The SQ tree SLIT-tablet is highly effective and well tolerated: Results from a randomized, double-blind, placebo-controlled phase III trial

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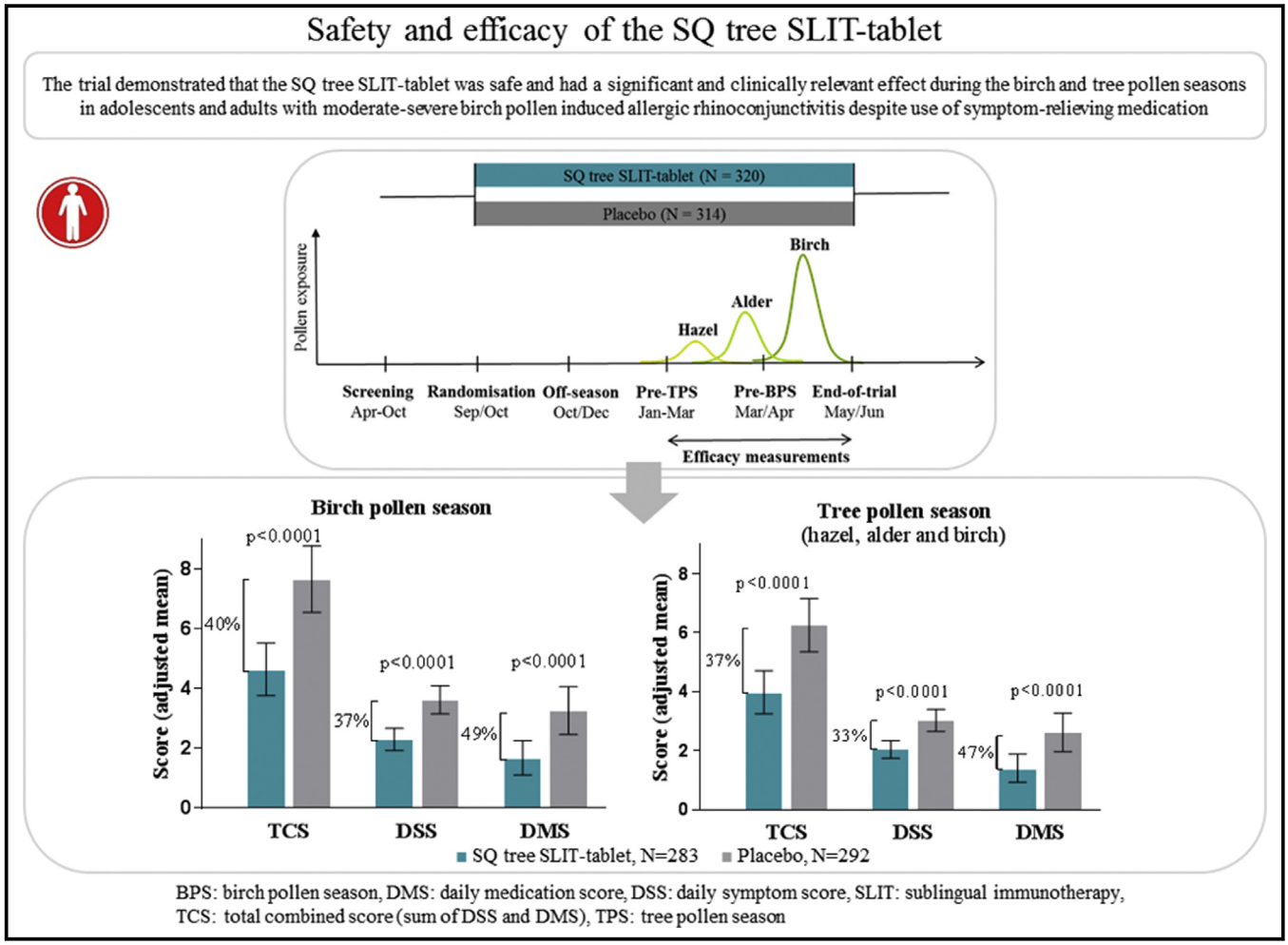
GRAPHICAL ABSTRACT



Background: The SQ tree sublingual immunotherapy (SLIT)–tablet (ALK-Abelló, Hørsholm, Denmark) is developed for treatment of tree pollen–induced allergic rhinoconjunctivitis (ARC).

Objective: The aim of this pivotal phase III trial was to demonstrate the efficacy and safety of the SQ tree SLIT-tablet. Methods: This was a randomized, double-blind, placebo-controlled trial with 634 subjects (12-65 years) with

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moderate-to-severe ARC despite use of symptom-relieving medication. Eligible subjects were randomized 1:1 to active or placebo treatment. The primary end point was the average daily ARC total combined score (TCS) during the birch pollen season (BPS) analyzed for subjects with diary data during the BPS. Secondary end points included average daily symptom scores (DSS) during the BPS, average TCS and DSS during the tree pollen season (TPS), and average daily medication scores (DMS) in the BPS and TPS.

Results: The primary and key secondary end points demonstrated statistically significant and clinically relevant effects of the SQ tree SLIT-tablet compared with placebo. For the BPS, absolute (relative) differences from placebo were 3.02 (40%) for TCS, 1.32 (37%) for DSS, and 1.58 (49%) for DMS (all $P < .0001$). For the TPS, absolute (relative) differences from placebo were 2.27 (37%) for TCS, 0.99 (33%) for DSS, and 1.20 (47%) for DMS (all $P < .0001$). Treatment was well tolerated. The most frequently reported treatment-related adverse events were mild or moderate local reactions related to sublingual administration.

Conclusion: The trial demonstrated the efficacy and safety of the SQ tree SLIT-tablet compared with placebo during the BPS and TPS in adolescents and adults with birch pollen–induced ARC (EudraCT 2015-004821-15). (J Allergy Clin Immunol 2019;143:1058-66.)

