

Similar Efficacy and Safety Between Adolescents and Adults Receiving House Dust Mite Sublingual Immunotherapy Tablet

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Introduction

House dust mite (HDM) sensitivity is common in adults and adolescents and is a significant inducer of allergic rhinitis/conjunctivitis (AR/C).¹⁻³ Allergy immunotherapy is the only treatment that can alter the underlying disease mechanisms of AR/C.⁴ Sublingual immunotherapy (SLIT)-tablets provide a convenient, at-home administration form of allergy immunotherapy. Two large, phase 3, double-blind, placebo-controlled trials of the HDM SLIT-tablet were previously conducted in individuals aged ≥ 12 years with AR/C.^{5,6}

Objective

This post hoc analysis compared the efficacy and safety of the HDM SLIT-tablet between adults and adolescents with AR/C in the 2 trials.

Methods

Two double-blind, placebo-controlled trials were conducted in North America (NCT01700192) and Japan (JapicCTI number 121848).^{5,6} Subjects aged ≥ 12 years with HDM-induced AR/C were randomized to approximately one year of 12 SQ-HDM or placebo. Symptom-relieving rescue medication was provided to all subjects.

Primary endpoint was the average total combined rhinitis score (TCRS; sum of the rhinitis daily symptom and medication scores) during the last 8 weeks of treatment. Adverse events (AEs) in the North American trial were assessed and solicited by the use of a SLIT side effect report card during the first 28 days of treatment.⁷ AEs in the Japanese trial were assessed by general questioning by the investigator during study visits. Post hoc analyses were conducted in the subgroups of adolescents 12-17 years of age and adults ≥ 18 years of age in each trial.

Results

Overall, 395 adolescents and 1719 adults were included in the analysis.

Efficacy

Treatment effect on the TCRS during the last 8 weeks of treatment was similar between adolescents and adults in both trials (**Table 1**). In the North American trial, average TCRS significantly improved by 22% in adolescents and 16% in adults with 12 SQ-HDM versus placebo (**Figure 1**). In the Japanese trial, average TCRS significantly improved by 19% in adolescents and 20% in adults with 12 SQ-HDM versus placebo (**Figure 1**). By the end of the trials, 57% of subjects in the North American trial and 60% of subjects in the Japanese trials had not used symptom-relieving rescue medications.

Table 1. Total combined rhinitis score (TCRS) with 12 SQ-HDM versus placebo in adolescents and adults.

Population	Treatment Effect of 12 SQ-HDM vs Placebo		P value
	TCRS Absolute Difference, (95% CI)	TCRS Relative Difference [‡]	
North American Trial			
Adolescents	-1.0 (-2.0, -0.1)*	22%	0.02
Adults	-0.7 (-1.1, -0.3)*	16%	<0.001
Japanese Trial			
Adolescents	-1.0 (-1.9, -0.1) [†]	19%	0.04
Adults	-1.0 (-1.7, -0.4) [†]	20%	0.001

HDM, house dust mite.

*Analysis by non-parametric method with Hodges-Lehmann estimate as absolute difference and the relative difference based on medians.

[†]Analysis by linear mixed-effects model on square root transformed values. Differences were based on back-transformed least square means.

[‡]Relative difference to placebo: (placebo-12 SQ-HDM)/placebo x 100%.

Figure 1. Total combined rhinitis score (TCRS) in adolescents and adults.

