue T, Atamas SP. Regulation of inflammation by interleukin-4: a review of "alternatives." J Leukoc Biol 2012;92:753-64.
- Beck LA, Thaci D, Hamilton JD, Graham NM, Bieber T, Rocklin R, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 2014;371:130-9.

- Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 2018; 378:2486-96.
- 29. Hirano I, Dellon ES, Hamilton JD, Collins MH, Peterson K, Chehade M, et al. Efficacy of dupilumab in a phase 2 randomized trial of adults with active eosinophilic esophagitis. Gastroenterology 2020;158:111-22.e10.
- 30. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet 2019;394:1638-50.
- Efficacy and safety of dupilumab in participants ≥12 to <18 years of age, with moderate-to-severe atopic dermatitis. ClinicalTrials.gov, NCT03054428, last updated July 23, 2019.
- 32. A study to assess the efficacy and safety of dupilumab in participants with severe atopic dermatitis (AD) that are not controlled with oral cyclosporine A (CSA) or for those who cannot take oral CSA because it is not medically advisable. Clinical-Trials.gov, NCT02755649, last updated August 20, 2020.
- Study of dupilumab (REGN668/SAR231893) monotherapy administered to adult patients with moderate-to-severe atopic dermatitis (SOLO 2). ClinicalTrials.gov, NCT02277769, last updated June 2, 2020.
- Study of dupilumab monotherapy administered to adult patients with moderate-tosevere atopic dermatitis (SOLO 1). ClinicalTrials.gov, NCT02277743, last updated November 21, 2017.
- Study to assess the efficacy and long-term safety of dupilumab (REGN668/ SAR231893) in adult participants with moderate-to-severe atopic dermatitis (CHRONOS). ClinicalTrials.gov, NCT02260986, last updated October 17, 2017.
- Study of dupilumab and immune responses in adults with atopic dermatitis (AD). ClinicalTrials.gov, NCT02210780, last updated May 7, 2020.
- Study to determine the safety and effectiveness of dupilumab for treatment of atopic dermatitis (AD). ClinicalTrials.gov, NCT01979016, last updated March 18, 2020.
- Study of dupilumab administered to adult patients with moderate-to-severe atopic dermatitis. ClinicalTrials.gov, NCT01859988, last updated August 28, 2017.
- Study to assess the safety of dupilumab (REGN668/SAR231893) administered concomitantly with topical corticosteroids (TCS) in patients with moderate-tosevere atopic dermatitis (AD). ClinicalTrials.gov, NCT01639040, last updated October 13, 2017.
- Study of dupilumab in adult patients with extrinsic moderate-to-severe atopic dermatitis. ClinicalTrials.gov, NCT01548404, last updated August 10, 2018.
- Safety and tolerability of dupilumab in participants with moderate to severe atopic dermatitis. ClinicalTrials.gov, NCT01385657, last updated February 26, 2020.
- Sequential ascending dose study to assess the safety and tolerability of REGN668 (SAR231893) in patients with atopic dermatitis. ClinicalTrials.gov, NCT01259323, last updated October 4, 2012.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.
- Schwarzer G, Carpenter JR, Rücker G. Meta-analysis with R. New York (NY): Springer; 2015.
- 45. Strid J, Hourihane J, Kimber I, Callard R, Strobel S. Disruption of the stratum corneum allows potent epicutaneous immunization with protein antigens resulting in a dominant systemic Th2 response. Eur J Immunol 2004;34:2100-9.
- 46. Akei HS, Brandt EB, Mishra A, Strait RT, Finkelman FD, Warrier MR, et al. Epicutaneous aeroallergen exposure induces systemic T<sub>H</sub>2 immunity that predisposes to allergic nasal responses. J Allergy Clin Immunol 2006;118:62-9.
- 47. Spergel JM, Mizoguchi E, Brewer JP, Martin TR, Bhan AK, Geha RS. Epicutaneous sensitization with protein antigen induces localized allergic dermatitis and hyperresponsiveness to methacholine after single exposure to aerosolized antigen in mice. J Clin Invest 1998;101:1614-22.
- ISAAC. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet 1998;351:1225-32.
- 49. Olivieri M, Zock JP, Accordini S, Heinrich J, Jarvis D, Kunzli N, et al. Risk factors for new-onset cat sensitization among adults: a population-based international cohort study. J Allergy Clin Immunol 2012;129:420-5.
- Mendy A, Mersha TB. Comorbidities in childhood-onset and adult-onset asthma. Ann Allergy Asthma Immunol 2022;129:327-34.
- Erbagci E, Demirel Ogut N, Koc Yildirim S, Hapa FA. Is dupilumab effective in adult-onset atopic dermatitis: real-life experience of 16 patients. J Cosmet Dermatol. In press.
- Dunlop JH, Keet CA. Epidemiology of food allergy. Immunol Allergy Clin North Am 2018;38:13-25.
- Dutmer CM, Kim H, Searing DA, Zoratti EM, Liu AH. Asthma in inner city children: recent insights: United States. Curr Opin Allergy Clin Immunol 2018;18:139-47.

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- 54. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. J Invest Dermatol 2011;131:67-73.
- Brunner PM, Guttman-Yassky E. Racial differences in atopic dermatitis. Ann Allergy Asthma Immunol 2019;122:449-55.
- 56. Kaufman BP, Guttman-Yassky E, Alexis AF. Atopic dermatitis in diverse racial and ethnic groups—variations in epidemiology, genetics, clinical presentation and treatment. Exp Dermatol 2018;27:340-57.
- Silverberg JI. Racial and ethnic disparities in atopic dermatitis. Curr Derm Rep 2015;4:44-8.
- Eichenfield LF, Beck L. Elidel (pimecrolimus) cream 1%: a nonsteroidal topical agent for the treatment of atopic dermatitis. J Allergy Clin Immunol 2003;111:1153-68.
- Spergel JM, Paller AS. Atopic dermatitis and the atopic march. J Allergy Clin Immunol 2003;112:S118-27.
- Paller AS, Spergel JM, Mina-Osorio P, Irvine AD. The atopic march and atopic multimorbidity: many trajectories, many pathways. J Allergy Clin Immunol 2019;143:46-55.