Key words: *Allergic rhinoconjunctivitis, allergy immunotherapy, birch pollen, clinical efficacy, clinical trial, safety, sublingual immunotherapy tablet, total combined score, tree pollen*

Abbreviations used

AE: Adverse event
ARC: Allergic rhinoconjunctivitis
BPS: Birch pollen season
DMS: Daily medication score
DSS: Daily symptom score
EAACI: European Academy of Allergy and Clinical Immunology
ICH: International Conference on Harmonisation
RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire
RQLQ(S): Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities
SLIT: Sublingual immunotherapy
TCS: Total combined score (sum of rhinoconjunctivitis DSS and DMS)
TPS: Tree pollen season

Allergic rhinitis is estimated to affect 500 million individuals worldwide and is considered a global health problem. It is a frequent reason for visits in general practice and can decrease quality of life and lead to lower school and work performance. Furthermore, allergic rhinitis is a recognized risk factor for asthma development.[1]

Exposure to tree pollen is prominent across Europe and North America[2,3] and reflected by a high prevalence of sensitization to tree pollen. Tree pollen–induced allergic rhinoconjunctivitis (ARC) is commonly caused by allergens from the birch-homologous group, which includes birch, alder, hornbeam, hazel, and oak.[4] Pollens from these trees are characterized by having Bet v 1–homologous allergens with high sequence identity, leading to extensive cross-reactivity and ultimately prolonging the season and extending the geographic area in which allergic reactions are triggered.[2,4,5] Although geographic variations occur, the prevalence of sensitization to birch pollen in 14 European countries has been estimated to be 24%,[6] and in the United States (Portland) it has been estimated to be 16%.[7] Likewise, in Europe alder and hazel pollen sensitization has been estimated to be 21% and 23%.[6]

Current treatment modalities include allergen avoidance and symptom-relieving medication, such as antihistamines and nasal corticosteroids. The only long-term strategy is immunomodulation through allergy immunotherapy that consequently plays an important role in the management and treatment of ARC both as subcutaneous and sublingual formulations.[8-10]

The SQ tree sublingual immunotherapy (SLIT)–tablet (12 SQ-Bet; ALK-Abelló, Hørsholm, Denmark) was developed for treatment of moderate-to-severe ARC induced by pollen from the birch-homologous group despite use of symptom-relieving medication. The SQ tree SLIT-tablet is an oral lyophilisate for at-home use containing a standardized allergen extract from white birch pollen (*Betula verrucosa*). Birch pollen is recommended as the representative allergen source for allergy immunotherapy targeting allergies caused by pollen from the birch-homologous group, primarily because of its high degree of inhibition of human IgE binding to alder, hazel, and oak allergen extracts.[4,5]

To date, 2 phase II trials have investigated the dose response for clinical efficacy of the SQ tree SLIT-tablet. In a field trial immunomodulatory changes indicated a dose-response relationship, but clinical efficacy parameters were inconclusive, most likely because of low pollen counts.[11] Subsequently, a second trial was conducted in an environmental exposure chamber to eliminate the seasonal and geographic variability in allergen exposure.

This trial was funded by ALK-Abelló, Hørsholm, Denmark, who assumes overall responsibility of the trial and has been involved in trial design and conduct, as well as analysis and interpretation of data.

Disclosure of potential conflict of interest: T. Biedermann is an advisory board member for and has received speaker's fees from ALK-Abelló, Novartis, and Mylan. P. Kuna is an advisory board member for and has received fees and travel support from ALK-Abelló; furthermore, P. Kuna is an advisory board member for and/or has received lecture fees from Adamed, Allergopharma, AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Chiesi, FAES, Novartis, and Polpharma. P. Panzner is an advisory board member for and has received investigator and lecture fees from ALK-Abelló; furthermore, P. Panzner is an advisory board member for and/or has received lecture or investigator fees from ASIT biotech, AstraZeneca, HAL Allergy, and Stallergenes Greer. E. Valovirta is an advisory board member for ALK-Abelló and AstraZeneca and has received fees from ALK-Abelló. M. Andersson has received lecture fees from ALK-Abelló. F. de Blay is a board member for and has received grants or fees from ALK-Abelló, AstraZeneca, Boehringer, Mundipharma, Novartis, Stallergenes Greer, and Teva. D. Thrane, S. H. Jacobsen, and B. S. Stage are employed by ALK-Abelló. L. Winther declares no relevant conflicts of interest.

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Here it was shown that the SQ tree SLIT-tablet was effective for treatment of ARC and that the optimal dose was 12 SQ-Bet.[12]

In this phase III clinical trial, the aim was to demonstrate the efficacy and safety of the SQ tree SLIT-tablet compared with placebo in adolescents and adults with birch pollen–induced ARC not only during the birch pollen season (BPS) but also during the tree pollen season (TPS), comprising hazel, alder, and birch.

METHODS

Trial design

This was a randomized, parallel-group, double-blind, placebo-controlled, multisite, phase III field trial conducted in 57 sites in Germany, France, Poland, Czech Republic, Denmark, Sweden, Finland, and Russia (EudraCT 2015-004821-15). Subjects were randomized 1:1 to once-daily treatment with the SQ tree SLIT-tablet or placebo for at least 16 weeks before the anticipated start of the TPS and until the end of the TPS. Treatment duration was 6.5 to 9.5 months for subjects completing the trial. The trial design is shown in Fig 1. The prespecified definitions of the pollen seasons are described in the Methods section in this article's Online Repository at www.jacionline.org.

The trial was designed and conducted in accordance with the Declaration of Helsinki[13] and in compliance with Good Clinical Practice guidelines as set by the International Conference on Harmonisation (ICH).[14] Relevant national ethics committees and regulatory authorities approved the trial protocol and amendments.

