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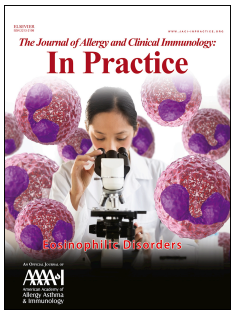

Sublingual tablet immunotherapy improves quality of life in adults with allergic rhinoconjunctivitis

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Abstract:

Background: Allergic rhinitis with or without conjunctivitis (AR/C) can negatively impact many aspects of quality of life (QoL). The efficacy and safety of SQ sublingual immunotherapy (SLIT)-tablets have been confirmed across large clinical trials in adults with grass, tree, ragweed, and house dust mite (HDM) AR/C.

Objective: This pooled analysis investigates whether the reduction in symptom burden found across the clinical trials is supported by improvements in QoL.

Methods: 11 phase II/III randomized placebo-controlled trials across the SQ grass, tree, ragweed and HDM SLIT-tablets (Grass: N=3179; Ragweed: N=767; Tree: N=634; HDM: N=2221) were included. QoL was assessed using the standardized Rhinitis Quality of Life Questionnaire (RQLQ) with the exception of three grass trials that used the non-standardized version. The overall RQLQ scores were expressed as a mean of seven domains. In the pooled analysis, treatment was used as fixed effect; the trial, and the interaction between region/country with the trial as random effects.

Results: The pooled analysis showed consistent and statistically significant improvements in overall RQLQ scores across all four SQ SLIT-tablets vs. placebo (Pooled estimate [95%CI], p value. Grass: -0.20 [-0.28, -0.12], P<0.001. Tree: -0.42 [-0.58, -0.26], P<0.001. Ragweed: -0.36 [-0.55, -0.17], P<0.001. HDM: -0.28 [-0.39, -0.17], P<0.001). Furthermore, significant improvements vs. placebo for all four SQ SLIT-tablets were seen across the 7 individual domains.

Conclusion: The proven efficacy of SQ SLIT-tablets to reduce symptoms across four of the most common respiratory allergens, is supported by concurrent significant improvements in RQLQ scores – overall and for all 7 domains.

Keywords: sublingual immunotherapy, allergic rhinoconjunctivitis, RQLQ, RQLQ domains, quality of life, grass pollen allergy, tree pollen allergy, ragweed pollen allergy, house dust mite allergy, pooled analysis

Clinical trials registry: GT-02: pre 2005, GT-08: NCT00227279 (Clinicaltrials.gov), P08067: NCT01385371 (Clinicaltrials.gov), P05238: NCT00562159 (Clinicaltrials.gov), GT-14: NCT00421655 (Clinicaltrials.gov), TT-04:

2015-004821-15 (EudraCT), P05233: NCT00783198 (Clinicaltrials.gov), P05234: NCT00770315 (Clinicaltrials.gov), MT-06: NCT01454544 (Clinicaltrials.gov), P001: NCT01700192 (Clinicaltrials.gov), P003: NCT01644617 (Clinicaltrials.gov)

Highlights box:

1. What is already known about this topic? Individual trials have shown that treatment with SQ SLIT-tablets can improve quality of life in patients suffering from allergic rhinitis with or without conjunctivitis
2. What does this article add to our knowledge? This pooled analysis of 11 trials with SQ SLIT-tablets covering 4 common allergens, i.e. grass, tree, ragweed and HDM, demonstrated consistent improvements in quality of life.
3. How does this study impact current management guidelines. It underscores the clinical relevance of utilising SLIT-tablet more frequently in the treatment of AR/C to both ameliorate the burden of symptoms and ultimately, improve QoL

List of abbreviations: AIT: allergy immunotherapy; AR: allergic rhinitis; AR/C: allergic rhinitis with or without conjunctivitis; ARIA: Allergic Rhinitis and its Impact on Asthma; BAU: Bioequivalent Allergy Unit; DBPC: double blind placebo controlled; DBRPC: double blind randomized placebo controlled; EEC: environmental exposure chamber; FEV1: Forced Expired Volume in the first second; GINA: Global Initiative for Asthma; HDM: House dust mite; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ICS: inhaled corticosteroid; IgE: immunoglobulin E; INCS: Intranasal corticosteroid; MCID: Minimum clinically important difference; PRQLQ: paediatric rhinitis quality of life questionnaire; QoL: quality of life; RCT: randomised controlled trial; RQLQ: rhinitis quality of life questionnaire; RQLQ(S): standardised rhinitis quality of life questionnaire; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy; SPT: skin prick test; SQ: standardised quality; SQ-T: Standardised Quality units Tablet; SQ-U: standardized quality unit

Introduction:

Allergic rhinitis with and without conjunctivitis (AR/C) is one of the most common manifestations of respiratory allergic disease. Up to around 20% of populations are affected, and alarmingly, the prevalence is still on the rise [1]. AR/C can be triggered by e.g., airborne pollens, spores from fungi/mold, pets or house dust mites. Pollen and fungi/mold allergy are typically seasonal and limited to the period of the year where the offending pollens or spores are present in the air (intermittent AR/C) whereas house dust mite allergy, pet allergy and some indoor molds are perennial and therefore affects sufferers throughout the year (persistent AR/C) [2]. Symptoms of AR/C include runny, red eyes and nose, blocked nose, itching, and sneezing. AR/C is known to affect the quality of life (QoL) of people suffering from AR/C [3–6]. Thus, AR/C sufferers often have impaired sleep and many function sub-optimally in work, school, and social activities due to the direct and indirect effects of AR/C (e.g., absenteeism, reduced productivity, and daytime tiredness), with high costs to society [2, 7–11].

AR/C is often treated by allergen avoidance or symptom-relieving medications like antihistamines or corticosteroids (nasal or systemic) [2, 12]. Despite symptom-relieving treatment, many patients feel that their disease is not well controlled, and they are still experiencing significant impact on their daily lives. In a self-administered satisfaction questionnaire, 83% of adults and 75% of children were not satisfied with their current allergy treatment, with the main reason being a perceived lack of efficacy in relieving their symptoms (56.6%) [13]. In fact, it has been estimated that up to 90% of AR/C patients are untreated, insufficiently treated or inappropriately treated [8]. Allergy immunotherapy (AIT) is the only causal treatment for AR/C with the potential to modify the cause of the disease. In recent years, several large randomized controlled trials (RCTs) have confirmed the efficacy and safety of AIT when administered as sublingual immunotherapy (SLIT)-tablets in grass, tree, ragweed, and HDM AR/C. In addition to reduce both symptom burden and the need for symptom-relieving medications, the impact of SLIT-tablets on QoL was also assessed in RCTs, using the validated Juniper and Guyatt's Rhinitis Quality of Life Questionnaire (RQLQ)

115 [14]. The questionnaire comprises 28 questions covering 7 domains, and based on the answers, a doctor is
116 able to evaluate which aspects of a patient's life is affected by the AR condition and to what degree.

117 AIT SQ SLIT-tablets (ALK, Denmark) are approved for the treatment of AR and available for major allergen
118 groups (grass, house dust mite, ragweed, birch homologues trees – and in Japan also cedar) in many
119 countries in Europe, North America, and other parts of the world. All have been shown to be effective in
120 treating AR in adults in large DBPC trials (Table 1). As well as presenting new data on the 7 individual
121 domains that together comprises the overall RQLQ score, the paper also presents a new post-hoc pooled-
122 analysis aimed at assessing the impact of SLIT-tablets on QoL using RQLQ data from 11 major randomized,
123 double-blind, placebo-controlled phase III clinical trials from Europe or North America (United States and
124 Canada). As data on individual domains in the RQLQ from other SLIT-tablet formulations are not generally
125 published, this paper focuses on the clinical trials performed with SQ SLIT-tablets alone, where access to all
126 data was available.

127 **Material and Methods:**

128 QoL was assessed across 11 randomised, double-blind, placebo-controlled trials in adults (limited number of
129 adolescents and children also included) with grass (5 trials: N=3179), ragweed (2 trials: N=767), tree (1 trial:
130 N=634), and HDM (3 trials: N=2221) AR (see Table 1). All major phase III trials performed with the SQ SLIT-
131 tablets were included, since data on both overall RQLQ score as well as data on the 7 individual domains
132 were available for analysis. Trials were conducted between 2002 and 2017. Per QoL domain, all subjects per
133 study with reported QoL outcome are included.

134 [Insert: Table 1]

135 Ethics:

136 All trials were designed and conducted in accordance with the principles of the Declaration of Helsinki [15]
137 and conducted in compliance with the principles of the International Council for Harmonisation of Technical
138 Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice [16]. Institutional review

boards approved the protocol, and written informed consent was obtained from the subject or the subject's legal representative.