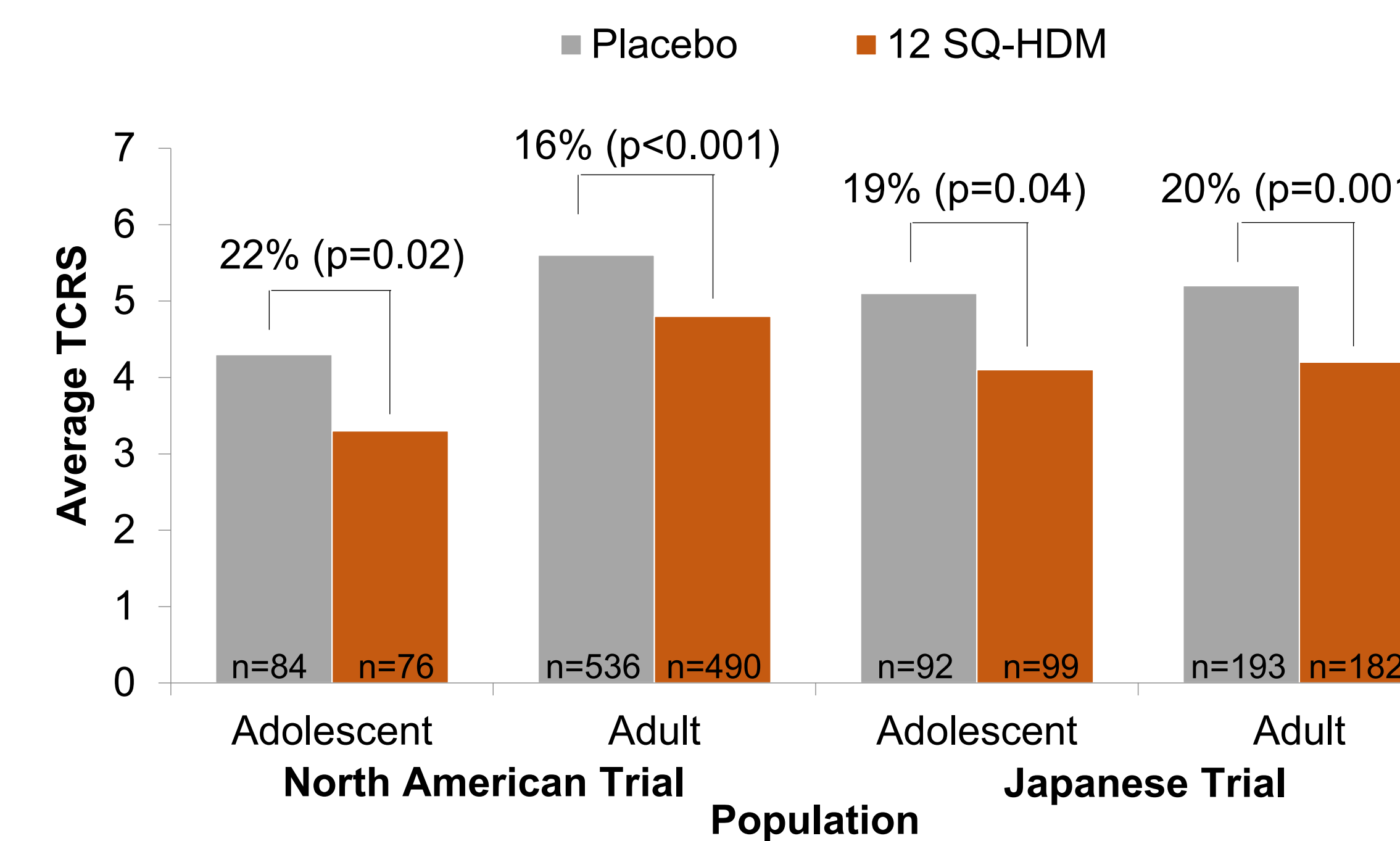


Table 2. Summary of adverse events with 12 SQ-HDM and placebo in adolescents and adults.

	North American Trial*				Japanese Trial			
	Adolescents		Adults		Adolescents		Adults	
	Placebo (n=95)	12 SQ-HDM (n=94)	Placebo (n=643)	12 SQ-HDM (n=649)	Placebo (n=99)	12 SQ-HDM (n=107)	Placebo (n=220)	12 SQ-HDM (n=207)
AEs, %								
Any TEAE	79%	95%	72%	90%	83%	93%	79%	89%
Severe TEAE [†]	3%	3%	5%	7%	0	0	0	0
Any TRAE	47%	93%	40%	83%	19%	66%	16%	62%
TRAE leading to discontinuation	0	10%	<1%	8%	1%	2%	1%	<1%
Serious TRAE [‡]	0	0	0	<1%	0	0	0	0

HDM, house dust mite; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

*Pre-specified local application site reactions were collected in the side effect report card for the first 28 days of treatment.