Trial population

The trial population was composed of adolescents and adults (12-65 years) with persistent moderate-to-severe ARC induced by birch pollen, despite having received symptom-relieving medication during the 2 previous TPS. Subjects had to have a positive skin prick test response (wheal diameter, ≥3 mm) to birch, a positive Bet v 1–specific IgE level (IgE class 2 or greater, ≥0.7 kU/L), and affected quality-of-life items (sleep disturbance; impairment of daily activities, leisure, and/or sport; impairment of school or work; or troublesome symptoms) because of ARC during the previous BPS. Patients with uncontrolled asthma or severe asthma exacerbations were excluded from the trial. For details, see the Methods section in this article's Online Repository.

Intervention medication

Subjects were randomized 1:1 in a double-blind fashion to receive 1 daily tablet of either SQ tree SLIT-tablet or placebo (details of the randomization and blinding are found in the Methods section in this article's Online Repository). The first tablet was administered under medical supervision for 30 minutes. The SQ tree SLIT-tablet is a fast dissolving lyophilisate for sublingual administration containing standardized allergen extract from birch pollen. The dose tested was 12 SQ-Bet. SQ-Bet is a measure of the biological allergen activity based equally on the major allergen content (Bet v 1) and total allergenic activity. The tablet was produced by using Zydis technology (Catalent UK Swindon Zydis Ltd, Swindon, United Kingdom), which has been shown to provide high allergen stability, as well as rapid and consistent release on administration.[15,16] The SQ tree SLIT-tablet and placebo were manufactured and provided by ALK-Abelló and were similar with respect to appearance, smell, and taste.

Before the start of the TPS, subjects were provided symptom-relieving medication for allergic rhinitis and conjunctivitis as predefined, open-label medication to be used freely in addition to intervention medication. Medication not provided as a part of the trial was to be kept to a minimum during the trial.

End points and assessments

Efficacy assessments were recorded by the subjects in an electronic diary during the TPS.

The primary end point of the trial was the average daily ARC total combined score (TCS) during the BPS. The daily TCS equaled the sum of the ARC daily symptom score (DSS) and the ARC daily medication score (DMS; for details, see the Methods section in this article's Online Repository). Symptoms were recorded in the evening. If symptom-relieving medication was used, the reported symptom score should reflect symptom severity after medication use.

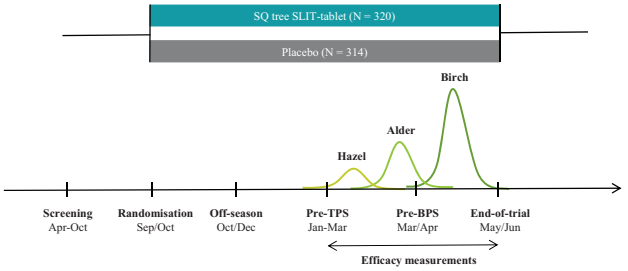

FIG 1. Trial design. Subjects were treated for at least 16 weeks before and during the 2017 TPS. Efficacy was assessed throughout the TPS.

Key secondary end points were average DSS during the BPS and average TCS and DSS during the TPS. Secondary end points included the average DMS during the BPS and TPS. As an exploratory predefined end point, the average TCS during the BPS and TPS was analyzed by using the score proposed by the European Academy of Allergy and Clinical Immunology (EAACI; with the exception that oral corticosteroids were not allowed, and hence the maximum medication score was 2),[17] and *post hoc* the average TCS, DSS, and DMS were analyzed for the combined alder and hazel pollen seasons.

Other secondary ARC end points included the average number of mild and severe days, as well as the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ),[18-20] during the BPS and TPS. As a predefined exploratory end point, subjects with asthma assessed their asthma control using the Asthma Control Test.[21] Other end points included immunologic parameters (birch-specific IgE and IgG_4) and adverse events (AEs) as per ICH Harmonised Tripartite Guideline E2A, Step 5.[22] Assessments are further described in the Methods section in this article's Online Repository.

Statistical methodology

A sample size of 300 per treatment group was needed to have at least 90% power to detect a significant difference between active and placebo treatment in the primary end point. The power calculation was based on a 2-sided *t* test with a 5% significance level assuming use of all observed data, a 20% reduction in TCS in the active compared with placebo groups, a 10% dropout rate, and a coefficient of variation of 0.79 in both treatment groups (based on previous trial with the SQ tree SLIT-tablet).[11]

Average TCS (including TCS with EAACI scores), DSS, and DMS during the BPS and TPS were analyzed for all subjects from the full analysis set with diary data during the BPS with a linear mixed-effects model using the square root–transformed average score as a response variable, treatment group as fixed effect, pollen region as random effect, and different residual errors for each treatment group specified. The primary and key secondary end points were controlled for multiplicity by means of hierarchical testing to ensure a maximum overall type I error rate of 5% in hypothesis testing. The subjects in the full analysis set who had at least 1 diary entry during the BPS were used for efficacy analyses, except for the Asthma Control Test. Sensitivity analyses were conducted by using the per-protocol analysis set, as well as all randomized subjects (ie, the intent-to-treat population), with 2 types of multiple imputation to evaluate robustness and possible bias of the results of the analyses of primary and key secondary end points.

The trial was not powered to detect treatment effect within subgroups. However, a prespecified subgroup analysis of the TCS during the BPS was performed, adding an interaction term between treatment and age group to the linear mixed effects model, to investigate whether there was a difference in effect between adolescents (12-17 years) and adults (18-65 years).