Trial design and study population:

All trials were randomised, double-blind, placebo-controlled trials. Details of the efficacy and safety results have been published previously including design, Consort diagram and pre-specified primary and secondary endpoints (Grass [17–21], Ragweed [22, 23], Tree [24], HDM [25–27]).

Treatment:

The SLIT-tablets (ALK, Denmark) are fast-dissolving (<10 seconds) freeze-dried tablets containing grass (75,000 SQ-T/2800 BAU), HDM (12 SQ-HDM), tree (12 SQ-Bet), or ragweed (12 SQ-Amb/12 Amb a 1-U) allergen extracts. First administration of treatment occurred at the trial site, followed by a 30-minute observation under medical supervision. Subsequent doses, when tolerated, comprising one SLIT-tablet daily, were self-administered at home. Treatment for pollen allergies were initiated pre-seasonally.

Analysis:

QoL was assessed using the standardised Rhinitis Quality of Life Questionnaire with the exception of three grass trials (GT-02, GT-08, GT-14) that used the non-standardised version (please refer to https://www.qoltech.co.uk/index.htm for details of the two questionnaires). Per trial, subjects reported RQLQ, evaluating 28 questions covering 7 domains (activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems, and emotional function) with scores from 0 (not troubled) to 6 (extremely troubled). Each trial had a pre-defined efficacy assessment period at the end of the trial, the last week, where the scores used in the between-group comparison were collected. Statistical analyses:

Overall RQLQ analyses per trial are based on the respective pre-defined model per trial (see Supplemental Table E1) and consistent with earlier reported outcomes. In addition, each of the 7 RQLQ domains that

together comprise the overall RQLQ score were analysed. The same model as for overall RQLQ was applied for the 7 per-domain analyses per trial.

Pooled analyses are per therapeutic allergen, given individual subjects data. To facilitate the comparison of results across the allergen species, the pooled model was also applied to Tree even though this allergen currently only comprises 1 phase III clinical trial. With the purpose of facilitating pooling of the data, an adapted analysis model was consistently applied for all therapeutic allergens. The adapted linear mixed model is based on treatment as fixed effect, trial as random effect, and the interaction of trial and geographical region as random effect, with geographical region being based on the respective pre-defined model per trial.

The outcome per trial for the pooled analysis is as pre-defined, except for trials with repeated measurements per trial subject: For TT-04, GT-08, and GT-14 the mean over the measure in the efficacy assessment period is the outcome, and for GT-02, the 1st seasonal visit is the outcome.

All estimates shown are based on the placebo and respectively approved marketed dose in North America and Europe, per trial. The pre-defined models were based on all treatment arms per trial, while for the pooled analyses, only the placebo and the respectively approved marketed dose were included in the model.

Sensitivity analyses based on pooled overall RQLQ were conducted by regulating for age and adjusting for sex and age, supporting the robustness of the analyses by controlling for potential confounding. Shown per therapeutic allergen, the first approach is based on excluding subjects under the age of 18 years. The second approach similarly excludes subjects over the age of 49 years. The third approach addresses potential bias related to sex by integrating sex as fixed effects, and the fourth approach adds in addition the age group per subject as fixed effect. The age group are defined based on these criteria: <20, 21-30, 31-40, 41-50, >50.

Reported outcomes are presented as forest plots, showing trial, estimate, 95% CI of the estimate, p-value, and number of subjects given active and placebo treatment. Estimate and 95% CI summarize the model

output per statistical analysis, with estimate being the absolute difference in effect between active and placebo treatment.

Results:

Baseline and key demographics

Table 2 gives an overview of the key baseline demographics for each of the trials. In general, subjects across the trials were in their mid-30s, with long-standing AR/C disease duration of 9.9 to 21.0 years and a high prevalence of polysensitisation (75% were poly-sensitized).

[Insert Table 2]

[Insert Figure 1]

[Insert Figure 2]

RQLQ was assessed both as the overall RQLQ score and across each of the 7 domains. The RQLQ results are presented for each individual trial and pooled for each therapeutic allergen (Figure 1). Across all trials, the point estimates for overall RQLQ consistently favor active treatment and reach statistically significant differences versus placebo in all individual trials except GT-14. The pooled analyses for each of the 4 allergy SLIT-Tablets demonstrated a highly significant improvement in overall RQLQ vs placebo. – Grass tablet: -0.2 ($p<0.001$), HDM tablet: -0.28 ($p<0.001$), Ragweed tablet: -0.36 ($p<0.001$), and Tree tablet: -0.42 ($p<0.001$).

The results of overall RQLQ were consistent, as the pooled analyses across all 7 domains and across all 4 therapeutic allergens significantly favoured active treatment (Figure 2 and Supplementary Figures E1-E7). For both nasal, eye, and non-nose/eye symptom domains, the pooled analyses significantly favoured active treatment: Grass (nasal: $P<0.001$; ocular: $P<0.001$; non-nose/eye: $P=0.004$), ragweed (nasal: $P=0.002$; ocular: $P<0.001$; non-nose/eye: $P<0.001$), tree (nasal: $P<0.001$; ocular: $P<0.001$; non-nose/eye: $P<0.001$), HDM (nasal: $P<0.001$; ocular: $P<0.001$; non-nose/eye: $P<0.001$).

The pooled analyses also showed significant improvements for active treated subjects compared to placebo for both sleep and emotional domains: Grass (sleep: P=0.009; emotional: P<0.001), ragweed (sleep: P<0.001; emotional: P=0.001), tree (sleep: P<0.001; emotional: P<0.001), HDM ((sleep: P<0.001; emotional: P<0.001), and consistently, the pooled analyses also favoured active treatment for practical problems and activities: Grass (Practical: P<0.001; activities: P<0.001), ragweed (Practical: P=0.003; activities: P<0.001), tree (Practical: P<0.001; activities: P<0.001), HDM (Practical: P<0.001; activities: P<0.001).

Since the trials included subjects varying in age from adolescents (>12 and <18 years of age) to older adults (18 – 49 years of age) to elderly (>49 years of age) as well as both male and female subjects, sensitivity analyses of both these parameters were performed for the overall RQLQ score within each allergen species. The overall RQLQ score remained significant with little variation when regulating for age and accounting for sex or sex and age groups (Supplemental Figure E8).

Discussion:

AR/C is a highly prevalent and chronic disease that negatively impacts many aspects of patients' daily living and ultimately, can have a detrimental impact on QoL [3–6]. In recent years, a favorable efficacy and tolerability profile of the SLIT-tablets, has been confirmed in more than 6500 adults with AR/C, who were enrolled in 11 phase III trials across the most common respiratory allergens (i.e. grass [17–21], ragweed [22, 23], tree [24], HDM [25–27]). In the trials, the impact of SLIT-tablets on QoL was assessed using the validated RQLQ questionnaire [14] as supportive evidence for the primary and key secondary efficacy endpoints of AR/C symptoms and use of symptom-relieving medication . This pooled analysis utilized data from the 11 phase III trials and found statistically significant improvements in QoL for all four SLIT-tablets compared to placebo, when assessed by overall RQLQ. Importantly, the significant improvements in QoL were found in AR/C subjects, who had free access to symptom-relieving medication (antihistamines, oral, and nasal glucocorticosteroids) during the trial period. Symptom-relieving medications such as oral and ocular antihistamines and intranasal corticosteroids (INCS) have previously shown to improve QoL, when assessed by RQLQ [28–30], thus the significant improvements in QoL found for SLIT-tablets are compelling,

232 considering that the results are incremental symptom improvements in AR/C patients, who during the trial
233 period had free access to symptom-relieving medications. In addition, subjects on SLIT-tablets were able to
234 reduce need for symptom-relieving medication [31, 32]

235 The effect sizes of improvement in overall RQLQ for SLIT-tablets compared to placebo varied between 0.20
236 and 0.42 in the pooled analyses. The magnitude of improvement in overall RQLQ score seen across the trials
237 is comparable to that reported for other SLIT tablets [33, 34]). Furthermore, two meta-analyses have
238 reported improvement in QoL for AIT, when administered as SCIT and SLIT. One meta-analysis included both
239 SCIT and SLIT trials, and found mean improvements in RQLQ for SCIT of -0.24 (95% CI -0.04 to -0.44) and for
240 SLIT of -0.32 (95% CI -0.20 to -0.43) [35], while another meta-analysis found improvements in standard mean
241 difference in RQLQ for SCIT over placebo of -0.70 (95%CI -0.12 to -1.29) [36]. Additionally, two SCIT trials also
242 found significant improvement in RQLQ score for active treatment over placebo. Frew et al [37] reported
243 improvements in overall RQLQ score of 0.44 to 0.88 for 10,000 and 100,000 SQ-U, respectively, in a DBRPC
244 trial of Grass SCIT treatment for AR. For the high SCIT dose, all seven domains improved significantly over
245 placebo, while for the low SCIT dose, only two out of the seven domains improved significantly, indicating a
246 dose-response favoring the 100,000 SQ-U [38]. And finally, an open-label retrospective multicenter study
247 (N=1257) of three-year SCIT treatment (grass and rye) also found significantly improvements in the RQLQ
248 score [39]. The effect was seen both for the overall RQLQ score as well as for each of the 6 domains
249 assessed, and the effect size increased year-on-year.