[†]Assessed by study investigator as incapacitating with inability to do normal activities, had significant effect on clinical status, or warranted intervention.

[‡]Events that caused death or were life-threatening, resulted in persistent or significant disability, resulted in (or prolonged) inpatient hospitalization, were a congenital birth defect in an offspring of the subject, or resulted in any other medically important event that required intervention or may have jeopardized the subject.

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Safety

The proportion of adolescent and adult subjects reporting treatment-emergent AEs in the HDM SLIT-tablet group was 95% and 90%, respectively, in the North American trial and 93% and 89% in the Japanese trial (**Table 2**). The most common 12 SQ-HDM treatment-related AEs in the North American trial were oral pruritus, throat irritation, and ear pruritus in both adolescents and adults. The most common 12 SQ-HDM treatment-related AEs in the Japanese trial were oral pruritus, mouth edema, and oropharyngeal discomfort in adolescents and oral pruritus, throat irritation, and ear pruritus in adults.

Conclusion

Efficacy and safety of the HDM SLIT-tablet appear similar in adolescents and adults with AR/C. Treatment with the HDM SLIT-tablet significantly improved the composite measure of symptoms and rescue medication use compared with placebo and was well tolerated in both adolescents and adults. The higher proportion of TRAEs in the North American trial is likely because of the active AE solicitation with the side effect report card. The results indicate that the HDM SLIT-tablet is insensitive to ethnicity, age, or regional differences, with a similar efficacy and safety response.

Similarities in Efficacy and Safety of Sublingual Immunotherapy

Tablets Across Geographic Regions in Clinical Trials

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Introduction

Allergic rhinitis with or without conjunctivitis (AR/C) affects 10-30% of adults and up to 40% of children worldwide.¹ The clinical development programs of the timothy grass, ragweed, tree, and house dust mite (HDM) sublingual immunotherapy (SLIT)-tablets for AR/C included large clinical trials conducted in North America, Europe, or Japan. Environmental differences and cultural variables among geographic regions can impact the immune system,^{2,3} potentially affecting responses to immunomodulatory treatments.⁴ Geographic variability has been shown to affect responses to pneumococcal conjugate vaccines.^{5,6}

Objective

Because of the diversity of participants in the trials and the large sample sizes, the objective of these analyses was to use pooled data from the SLIT-tablet trials to assess efficacy, immunology, and safety outcomes across geographic regions.

Methods

Ten double-blind, placebo-controlled trials of timothy grass, ragweed, tree, and HDM SLIT-tablet in subjects with AR/C were conducted in North America, Europe, or Japan (N=5,935 analyzed). Trials were designed similarly with respect to medical practice, target population, eligibility criteria, efficacy and safety monitoring. Open-label symptom-relieving medications were provided to subjects in all trials. Data were analyzed for the approved doses in North America and Europe.

Efficacy endpoints were based on primary efficacy outcomes originally prespecified for each trial.

- Pollen trials primary endpoint: total combined score (TCS; sum of the rhinoconjunctivitis daily symptom and medication score) during the trial assessment period
- HDM trials primary endpoint: total combined rhinitis score (TCRS; sum of the rhinitis daily symptom and medication score) over the last ~8 weeks of treatment

The immunology endpoint was the change from baseline in allergen-specific IgE and IgG₄ in each trial. The safety endpoint was the percentage of subjects with treatment-related adverse events (TRAEs); 2 trials actively solicited adverse events (AEs) using a SLIT report card.

TRAE data from the 10 trials were pooled by SLIT-tablet allergen and analyzed by region (North America, Europe, and Japan) and severity (mild, moderate, severe).

Funding: These trials were funded by ALK, Hørsholm, Denmark, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and Torii Pharmaceuticals Co., Ltd., Tokyo, Japan. Medical writing and editorial assistance were funded by ALK, Hørsholm, Denmark.
Disclosure of presenting author: H. Nolte is an employee of ALK.