All statistical analyses were carried out by the sponsor. The principal statistical software used was SAS (version 9.4; SAS Institute, Cary, NC). For

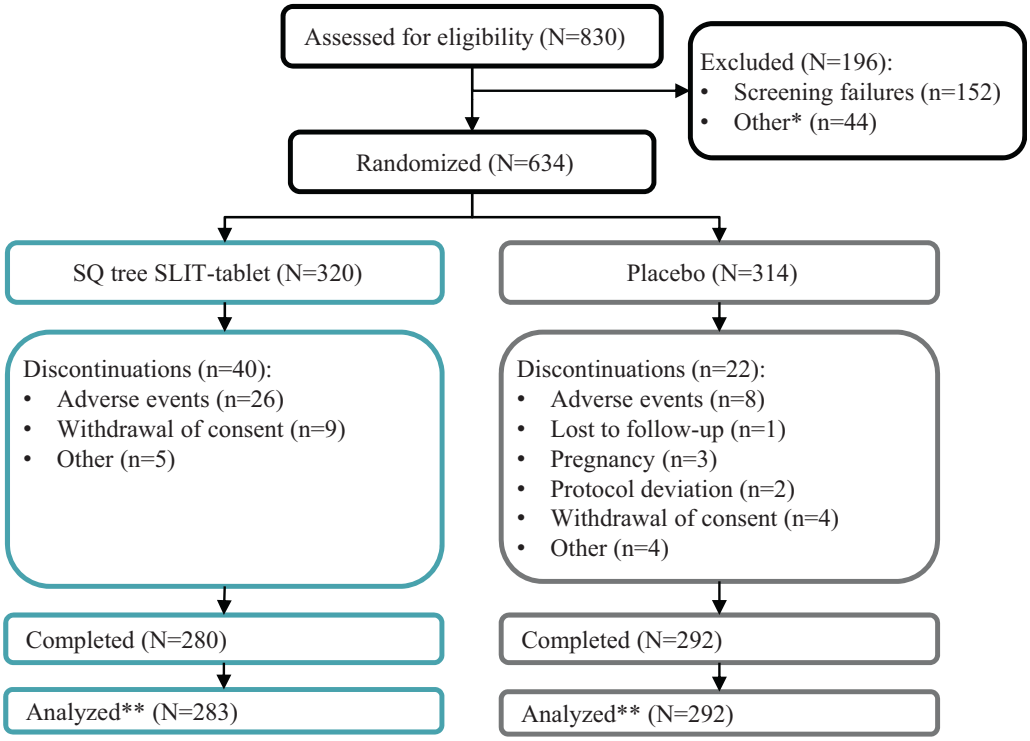

FIG 2. Subject disposition. *Primarily subjects who withdrew consent or were lost to follow-up before randomization. **Subjects with a valid value for the primary end point in the BPS.

further details regarding statistical methodology, see the Methods section in this article's Online Repository.

RESULTS

Population

Subject disposition is shown in Fig 2. Six hundred thirty-four subjects were randomized, 320 to SQ tree SLIT-tablet and 314 to placebo. Ninety percent of the randomized subjects completed the trial. The rate of discontinuation was greater in the SQ tree SLIT-tablet group (13%) compared with the placebo group (7%), mainly driven by a greater number of discontinuations because of AEs in the SQ tree SLIT-tablet group (8%) compared with the placebo group (3%; see the Results section in this article's Online Repository at www.jacionline.org for details of trial discontinuations).

Subjects' baseline characteristics are shown in Table I. Overall, treatment groups were similar. Sixty (9%) subjects were adolescents. On average, subjects had birch pollen allergy for almost 16 years. All subjects were sensitized to birch pollen, and 57% belonged to IgE class 4 to 6 (≥17.5 kU/L). The majority were also sensitized to alder (92%) and hazel (86%). Forty-four percent had asthma (any cause).

On average, subjects were exposed to treatment for 224 days (median, 239 days), with mean compliance of greater than 95% for both treatment groups.

Pollen seasons

The 57 sites were assigned to 30 pollen regions. On average, the BPS lasted 24 days (range, 10-42 days), and the TPS lasted 50 days (range, 14-68 days). Average daily pollen counts were 284 grains/m^3 (range, 69-784 grains/m^3) for birch, 100 grains/m^3 (range, 28-330 grains/m^3) for alder, and 40 grains/m^3 (range, 18-110 grains/m^3) for hazel during the respective seasons. The alder and hazel seasons did not coincide with the BPS, except in one region, where the alder season overlapped the BPS for 6 days (7 subjects in each treatment group).

Efficacy

Results of the statistical analyses of ARC symptoms and medication use during the BPS and TPS are shown in Fig 3 for all subjects in the full analysis set with diary data during the BPS. Further details, including intent-to-treat analyses with multiple imputation of missing data, are available in Table E1 in this article's Online Repository at www.jacionline.org.

The primary analysis demonstrated a statistically significant improvement in average TCS during the BPS with the SQ tree SLIT-tablet compared with placebo, thereby meeting the primary end point. The estimated absolute difference was 3.02, corresponding to a difference of 40% relative to placebo ($P < .0001$) and thus exceeding the prespecified clinically relevant difference of 20% compared with placebo. Similar results were obtained in sensitivity analyses (see Table E1). Subgroup analysis of TCS during the BPS showed no statistical difference in treatment effect between adolescents and adults ($P = .54$). The estimated absolute differences were 1.94 for adolescents and 3.16 for adults, corresponding to 31% and 41% reductions relative to placebo.