250 As pointed out by Wright et al (2012), a single, universally accepted MCID value for a specific outcome
251 measure does not exist as currently reported MCID values will vary based on the population studied and the
252 methodology chosen to derive the reported MCID value [40]. A minimal clinical importance (MCID) of 0.5 for
253 overall RQLQ score has previously been suggested, based on a within-group improvement from baseline and
254 only in trials of AR patients treated with antihistamines and INCS [14, 41, 42]. Unfortunately, the MCID
255 cannot be easily applied for AIT trials, especially the pollen trials, as subjects are initiating treatment outside
256 the pollen season to allow tolerance to build, i.e. baseline is captured at a time where the relevant pollen is

not prevalent resulting in no symptoms and therefore, no valid measure for the impact on QoL [43]. A between group MCID for RQLQ assessment in AIT trials has been discussed recently by Blaiss et al, who estimated a MCID of AIT treatment versus placebo during the different pollen seasons [43]. For grass pollen allergy, anchor-based derived between-group MCIDs were 0.22 for the entire pollen season (n = 343) and 0.10 for the peak pollen season (n = 335). For tree pollen allergy, anchor-based derived between-group MCIDs were 0.26 for the tree pollen season (n = 306) and 0.16 for the birch pollen season (n = 305) (representative of peak season). Distribution-based derived MCIDs were supportive of the anchor-based values. The suggested MCID have not yet been fully validated across multiple AIT trials, but the results of the pooled analyses are overall in agreements with their findings. The improvements in QoL found in the analyses appear robust, as significant improvements in QoL for the SLIT-tablets compared to placebo, were consistently found for both the overall RQLQ score (supported by the sensitivity analysis for age and sex), and across each of the individual domains that constitute the overall RQLQ score. The improvements in the domains related to nasal, eye, and non-nose/eye symptoms are expected, since SLIT-tablets have previously demonstrated significant reductions in daily symptom scores based on local nasal and ocular symptoms (i.e. Grass [17–21], Ragweed [22, 23], Tree [24], HDM [25–27]). However, it is important to note, that significant improvements were found across all seven individual RQLQ domains, thereby demonstrating, that the effect of the treatment extends beyond improving local symptoms (nasal, eye, and non-nose/eye symptoms), by acting on a more systemic level and improving QoL domains covering aspects of sleep, activities, practical problems and emotional [14, 41, 42].

A common symptom of AR is nasal congestion, which is closely related to poor sleep quality [3, 44–48]. In a study by Leger et al, 50% of adult AR patients reported poor sleep quality, 38% reported nocturnal awakenings, and 27% reported difficulty in falling asleep [13]. Moreover, the evidence suggests, that the detrimental impact of AR on sleep, often results in negative consequences for learning ability, productivity at work or school, and QoL in general [3–6]. Consequently, demonstrating significant improvements across both local and the more systemic RQLQ domains like sleep, are highly clinically relevant and of great importance to patients, particular those patients suffering from perennial allergies such as HDM AR.

Recently, another study showed that 66% of AR subjects with perennial AR, reported sleep problems and woke an average of 3.8 times per night [49]. In the study, disturbances in daily functioning due to sleep issues were reported by 85-95% of subjects with sleep problems, with significant (very impacted or moderately impacted) impact on work and other activities reports by 58-68% of these subjects [49]. The significant improvement in sleep found in this post-hoc analyses are supported by the study, as subjects receiving AIT treatment more often reported improvement in sleep than those on other prescribed treatments, and their satisfaction with their sleep was higher [49]. While symptom-relieving treatments such as oral antihistamines and INCS can alleviate AR symptoms [3, 44, 50, 51], they are only effective for as long as the treatment is taken. In contrast, long-term and sustained effects of SLIT-tablets have been shown post-treatment [52], and therefore, this treatment modality could be an attractive alternative to symptom-relieving medication in people with sleep disturbances due to AR. As sleep disturbances are linked to loss of productivity, it is not surprising, that SLIT-tablets have been found to be a cost-effective treatment option [53, 54], and thus present both an effective and socio-economic attractive treatment option for AR.

The pooled analyses were done *post-hoc* based on RQLQ data collected as supportive secondary endpoints. Although the pooled analyses were done *post-hoc*, RQLQ was a pre-defined secondary endpoint across the 11 randomised, double-blind, placebo-controlled, multi-national trials with around 6000 AR/C adults enrolled (Grass [17–21], Ragweed [22, 23], Tree [24], HDM [25–27]). Three trials (P08067, TT-04, P001) enrolled a total of 323 adolescent subjects (12-18 years of age), and one trial (P08067) enrolled 109 children (5-11 years of age). The strengths of the analyses include both the comprehensive dataset as well as the consistent results found for all four SLIT-tablets and for both overall RQLQ as well as across all individual domains. QoL was assessed using the validated RQLQ, which is the most widely used instrument for measuring QoL data in AR/C clinical trials. It is an identified limitation, that the RQLQ has only been validated for trials investigating effects of antihistamine and intranasal steroid treatment in AR patients [14, 41], and not specifically for use in AIT trials, when AIT is added to free access to symptom-relieving medications. Similarly, no MCID for between-group differences has yet been widely accepted for RQLQ in AIT trials although the effect sizes found in the present analyses were in overall agreement with the suggested MCID

from a recent publication by Blaiss et al [43]. Despite the limitations, the results are robust, with consistent and statistically significant improvements in QoL in AR/C patients treated with SLIT-tablets across four of the most common respiratory allergens.

Conclusion:

This pooled analyses further substantiate, that the SLIT-tablets improve QoL in patients with AR/C. The analyses found both consistent, reproducible, and significant improvements in both overall RQLQ and across all individual RQLQ domains including sleep, thus, providing important, complementary evidence of efficacy for the SLIT-tablets. As many patients suffering from AR/C, are not well-controlled despite using symptom-relieving medications, the results underscore the clinical relevance of utilizing SLIT-tablet more frequently in the treatment of AR/C to both ameliorate the burden of symptoms and ultimately, improve QoL.

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Table and Figure legends:

Table 1 legend: Overview of clinical trials included in analyses

Footnote to Table 1:

*: N shown for GT-02 are excluding the group of patients receiving Placebo Loratidine (antihistamine).

**: GT-08 Y1: This was a 5-year trial, but year-1 data are used in this analysis to make them more comparable with the other trials

***: GT-14: This trial, as the only one, did not meet its primary endpoint likely due to various trial execution issues – lack of correlation between pollen count and symptom score (see primary publication)

****: P003: Exposure Chamber trial – RQLQ data were collected outside of the Chamber setting prior to the chamber challenge and are thus comparable to the data collected in the other trials

Table 2 legend: Baseline characteristics

Footnote to Table 2:

NA: not available for that trial; a: Three trials enrolled a total of 323 adolescent subjects (12-18 years of age) - P08067: n=174; TT-04: n=60; P001: n=189, and one trial enrolled 109 children (5-11 years of age) - P08067: n=109, but no RQLQ data were collected for the children as per trial protocol.

Figure 1 legend: Overall RQLQ analysis. The absolute treatment effect given the respective model as pre-specified per study is shown, with the change of using compound symmetry as covariance structure for GT-14. In addition, for every tablet type a pooled analysis with a standardised model is included. All pooled analysis models are with treatment as fixed effect, study as random effect and the interaction of region or country, dependent on the respective pre-specified model, with study as random effect. For TT-04, GT-08 and GT-14 pooled analysis, the mean over the measure in the efficacy assessment period is the outcome. For

500 the GT-02 pooled analysis, the 1st seasonal visit is the outcome. Shown data is the approved dose in Europe
501 and North America relative to Placebo.