Statistical analysis methods for the primary efficacy endpoint varied among trials. A progression of analysis was used to make analyses among trials more comparable:

- Step 1: Model as predefined per protocol for each trial
- Step 2: Model as predefined per protocol for each trial with the absolute treatment effect given as back transformed estimate of the square root transformed model. Fixed effects, random effects, and other parameters remained as predefined per protocol. Relative effect is the percentage difference from placebo based on adjusted means estimated by the respective non-transformed model per trial
- Step 3: Step 2 model plus standardization of fixed effects, random effects, and other parameters

Results

Statistically significant improvements versus placebo for the primary efficacy endpoint were demonstrated with all SLIT-tablet allergens when using the predefined protocol model analysis (Step 1 model; **Figure 1**). Absolute improvements versus placebo for the primary endpoint remained statistically significant ($p \leq 0.007$) when a square root transformation was applied (Step 2 model; **Figure 2**).

Figure 1. Treatment effect per trial by the predefined protocol model analysis (Step 1 model). Data are the primary endpoint for each study analyzed. Number of subjects are for active/placebo. HDM, house dust mite.

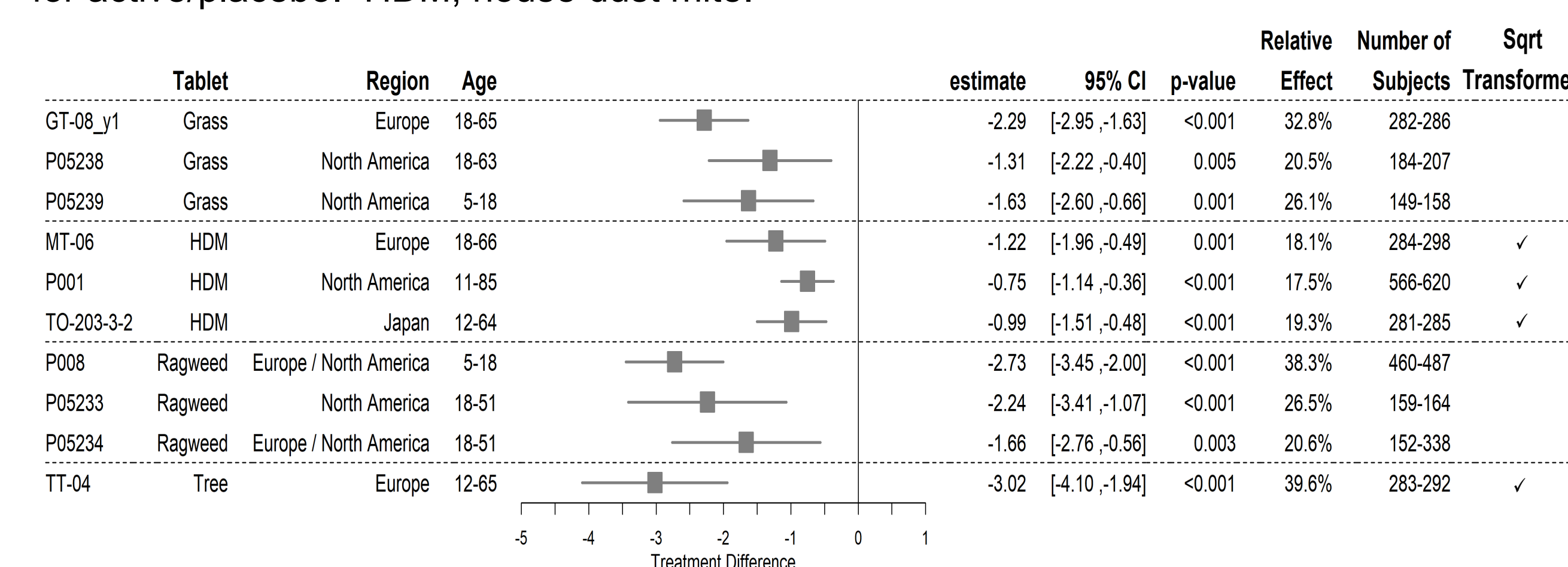
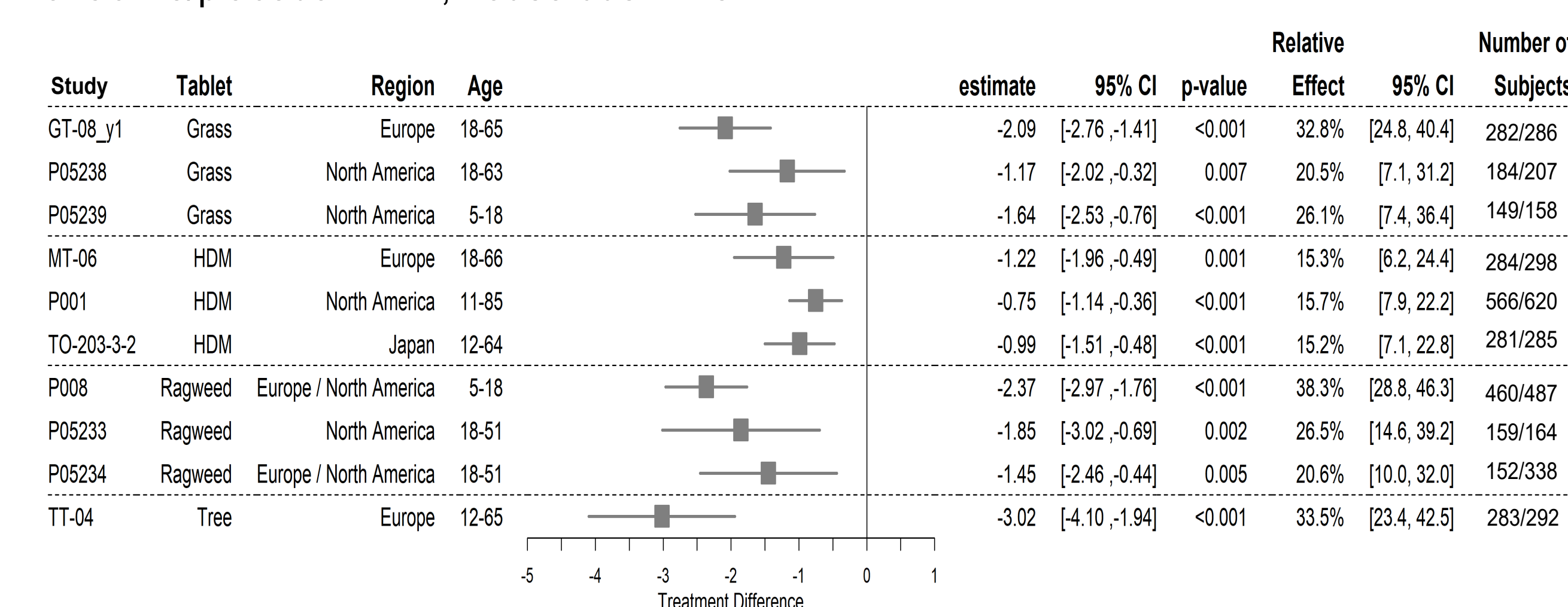