All analyses of key secondary end points supported the primary analysis result. Both the combined and symptom scores (ie, TCS and DSS) showed statistically significant improvements for the SQ tree SLIT-tablet compared with placebo during the BPS and TPS. Relative differences from placebo ranged from 33% to 37%

TABLE I. Baseline characteristics

Treatment group	SQ tree SLIT-tablet (n = 320)	Placebo (n = 314)
Years with birch pollen allergy, mean (minimum-maximum)	15 (2-53)	17 (2-55)
Asthma (all causes), no. (%)	142 (44)	134 (43)
Pollen-food syndrome, no. (%)	212 (66)	209 (67)
Sex, no. (%)		
Male	152 (48)	146 (46)
Female	168 (53)	168 (54)
Age (y)		
Mean (SD)	37 (14)	35 (14)
Minimum–maximum	12-65	12-65
Adolescents, no. (%)	28 (9)	32 (10)
Ethnic origin, no. (%)		
White	314 (98)	304 (97)
Asian	4 (1)	3 (<1)
Black/African American	—	1 (<1)
Hispanic/Latino	1 (<1)	2 (<1)
Other/unknown	1 (<1)	4 (1)
Bet v 1–specific IgE, no. (%)		
Class 2-3: 0.7 ≤ x < 17.5 kU/L	137 (43)	134 (43)
Class 4-6: ≥17.5 kU/L	183 (57)	180 (57)
Positive skin prick test response (wheal ≥3 mm), no. (%)		
Birch	320 (100)	313 (100)*
Alder	293 (92)	288 (92)
Hazel	270 (84)	274 (87)
Polysensitized†	238 (74)	242 (77)
ARIA quality of life, no. (%)		
Impairment of daily activities, leisure and/or sport	278 (87)	264 (84)
Impairment of school or work	242 (76)	228 (73)
Sleep disturbance	212 (66)	211 (67)
Troublesome symptoms	307 (96)	299 (95)

ARIA, Allergic Rhinitis and its Impact on Asthma.
*Baseline value missing for 1 subject.
†Positive skin prick test response to allergens within (birch, alder, and hazel) and outside (grass, dog, cat, house dust mite [*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*], ragweed, ash, and mold) the birch-homologous group.

(all $P < .0001$, Fig 3). Sensitivity analyses supported these results (data not shown). Furthermore, analysis of TCS by using the EAACI score[17] showed similar results in relative differences (38% for BPS and 35% for TPS, both $P < .0001$).

Post hoc analysis demonstrated improvements in treatment effect during the alder and hazel season also. Relative differences from placebo were 30% for average TCS, 26% for average DSS, and 44% for average DMS (all $P < .01$, see Fig E1 in this article's Online Repository at www.jacionline.org).

The clinical relevance for subjects was further analyzed in terms of proportion of severe and mild days. The results of the statistical analyses during the BPS are shown in Fig 4. The odds for experiencing a severe day halved with SQ tree SLIT-tablet treatment compared with placebo (odds ratio, 0.47; $P < .0001$), whereas the odds for experiencing a mild day doubled (odds ratio, 1.92; $P < .0001$). Similar results were seen during the TPS (data not shown).

The ARC-related quality of life was significantly better with the SQ tree SLIT-tablet than with placebo both during the BPS and TPS. The overall RQLQ adjusted mean for the SQ tree SLIT-tablet (BPS, 0.99; TPS, 0.95) was lower than for placebo (BPS, 1.45; TPS, 1.32), with relative differences of 31% for the BPS and 28% for the TPS (both seasons $P < .0001$).

In general, for the subpopulation with asthma, Asthma Control Test scores were high, indicating good asthma control. Nevertheless, the average Asthma Control Test score during the BPS was higher in the SQ tree SLIT-tablet group (adjusted mean, 22.24) than in the placebo group (adjusted mean, 21.02; absolute difference, −1.22; $P = .0365$). There was no difference between groups during the TPS ($P = .53$).

Results of statistical analyses of the immunologic parameters are shown in Fig 5. The SQ tree SLIT-tablet increased serum-specific levels of both birch-specific IgE and IgG_4 at all time points compared with placebo ($P < .0001$ for all). Levels at each visit are shown in Table E2 in this article's Online Repository at www.jacionline.org.

Safety

In general, the SQ tree SLIT-tablet was well tolerated, with no major difference between adolescents and adults. An overview of AEs by age group is shown in Table II.

The most frequently reported treatment-related AEs were mild or moderate local reactions related to sublingual administration of the tablet (SQ tree SLIT-tablet, 94%; placebo, 89%), the most common being oral pruritus and throat irritation (Fig 6). A majority of these had median onset on the first or second day of treatment and median duration of 1 to 2 weeks. Typically, local reactions had onset within a few minutes after treatment (see Fig E2 in this article's Online Repository at www.jacionline.org), and recurrent events had median daily durations of 10 to 45 minutes. Twenty-five (8%) subjects in the SQ tree SLIT-tablet group discontinued the trial because of 98 AEs. These were mainly characterized as irritation or swelling in the mouth or throat of mild to moderate intensity. Four subjects in the SQ tree SLIT-tablet group and 6 subjects in the placebo group experienced serious AEs. Two of these were considered treatment related, 1 in each treatment group. Both events involved children not part of the trial who were accidentally exposed to trial medication intended for their parent. None of the children had registered allergies, and both were asymptomatic during the event. There were no reports of death, anaphylactic shock, airway obstruction, administration of epinephrine, or treatment-related anaphylactic reactions. Details on safety results are described in the Results section in this article's Online Repository.

DISCUSSION

The SQ tree SLIT-tablet was developed for treatment of ARC induced by tree pollen from the birch pollen–homologous group. This phase III, randomized, double-blind, placebo-controlled trial was the first to investigate the effect of the SQ tree SLIT-tablet not only during the BPS but also during the entire TPS. The trial was designed based on recommendations by the European Medicines Agency[23] and World Health Organization[24] and included adolescents and adults with moderate-to-severe ARC induced by tree pollen from the birch pollen–homologous group despite use of symptom-relieving medication. Thus the trial population represented the intended target population suitable for allergy immunotherapy.