502

503 Figure 2 legend: Pooled analysis for each SLIT-tablet species for each of the 7 RQLQ Domains.

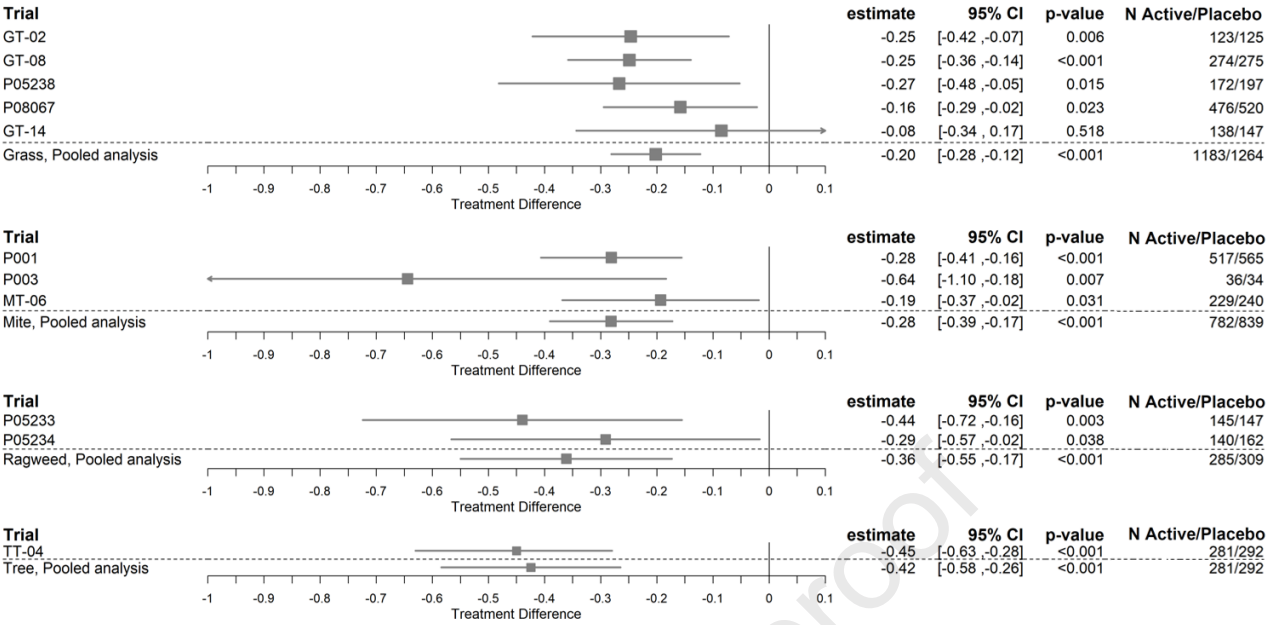
504

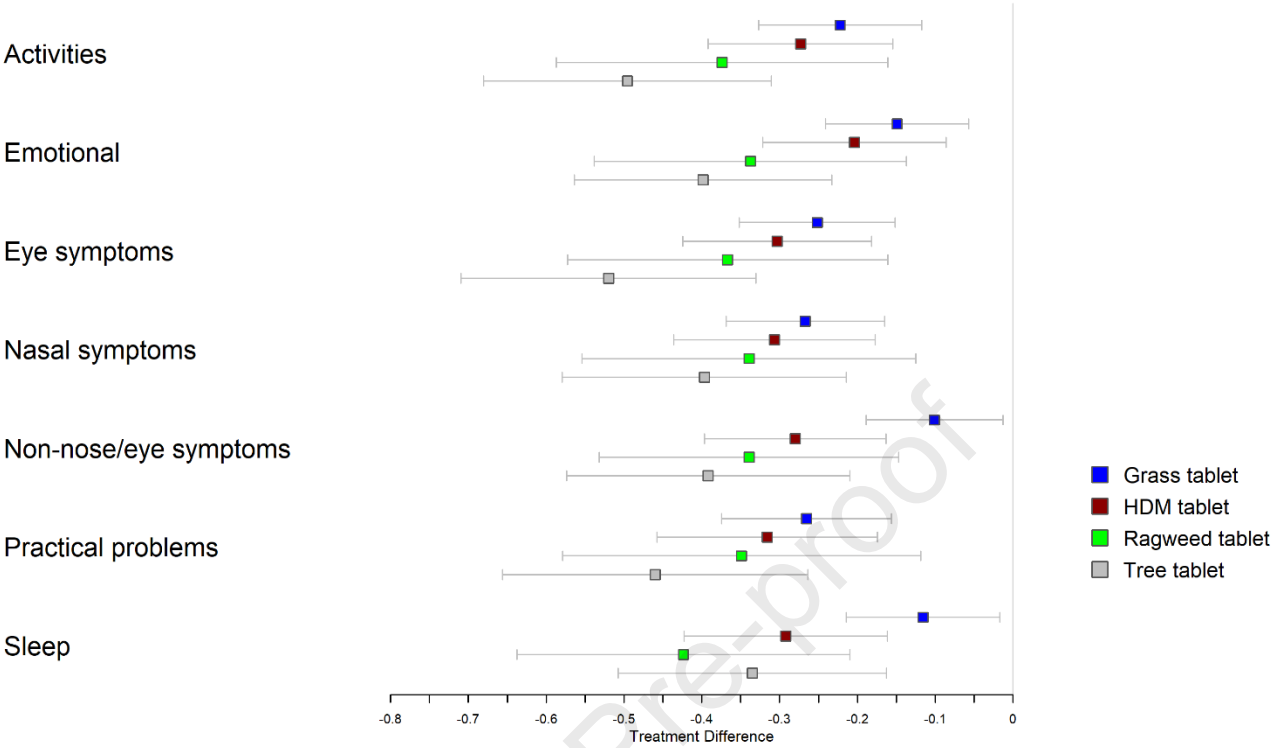
Clinical trial	Randomised subjects	Countries	Trial Duration	Key inclusion criteria	Key exclusion criteria	RQLQ assessment
Grass						
GT-02	N=277	Germany, Belgium, Denmark, Sweden, Austria, Norway, United Kingdom, Canada	1 pollen season	- Age: 18-65 years - Clinical history of significant grass pollen AR/C - Confirmed by positive SPT (wheal diameter ≥3 mm) and specific IgE (CAP allergy Class ≥2)	- Clinical history of significant asthma outside grass pollen season - FEV1 <70% of predicted value	Additional secondary objective: quality of life total domain score
GT-08 Y1	N=634	Austria, Germany, Denmark, Spain, Italy, Netherlands, Sweden, United Kingdom	5 pollen seasons (only 1st season results included in the pooled analysis)	- Age: 18-65 years - Clinical history grass pollen AR/C of at least 2 years - Confirmed by positive skin prick test (SPT) (wheal diameter ≥3 mm) and specific IgE (CAP allergy Class ≥2)	- (FEV1) < 70% of predicted value	Main secondary objective: Quality of Life (QoL) in the entire grass pollen season
P08067	N=1501	USA, Canada	1 pollen season	- Age: 5-65 years - Clinical history grass pollen AR/C with treatment during previous year - Confirmed by positive skin prick test (SPT) (wheal diameter ≥5 mm) and specific IgE (CAP allergy Class ≥2) - An FEV1 ≥70% of predicted value at screening	- A clinical history of severe asthma	Key secondary objective: the average Rhinoconjunctivitis Quality of Life Questionnaire With Standardised Activities for Subjects ≥12 Years of Age (RQLQ(S)12+) overall score over the peak grass pollen season Other secondary objectives: the average Paediatric Standardised Rhinoconjunctivitis Quality of life Questionnaire (PRQLQ) overall score over the peak grass pollen season (subjects 6 to <12 years of age)
P05238	N=438	USA, Canada	1 pollen season	- Age: 18-65 years - Clinical history grass pollen AR/C with treatment during previous year - Confirmed by positive skin prick test (SPT) (wheal diameter ≥5 mm) and specific IgE (CAP allergy Class ≥2) - An FEV1 ≥70% of predicted value at Screening	- A clinical history of severe asthma	Key secondary objective: The average weekly rhinoconjunctivitis quality of life total score for the entire grass pollen season
GT-14	N=329	USA	1 pollen season	- Age: 18-65 years - Clinical history grass pollen AR/C of at least 2 years - Confirmed by positive skin prick test (SPT) (wheal diameter ≥5 mm) and specific IgE (CAP allergy Class ≥2)	- A clinical history of severe asthma (Step 4, according to GINA definition) - FEV1 <70% of predicted value	Secondary objective: QoL in the grass pollen season
House dust mite (HDM)						
MT-06	N=656	Austria, Bosnia and Herzegovina, Croatia, Czech, Denmark,	12 months	- Age: 18-65 years - Clinical history consistent with moderate to severe persistent HDM allergic rhinitis (with or without asthma) for at least one year	- FEV1<70% of predicted value - Clinical history of uncontrolled asthma within 3 months prior to screening	Key secondary objective: The average overall Rhinoconjunctivitis Quality of Life Questionnaire RQLQ(S) score during the efficacy evaluation period