Figure 2. Treatment effect per trial with square root transformation applied (Step 2 model). Data are based on the primary endpoint for each study. Number of subjects are for active/placebo. HDM, house dust mite.



The Step 3 model had very little impact on the absolute improvement versus placebo compared with the Step 2 model for the grass, HDM, and tree SLIT-tablet. Absolute improvement versus placebo was reduced in 2 ragweed SLIT-tablet trials because the assessment period for these trials in the Step 3 model was changed from peak pollen season to entire pollen season.

SLIT-tablets induced a significant immunologic response versus placebo shortly after initiation (**Figure 3**). The pattern and magnitude of the response to HDM SLIT-tablet for both IgE and IgG₄ were similar across geographic regions (**Figure 4**). Similar kinetics were also observed for grass, ragweed, and tree SLIT-tablet-induced immunologic responses.

Figure 3. IgE and IgG₄ responses to SLIT-tablet treatment.

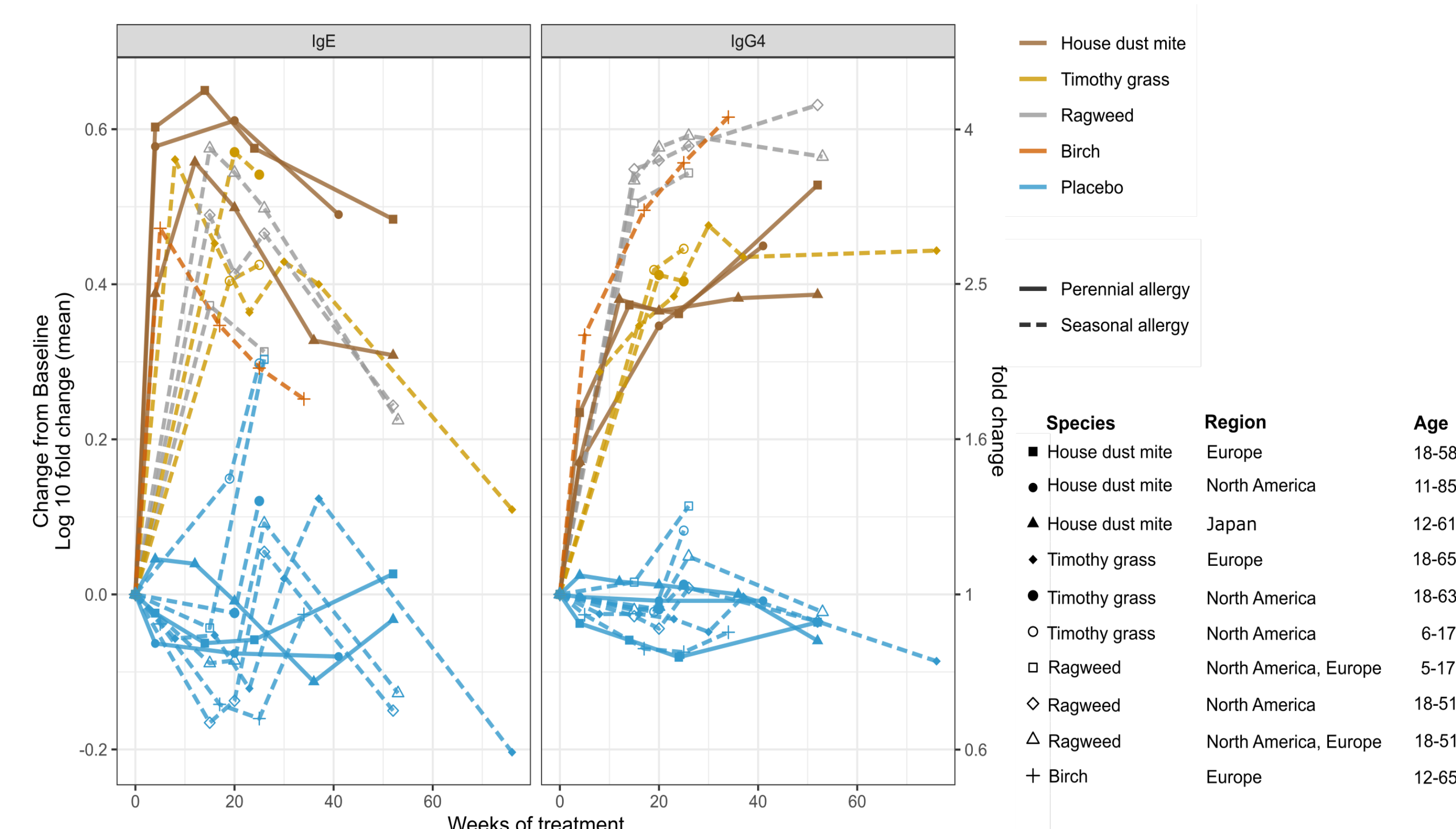
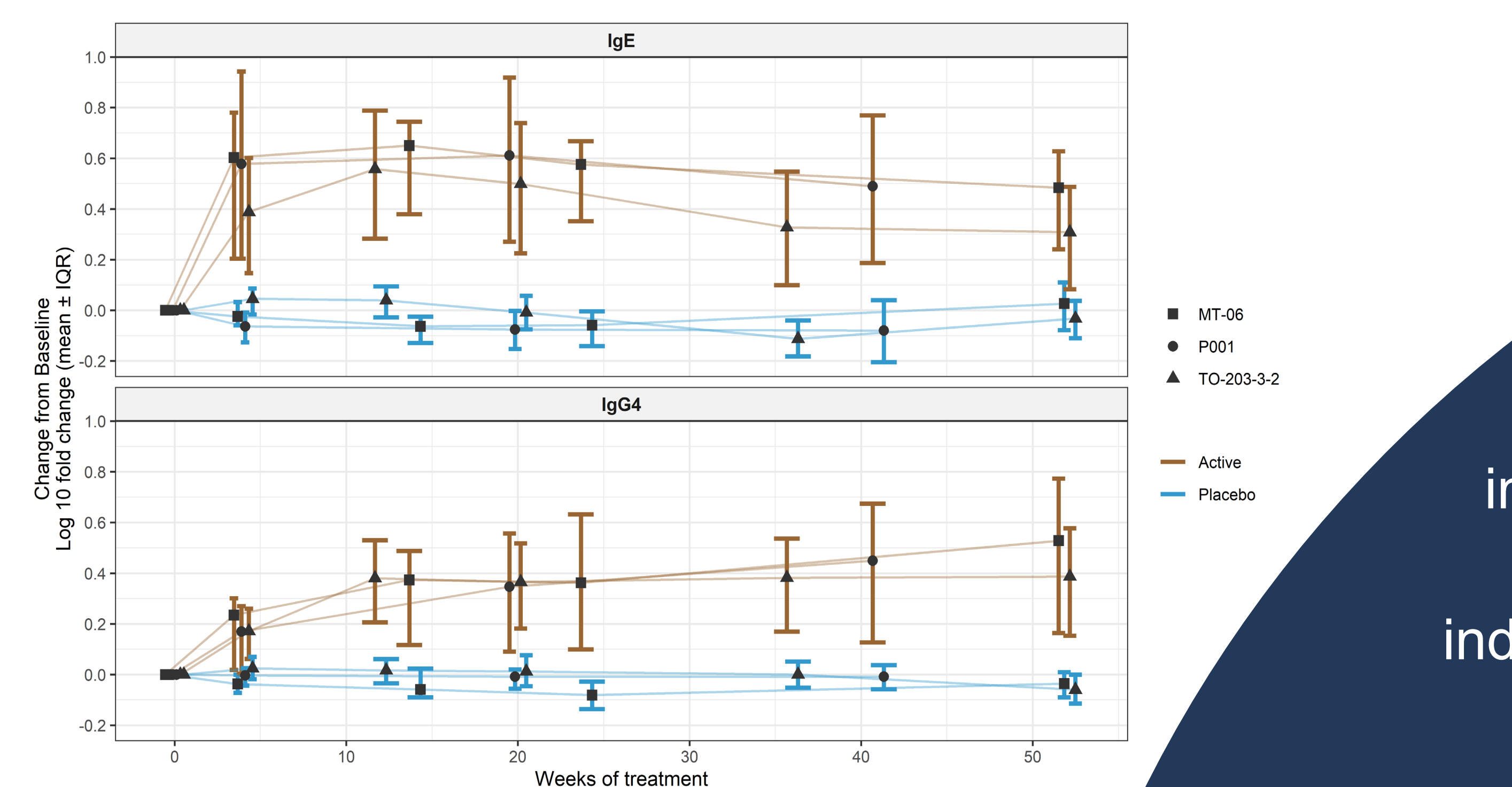
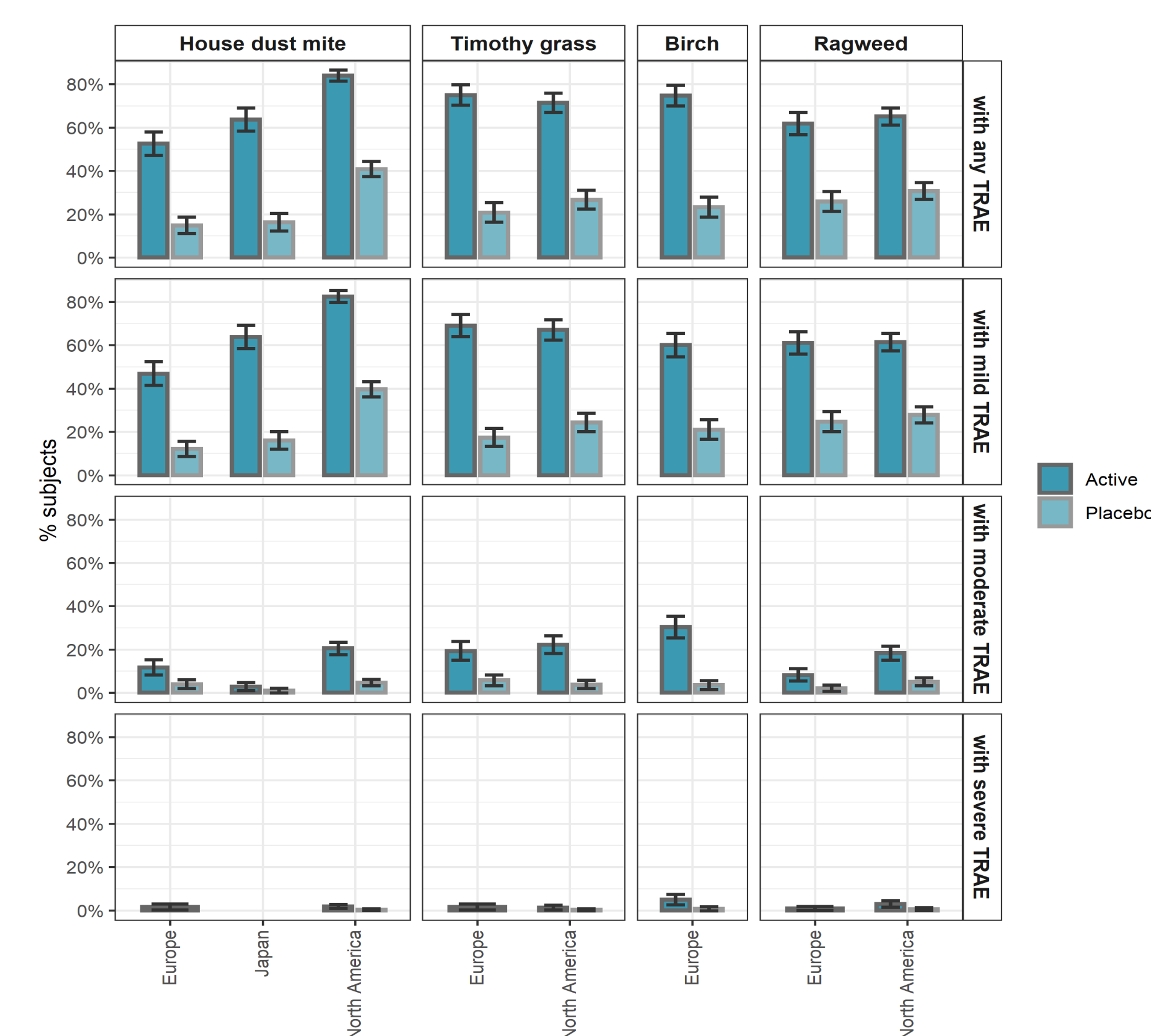


Figure 4. IgE and IgG₄ patterns for the house dust mite SLIT-tablet conducted across different geographic regions.



Local application site reactions were the most common treatment-related AEs in all regions. A similar proportion of TRAEs were observed across regions, except for a higher proportion in the North American trial of the HDM SLIT-tablet, in which AEs were actively solicited versus spontaneous reporting in most of the other trials (**Figure 5**). The majority of the TRAEs were mild to moderate in intensity (**Figure 5**).

Figure 5. Percentage of subjects with treatment-related AEs (TRAEs) by geographic region and AE severity. HDM, house dust mite.



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Conclusion

Confirmatory phase 3 trials conducted in different geographic regions showed similar efficacy, immunologic, and safety outcomes for SLIT-tablets in the treatment of AR/C. This is the first analysis indicating that AIT is insensitive to regional differences. SLIT-tablets are a treatment option for AR/C for patients living in various geographic regions.