The SQ tree SLIT-tablet demonstrated a statistically significant and clinically relevant treatment effect in the combined symptom

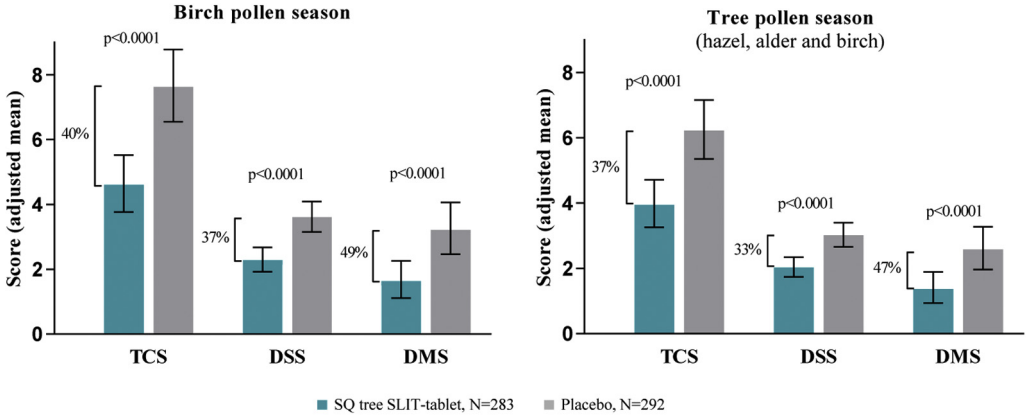

FIG 3. Primary and key secondary end points.

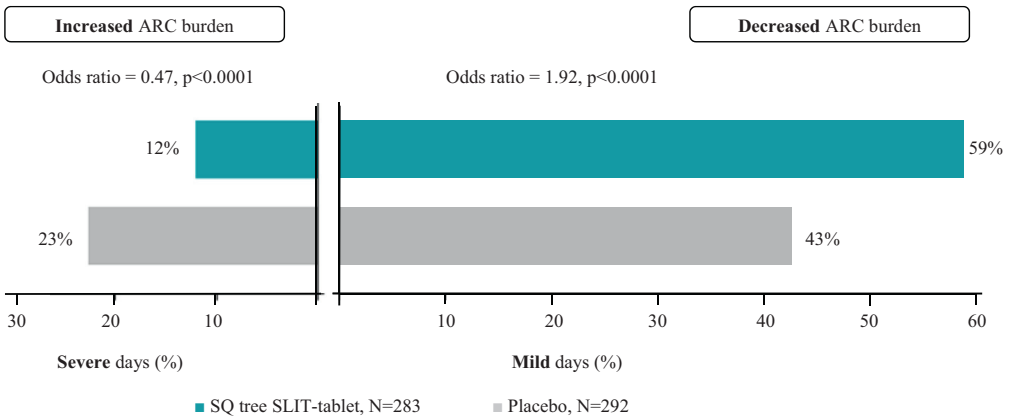

FIG 4. Proportion of mild and severe days during the BPS. *Mild days*, Days without intake of antihistamine tablet/eyedrops and no single symptom scoring greater than 1; *Odds ratio*, SQ tree SLIT-tablet/placebo; *Severe days*, days with DSS of 6 or greater and 2 or more moderate or 1 severe symptom.

and medication score prespecified for the primary end point, which exceeded by far the 20% improvement. The treatment effect was substantial and significant for average TCS, DSS, and DMS during the BPS (relative differences to placebo: 40%, 37%, and 49%, respectively; all $P < .0001$) and throughout the entire TPS (relative differences to placebo: 37%, 33%, and 47%, respectively; all $P < .0001$). Subgroup analysis of the average TCS during the BPS demonstrated efficacy regardless of age group. The magnitude of treatment effect was in line with that of other pollen SLIT-tablets, such as grass and ragweed.[25-27]

The clinically relevant effect seen throughout the TPS shows that subjects can benefit by symptom improvement and reduced need of medication not only during the BPS but also during the entire TPS, thus considerably prolonging the season in which treatment can benefit. In fact, *post hoc* analyses showed that the SQ tree SLIT-tablet improved symptoms and medication use during the alder and hazel seasons, suggesting that the previously identified immunologic cross-reactivity[4] also manifests as clinical effect. These results are also in line with previous results in which the SQ tree SLIT-tablet induced both an immunologic and clinically relevant treatment effect of ARC triggered by oak pollen.[12] However, a bystander effect on other pollen allergies outside the tree-homologous group cannot be expected.[28]

It is noteworthy that the treatment effect was driven by a simultaneous improvement in symptoms and a reduction in the need for symptom-relieving medication. During the trial, subjects had free access to pharmacotherapy in addition to the investigational medication. Therefore the effect measured provides an additional benefit to what can be achieved with symptom-relieving medication, which is especially important because the trial was conducted in subjects who previously had insufficient effects of symptom-relieving medication.

The primary end point reflects a combination of severity of ARC symptoms and intake of symptom-relieving medication, as recommended in guidelines.[23] A potential weakness of using the combined score is the lack of a validated method for assessing medication use.[29] The medication scale chosen in the current trial (ie, each used medication contributing to the score) was comparable with that used in other trials with SLIT-tablets.[8,11,27,30] Nonetheless, the end point was also assessed by using the recently proposed scale in the EAACI position paper (without oral corticosteroids), where the medication with the highest score was used to calculate the medication score.[17] The results were similar regardless of method used.

Secondary end points supported the clinically relevant treatment effect of the SQ tree SLIT-tablet. ARC-related quality of life