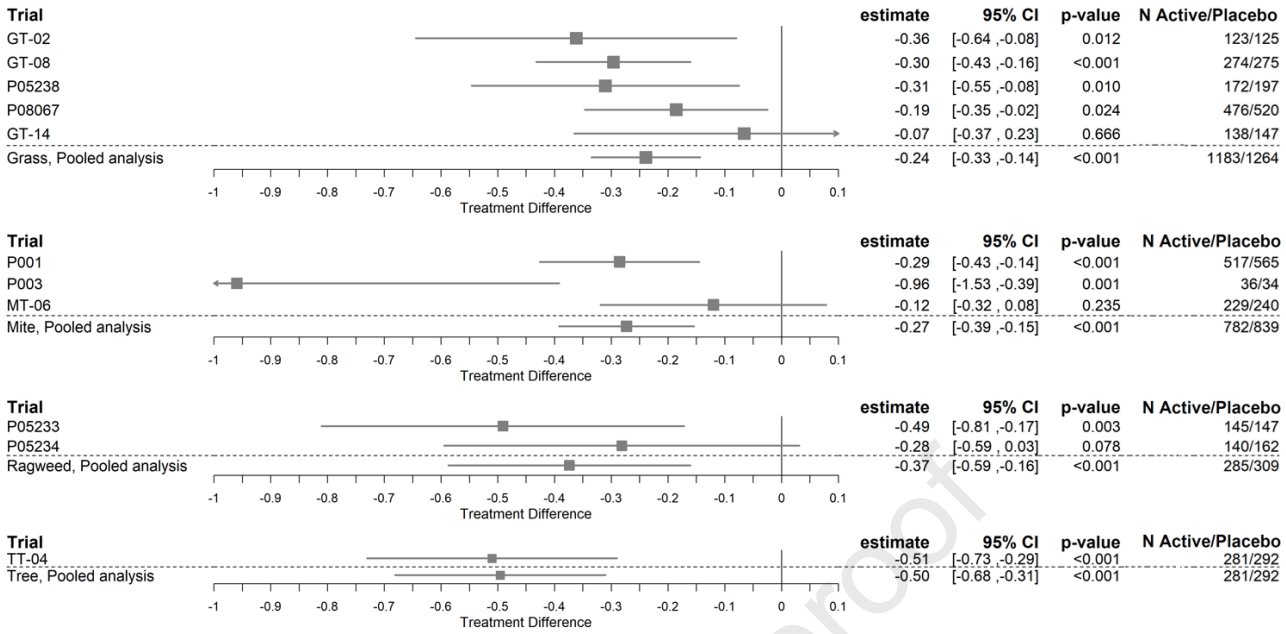
		France, Germany, Latvia, Poland, Romania, Serbia, Ukraine		- Moderate to severe HDM allergic rhinitis symptoms during the baseline period defined as a daily total rhinitis symptom score of at least 6 or a score of at least 5 with one symptom being severe, during at least 8 days of the 15-days baseline period - Use of symptomatic medication for treatment of HDM allergic rhinitis during at least 8 days of the 15-days baseline period. - Presence of one or more of the following ARIA quality of life items due to HDM allergic rhinitis during the baseline period: Sleep disturbance, Impairment of daily activities, leisure and/or sport, Impairment of school or work		Secondary endpoint: - The average overall RQLQ score at visit 3, 4, 5 and 6 - The change from baseline of overall RQLQ during the efficacy evaluation period and at visit 3, 4, 5 and 6 - Average individual domains in the RQLQ score during the efficacy evaluation period - The change from baseline of individual domains in the RQLQ score during the efficacy evaluation period
P001	N=1482	USA, Canada	12 months	- Age ≥12 years - Clinical history of allergic rhinitis/ rhinoconjunctivitis when exposed to HDM of 1 year or more - Positive skin prick test (at least 5 mm larger than the saline control) to D. pteronyssinus and/or D. farina - Positive specific IgE (CAP allergy Class ≥2) against D. pteronyssinus and/or D. farina - Have a rhinitis daily symptom score of at least 6, or a score of at least 5 with 1 symptom being severe, on 5 of 7 consecutive calendar days before randomization - Have a FEV1 of at least 80% of predicted value	- Has asthma requiring high-dose ICS within the last 6 months before Screening Visit	Explorative endpoint: Average Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities for Subjects ≥12 Years of Age (RQLQ(S) 12+) overall score during the last 8 weeks of treatment
P003	N=83	Austria	6 months	- Age ≥18 years - Clinical history of allergic rhinitis/ rhinoconjunctivitis when exposed to HDM of 1 year or more - Positive skin prick test (at least 3 mm larger than the saline control) to D. pteronyssinus and/or D. farina - Positive specific IgE (CAP allergy Class ≥2) against D. pteronyssinus and/or D. farina - Subject has a total nasal symptom score of at least 6 of 12 within the first two hours of the screening EEC session prior to randomization - Have a FEV1 of at least 70% of predicted value	- Subject has unstable uncontrolled/partially controlled or severe asthma - Subject has asthma requiring medium or high-dose inhaled corticosteroid (ICS) within the last 12 months prior to Screening	Exploratory objective: To evaluate the Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities for Subjects ≥12 Years of Age [RQLQ(S)12+] at Week 8, 16, and 24
Ragweed						
P05233	N=375	USA, Canada	1 pollen season	- Age: 18-50 years	- A clinical history of severe asthma	Additional secondary endpoint: (RQLQ(S)) score

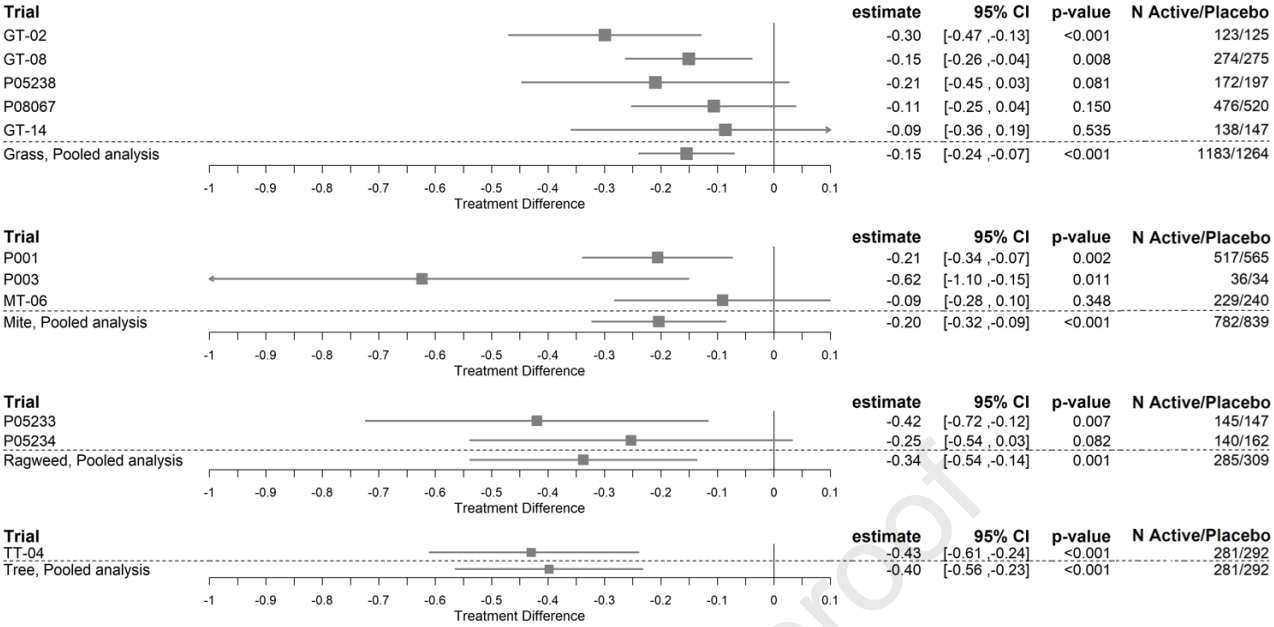
				- Clinical history ragweed pollen AR/C with treatment during previous year - Confirmed by positive skin prick test (SPT) and specific IgE (CAP allergy Class ≥2) - An FEV1 ≥70% of predicted value at Screening		during the peak ragweed season
P05234	N=392	USA, Canada, Hungary, Ukraine, Russia	1 pollen season	- Age: 18-50 years - Clinical history ragweed pollen AR/C with treatment during previous year - Confirmed by positive skin prick test (SPT) and specific IgE (CAP allergy Class ≥2) - An FEV1 ≥70% of predicted value at Screening	- A clinical history of severe asthma	Additional secondary endpoint: (RQLQ(S)) score during the peak ragweed season
Tree						
TT-04	N=634	Sweden, Finland, Denmark, Poland, Germany, the Czech Republic, France, Russia	1 pollen season	- Age: 18-65 years (in Poland adolescents 12-17 years were also recruited) - Clinical history birch pollen AR/C of at least 2 years - Positive skin prick test (SPT) (wheal diameter ≥3 mm) and specific IgE (CAP allergy Class ≥2) - Presence of one or more of the following ARIA quality of life items due to allergic rhinitis and/or conjunctivitis during the previous birch pollen season: Sleep disturbance, Impairment of daily activities, leisure and/or sport, Impairment of school or work, Troublesome symptoms	- Severe asthma exacerbation within the last 3 months - FEV1 < 70% of predicted value	Secondary objective: Demonstrate superiority of the tree SLIT-tablet versus placebo on rhinoconjunctivitis quality of life RQLQ(S) (adults) and RQLQ(S) + 12 (adolescents)

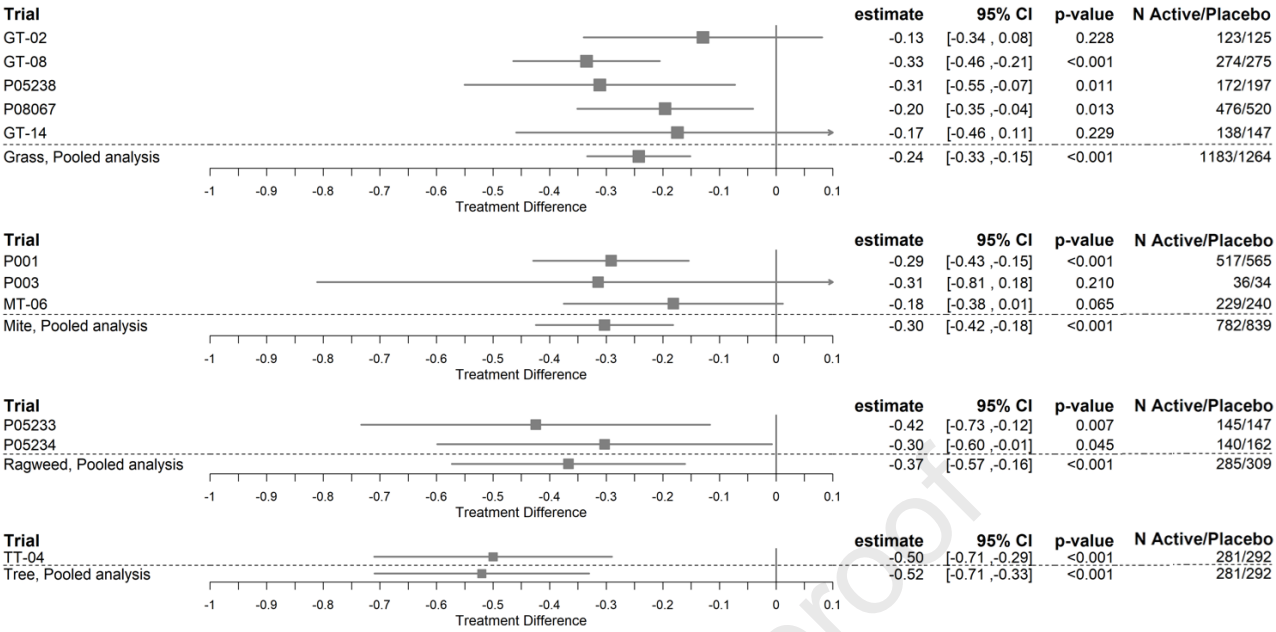
	Grass					HDM			Ragweed		Tree
Trial	**GT-02**	**GT-08 Y1**	**P08067**	**P05238**	**GT-14**	**MT-06**	**P001**	**P003**	**P05233**	**P05234**	**TT-04**
Randomised subjects (N)	277	634	1501	438	329	656	1482	83	375	392	634
Mean age (years)	35.0	34.2	33.2	35.9	35.9	32.2	35.1	27.1	35.4	36.2	36.1
Range (years)[a]	18-66	18-65	5-65	18-65	18-65	18-65	12-85	18-58	18-50	18-50	12-65
Male (%)	63	59	52	50	47	50	41	57	46	52	47
Ethnicity (% Caucasian)	93	96	84	84	82	98	77	91	79	88	98
Mean duration of AR/C (years)	19.2	15.8	17.7	21.0	21.0	9.9	18.6	16.4	18.9	17.8	15.9
Asthma at baseline (%)	NA	NA	25	24	27	46	31	23	23	18	44
Monosensitisation (%)	NA	NA	15	15	NA	33	24	15	15	22	24
Polysensitisation (%)	NA	NA	85	85	NA	67	76	86	85	78	76