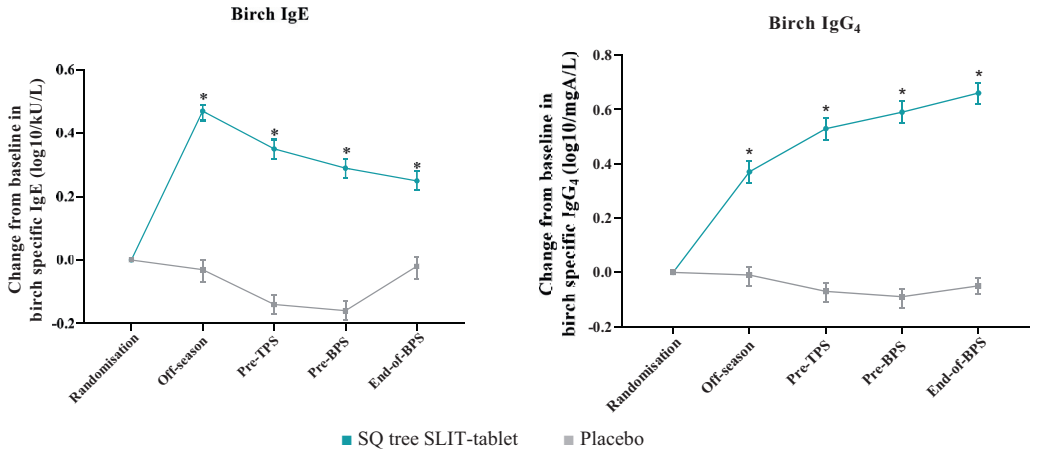

FIG 5. Immunology. Change from baseline in birch-specific IgE and IgG_4 levels. Adjusted means with 95% CIs are shown. *Statistically significant difference from placebo: $P < .0001$.

TABLE II. Overview of AEs

	SQ tree SLIT-tablet (n = 320)				Placebo (n = 314)			
	Adolescents (n = 28)		Adults (n = 292)		Adolescents (n = 32)		Adults (n = 282)	
Treatment group	n (%)	e (%)	n (%)	e (%)	n (%)	e (%)	n (%)	e (%)
All AEs	24 (86)	81 (100)	238 (82)	947 (100)	20 (63)	49 (100)	156 (55)	355 (100)
Causality								
Unlikely	10 (36)	18 (22)	117 (40)	227 (24)	18 (56)	24 (49)	127 (45)	247 (70)
Possible	23 (82)	63 (78)	216 (74)	720 (76)	8 (25)	25 (51)	65 (23)	108 (30)
Severity of all AEs								
Mild	21 (75)	45 (56)	197 (67)	538 (57)	16 (50)	25 (51)	118 (42)	233 (66)
Moderate	10 (36)	35 (43)	132 (45)	359 (38)	9 (28)	12 (24)	73 (26)	118 (33)
Severe	1 (4)	1 (1)	21 (7)	50 (5)	1 (3)	12 (24)	4 (1)	4 (1)
Seriousness								
Serious	—	—	4 (1)	4 (<1)	—	—	6 (2)	6 (2)
Nonserious	24 (86)	81 (100)	238 (82)	943 (>99)	20 (63)	49 (100)	155 (55)	349 (98)
Change in treatment								
None	24 (86)	70 (86)	216 (74)	758 (80)	17 (53)	41 (84)	137 (49)	278 (78)
Temporarily interrupted	5 (18)	10 (12)	42 (14)	92 (10)	7 (22)	8 (16)	31 (11)	62 (17)
Treatment discontinued	1 (4)	1 (1)	24 (8)	97 (10)	—	—	8 (3)	15 (4)
Outcome								
Recovered	24 (86)	81 (100)	236 (81)	904 (95)	19 (59)	48 (98)	149 (53)	321 (90)
Recovered with sequelae	—	—	3 (1)	3 (<1)	—	—	3 (1)	3 (<1)
Not recovered	—	—	25 (9)	35 (4)	1 (3)	1 (2)	19 (7)	22 (6)
Unknown	—	—	5 (2)	5 (<1)	—	—	8 (3)	9 (3)

e, Number of AEs; *N*, number of subjects in safety analysis set (all subjects exposed to at least 1 dose of treatment); *n*, number of subjects with AEs.

and the proportion of mild/severe days were improved compared with the placebo group, indicating an overall improved well-being. The clinical relevance of the "mild day" definition (based on a previous trial)[31] could potentially include the presence of most or all symptoms (eg, scores of 5 or 6). No standard definition of "mild days" exists; however, the term "well days" has been proposed defined as "days without intake of rescue medication and a symptom score below a predefined and clinically justified threshold," although the "clinically justified threshold" has not been specified and has been used heterogeneously across trials.[17] Both definitions include the absence of antihistamine use, suggesting a tolerable day for the subject. Furthermore, the clinical relevance is substantiated by severe days because these reflect the most troublesome days in the season having a significant effect on allergic subjects' daily life and affecting rhinoconjunctivitis quality of life,[9,31] emphasizing the relevance of allergen immunotherapy from the patient's perspective.

It is generally accepted that ARC and allergic asthma often occur concomitantly.[10] This trial showed that in the subpopulation with asthma at baseline, asthma control improved during the BPS. The clinical relevance of this improvement can be discussed; however, this trial was not designed as an asthma trial, and the subjects were well in control of asthma symptoms at baseline.

A potential weakness of the trial was that long-term efficacy beyond the first TPS was not investigated. Nevertheless, in contrast to symptom-relieving medication, allergy immunotherapy is known for its potential to modify the disease by

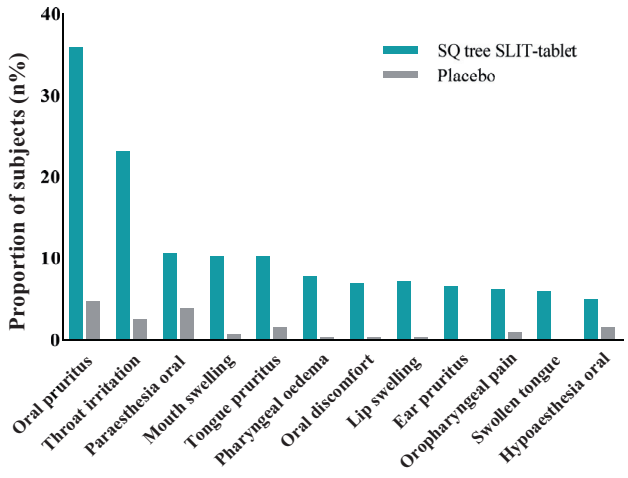

FIG 6. Percentage of subjects with the most frequent treatment-related AEs (experienced by ≥ 5% of subjects treated with SQ tree SLIT-tablet).

treating the underlying cause. This trial demonstrated a clear immunomodulatory effect. Treatment with the SQ tree SLIT-tablet resulted in immunologic changes similar to results from previous trials with subcutaneous birch allergy immunotherapy and the grass SLIT-tablet.[9,32] For the latter, sustained clinical effect has been demonstrated up to 2 years after the end of 3 years of treatment; this could suggest a potential long-term effect after completion of 3 years of treatment with the SQ tree SLIT-tablet as well.