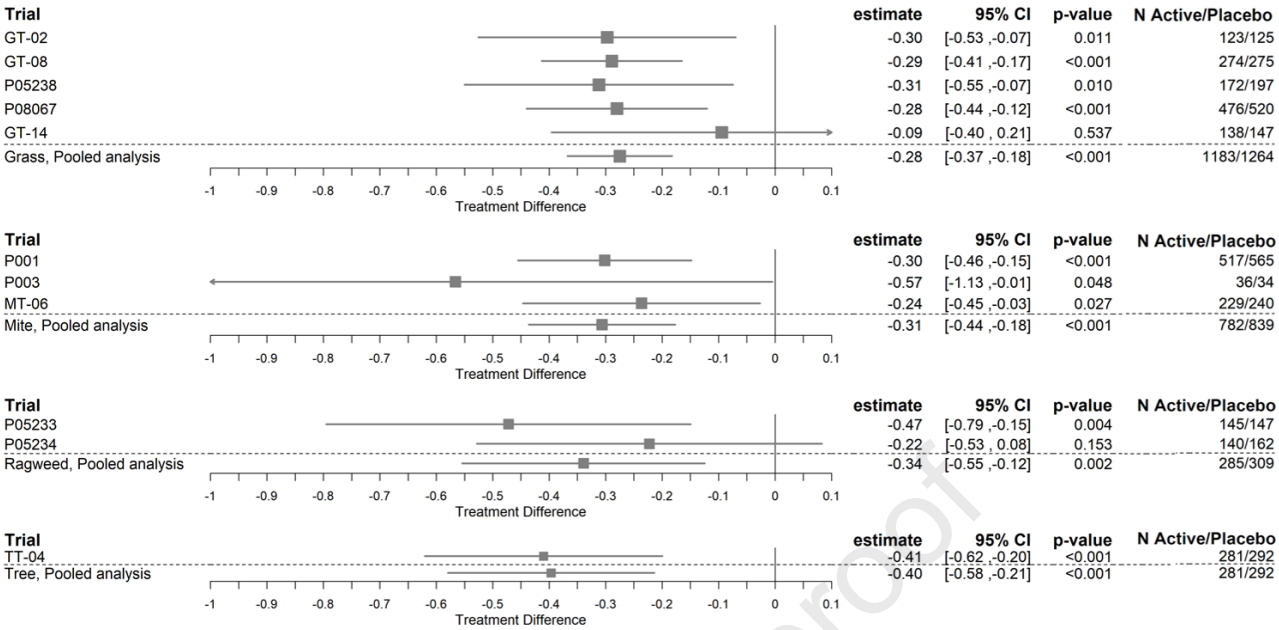


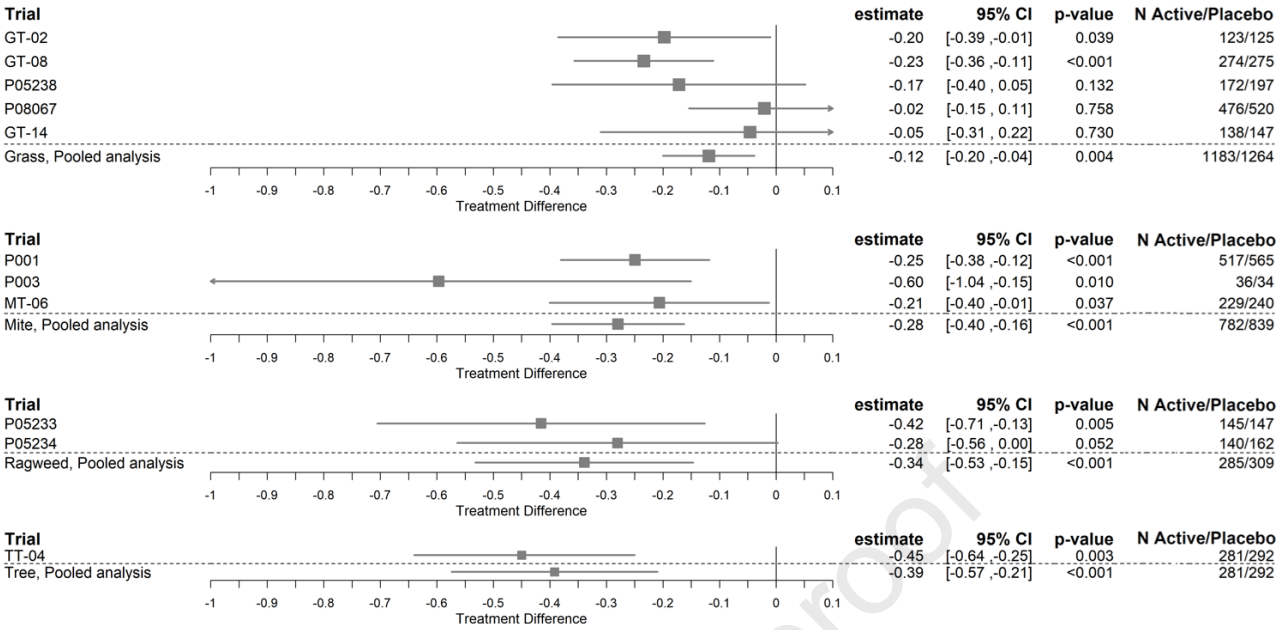


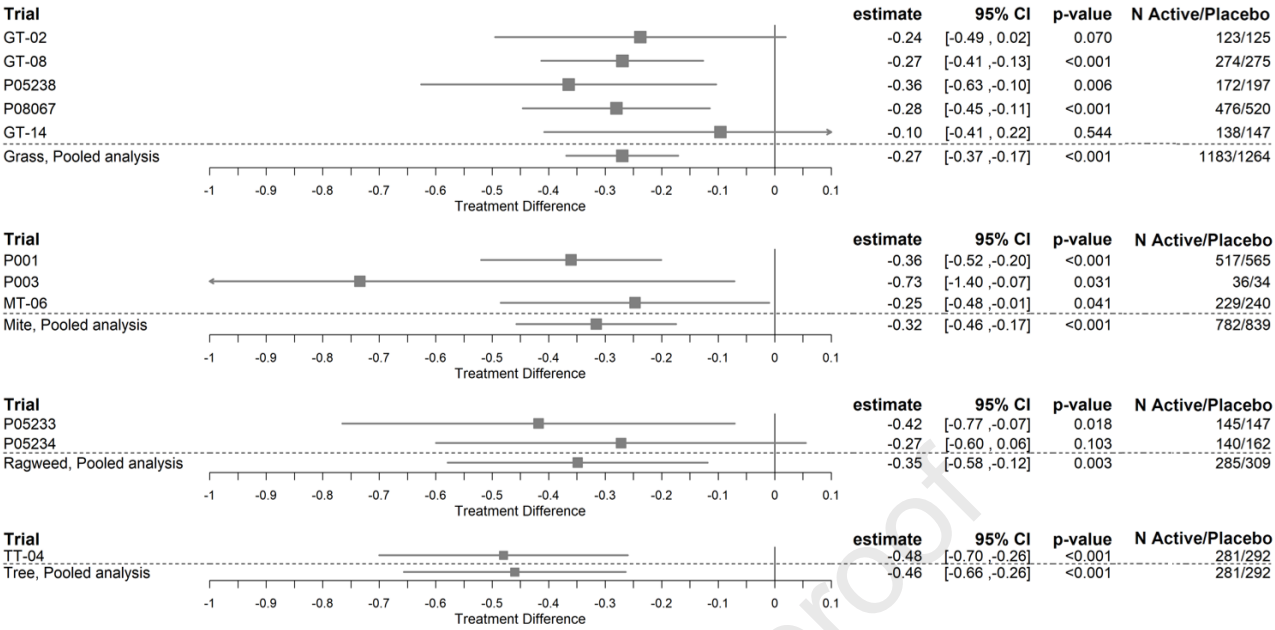


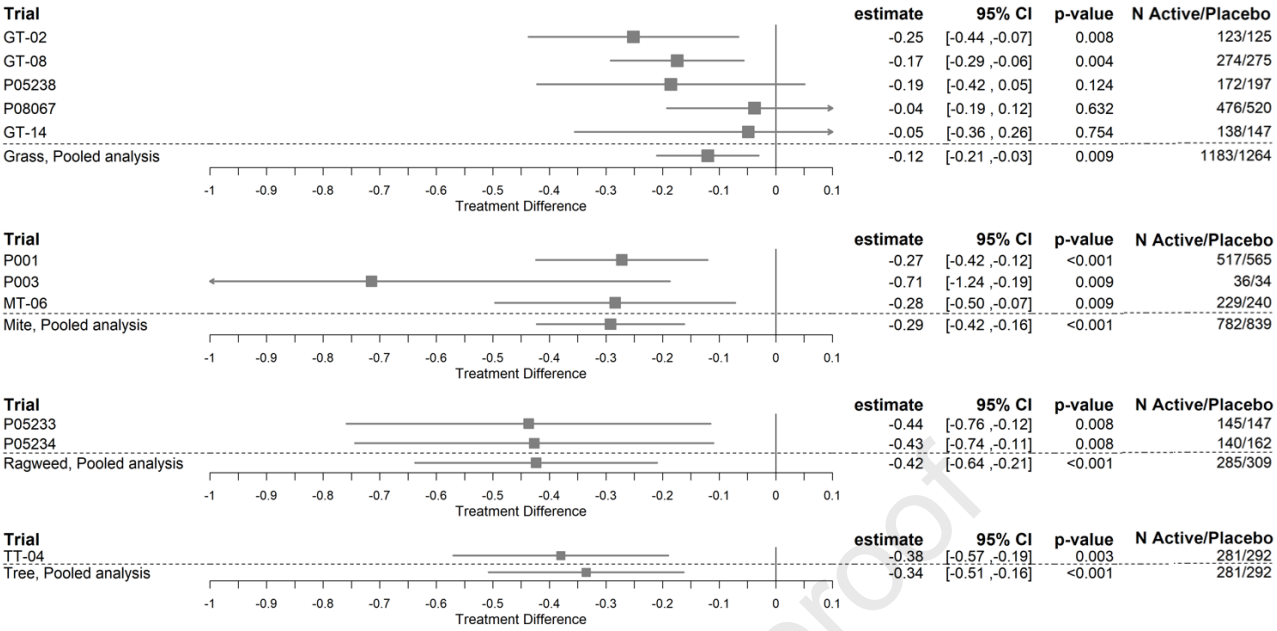


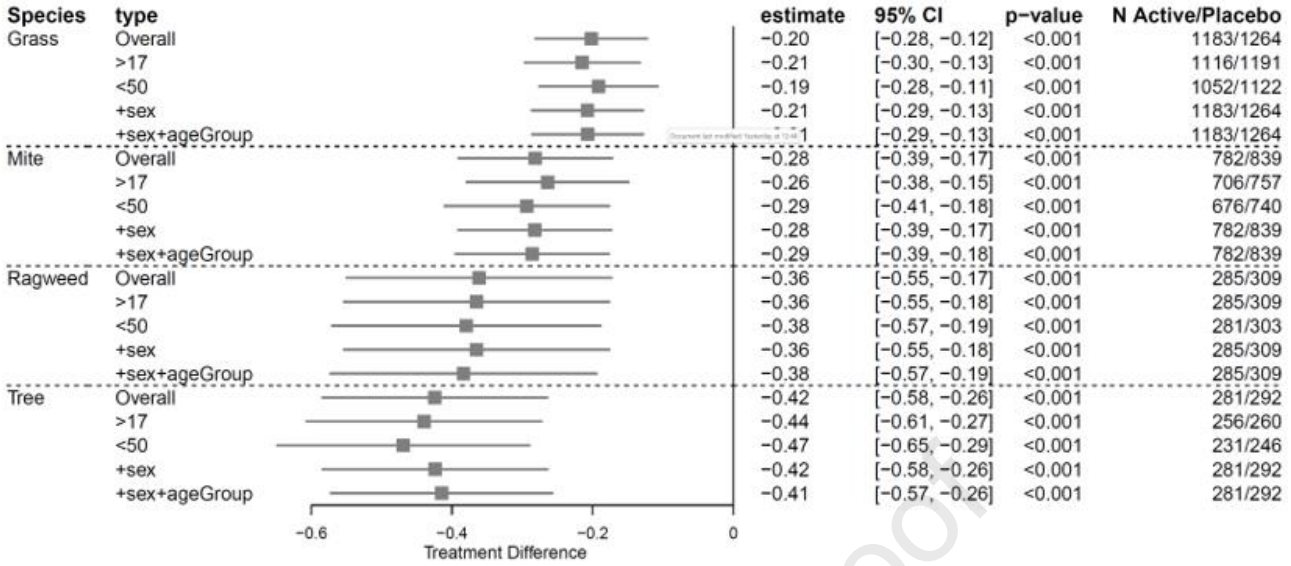












Species	type	estimate	95% CI	p−value	N Active/Placebo
Grass	Overall	−0.20	[−0.28, −0.12]	<0.001	1183/1264
	>17	−0.21	[−0.30, −0.13]	<0.001	1116/1191
	<50	−0.19	[−0.28, −0.11]	<0.001	1052/1122
	+sex	−0.21	[−0.29, −0.13]	<0.001	1183/1264
	+sex+ageGroup	−0.21	[−0.29, −0.13]	<0.001	1183/1264
Mite	Overall	−0.28	[−0.39, −0.17]	<0.001	782/839
	>17	−0.26	[−0.38, −0.15]	<0.001	706/757
	<50	−0.29	[−0.41, −0.18]	<0.001	676/740
	+sex	−0.28	[−0.39, −0.17]	<0.001	782/839
	+sex+ageGroup	−0.29	[−0.39, −0.18]	<0.001	782/839
Ragweed	Overall	−0.36	[−0.55, −0.17]	<0.001	285/309
	>17	−0.36	[−0.55, −0.18]	<0.001	285/309
	<50	−0.38	[−0.57, −0.19]	<0.001	281/303
	+sex	−0.36	[−0.55, −0.18]	<0.001	285/309
	+sex+ageGroup	−0.38	[−0.57, −0.19]	<0.001	285/309
Tree	Overall	−0.42	[−0.58, −0.26]	<0.001	281/292
	>17	−0.44	[−0.61, −0.27]	<0.001	256/260
	<50	−0.47	[−0.65, −0.29]	<0.001	231/246
	+sex	−0.42	[−0.58, −0.26]	<0.001	281/292
	+sex+ageGroup	−0.41	[−0.57, −0.26]	<0.001	281/292

Trial	Tablet	Fixed effects	Random effects	Allows different variances
GT-02	Grass	country, visit, screening, visit*treatment	subject	
GT-08	Grass	visit, treatment	pollenStation, subject	
GT-14	Grass	week_season*treatment	region	
P05238	Grass	asthmaStatus, site, treatment		treatment
P08067	Grass	asthma status, region, ageGroup, treatment		treatment
P001	HDM	asthmaBlFlag, baseline, ageGroup, region, treatment		treatment
P003	HDM	treatment		treatment
MT-06	HDM	baseline, treatment	country	treatment
P05233	Ragweed	asthmaStatus, region, treatment		
P05234	Ragweed	asthmaStatus, region, treatment		
TT-04	Tree	pollenStation, visit*treatment	subject	

Supplementary Table and Figure legends

Supplementary Table E1. Pre-defined model per study. Pre-defined fixed effects, random effects as well as potentially adjusting for different error variation for each treatment group are shown. GT-14 was pre-defined and analysed as a repeated measurement including treatment group, week and treatment by week interaction as a fixed effects, pollen area as a random effect and adjusting for subject variation, with AR(1) covariance structure applied.

Supplementary Figure E1: RQLQ activities domain analysis. Per study, the absolute treatment effect based on the pre-specified model (Figure 1) is shown. In addition, for every tablet type a pooled analysis with a standardised model is included. All pooled analysis models are with treatment as fixed effect, study as random effect and the interaction of region or country, dependent on the respective pre-specified model, with study as random effect. For TT-04, GT-08 and GT-14 pooled analysis, the mean over the measure in the efficacy assessment period is the outcome. For the GT-02 pooled analysis, the 1st seasonal visit is the outcome. Shown data is the approved dose in Europe and North America relative to Placebo.

Supplementary Figure E2: RQLQ emotional domain analysis. Per study, the absolute treatment effect based on the pre-specified model (Figure 1) is shown. In addition, for every tablet type a pooled analysis with a standardised model is included. All pooled analysis models are with treatment as fixed effect, study as random effect and the interaction of region or country, dependent on the respective pre-specified model, with study as random effect. For TT-04, GT-08 and GT-14 pooled analysis, the mean over the measure in the efficacy assessment period is the outcome. For the GT-02 pooled analysis, the 1st seasonal visit is the outcome. Shown data is the approved dose in Europe and North America relative to Placebo.

Supplementary Figure E3: RQLQ eye symptoms domain analysis. Per study, the absolute treatment effect based on the pre-specified model (Figure 1) is shown. In addition, for every tablet type a pooled analysis with a standardised model is included. All pooled analysis models are with treatment as fixed effect, study as random effect and the interaction of region or country, dependent on the respective pre-specified model, with study as random effect. For TT-04, GT-08 and GT-14 pooled analysis, the mean over the measure in the efficacy assessment period is the outcome. For the GT-02 pooled analysis, the 1st seasonal visit is the outcome. Shown data is the approved dose in Europe and North America relative to Placebo.

Supplementary Figure E4: RQLQ nasal symptoms domain analysis. Per study, the absolute treatment effect based on the pre-specified model (Figure 1) is shown. In addition, for every tablet type a pooled analysis with a standardised model is included. All pooled analysis models are with treatment as fixed effect, study as random effect and the interaction of region or country, dependent on the respective pre-specified model, with study as random effect. For TT-04, GT-08 and GT-14 pooled analysis, the mean over the measure in the efficacy assessment period is the outcome. For the GT-02 pooled analysis, the 1st seasonal visit is the outcome. Shown data is the approved dose in Europe and North America relative to Placebo.

Supplementary Figure E5: RQLQ non-nose/eye symptoms domain analysis. Per study, the absolute treatment effect based on the pre-specified model (Figure 1) is shown. In addition, for every tablet type a pooled analysis with a standardised model is included. All pooled analysis models are with treatment as fixed effect, study as random effect and the interaction of region or country, dependent on the respective pre-specified model, with study as random effect. For TT-04, GT-08 and GT-14 pooled analysis, the mean over the measure in the efficacy assessment period is the outcome. For the GT-02 pooled analysis, the 1st seasonal visit is the outcome. Shown data is the approved dose in Europe and North America relative to Placebo.

Supplementary Figure E6: RQLQ practical problems domain analysis. Per study, the absolute treatment effect based on the pre-specified model (Figure 1) is shown. In addition, for every tablet type a pooled analysis with a standardised model is included. All pooled analysis models are with treatment as fixed effect, study as random effect and the interaction of region or country, dependent on the respective pre-specified model, with study as random effect. For TT-04, GT-08 and GT-14 pooled analysis, the mean over the measure in the efficacy assessment period is the outcome. For the GT-02 pooled analysis, the 1st seasonal visit is the outcome. Shown data is the approved dose in Europe and North America relative to Placebo.

Supplementary Figure E7: RQLQ sleep domain analysis. Per study, the absolute treatment effect based on the pre-specified model (Figure 1) is shown. In addition, for every tablet type a pooled analysis with a standardised model is included. All pooled analysis models are with treatment as fixed effect, study as random effect and the interaction of region or country, dependent on the respective pre-specified model, with study as random effect. For TT-04, GT-08 and GT-14 pooled analysis, the mean over the measure in the efficacy assessment period is the outcome. For the GT-02 pooled analysis, the 1st seasonal visit is the outcome. Shown data is the approved dose in Europe and North America relative to Placebo.

Supplementary Figure E8: sensitivity analysis for age groups (excluding subjects <18 years of age; excluding subjects >49 years of age), sex (male/female as fixed effect to the model), and adjusted for sex and age group (male/female and age groups <20,21-30,31-40,41-50,>50 as fixed effect to the model) based on the 4 overall RQLQ pooled models/analyses.