The SQ tree SLIT-tablet was well tolerated, with no major safety concerns and a safety profile consistent with the safety profile in previous trials with the SQ tree SLIT-tablet,[11,33] as well as other SLIT-tablets (eg, house dust mite and grass).[8,9] However, there could be a tendency toward more subjects discontinuing because of local AEs in this trial compared with other SLIT-tablets. Overall, there was no difference in the safety profile for adolescents compared with adults. The limited number of subjects exposed and treatment duration of less than 1 year could reduce the chance of detecting rare AEs or AEs that might have a late onset. However, 2 clinical trials with adults or children treated for 3 years with the SQ grass SLIT-tablet did not detect any adverse reactions with a long latency period or caused by prolonged exposure.[9,34]

In conclusion, the trial demonstrated that the SQ tree SLIT-tablet was safe and had a significant and clinically relevant effect during the BPS and TPS compared with placebo in adolescents and adults with moderate-to-severe birch pollen–induced ARC, despite use of pharmacotherapy.

We thank all involved investigators for their work done in relation to this trial and the clinical trial team at ALK-Abelló for clinical project management, operational oversight, safety monitoring, data management, and statistics. Trine Møller Kruse and Bente Riis, ALK-Abelló, provided medical writing services for this manuscript (drafting, revising, and submission).

Clinical implications: The SQ tree SLIT-tablet had a significant and clinically relevant treatment effect on ARC symptoms and medication use during the TPS comprising the hazel, alder, and birch seasons.

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METHODS

Trial population

The principal inclusion criteria were as follows:

- moderate-to-severe allergic rhinitis, conjunctivitis, or both induced by birch pollen with or without asthma (controlled/partly controlled) despite having received treatment with symptom-relieving medication during the 2 previous TPS;
- an appropriate minimum level of ARC symptoms induced by birch pollen during the BPS of 2016;
- presence of 1 or more of the following ARIA quality-of-life items caused by allergic rhinitis, conjunctivitis, or both during the previous BPS;
- positive skin prick test response (wheal diameter ≥ 3 mm) to *Betula verrucosa* at screening;
- positive specific IgE level against Bet v 1 (IgE class 2 or greater, 0.7 kU/L) at screening; and
- presence of 1 or more of the Allergic Rhinitis and its Impact on Asthma quality-of-life items (sleep disturbance; impairment of daily activities, leisure, and/or sport; impairment of school or work; troublesome symptoms) caused by ARC during the previous BPS.

The principal exclusion criteria were as follows:

- a clinically relevant history of symptomatic (seasonal or perennial) allergic rhinitis or conjunctivitis caused by an allergen source (other than tree pollen from the birch group) overlapping the TPS;
- subject having rhinitis, conjunctivitis, or both caused by animal hair and dander to which the subject is regularly exposed;
- severe asthma exacerbation within the last 3 months;
- a clinical history of uncontrolled asthma (according to the Global Initiative for Asthma 2015) within 3 months before screening;
- reduced lung function (FEV_1 <70% of predicted value after adequate pharmacologic treatment);
- allergy immunotherapy treatment with birch pollen or a cross-reacting allergen within the last 5 years; and
- ongoing treatment with any allergy immunotherapy product.

Pollen seasons

The start and stop dates of the pollen season in each region were based on daily pollen counts. Each site was allocated to 1 of 30 pollen regions before unblinding. For each pollen region, the start of the BPS was defined as the first day of 3 consecutive days with 30 pollen grains/m^3 or greater, and the end was defined as the last day in the last occurrence of 3 consecutive days with 30 pollen grains/m^3 or greater. The TPS comprised the days included in any of the hazel or alder seasons and the BPS. The start and stop of the hazel and alder pollen seasons were defined as for the BPS, except with boundaries of 10 pollen grains/m^3 or greater. Pollen seasons were defined before unblinding.

Pollen exposure data were retrieved from the European Aeroallergen Network database, which was hosted and maintained by the Department of Oto-Rhino-Laryngology, Medical University of Vienna.

Randomization and blinding

Subjects, investigative staff, and sponsors were blind to treatment allocation. The randomization list was generated by a trial-independent statistician by using random sampling (block size, 4). To randomize a subject, the investigator allocated the lowest randomization number at the site to the subject. Two sets of sealed envelopes contained treatment allocation (1 at the trial site and 1 at the sponsor). The sequence was not accessible to trial personnel until database lock and trial unblinding. In case of medical emergency, the code could be broken for a particular subject if treatment knowledge was necessary for optimal treatment.

End points

Symptom and medication scores. The ARC DSS comprised 4 rhinitis symptoms (runny nose, blocked nose, sneezing, and itchy nose) and 2 eye symptoms (gritty feeling/red/itchy eyes and watery eyes), each assessed on a scale from 0 to 3 (ie, 0 = no symptoms and 3 = severe symptoms), thus ranging from 0 to 18. A symptom-scoring video was used to aid instruction of subjects.

The ARC DMS reflected the relief of symptoms and comprised the use of antihistamine tablets (5 mg of desloratadine, each tablet corresponding to a score of 6; maximal daily score, 6), ocular antihistamines (1 mg/mL olopatadine, each drop corresponding to a score of 1.5 per eye; maximal daily score, 6), and, if necessary, nasal corticosteroids (50 μg/dose mometasone, each spray corresponding to a score of 2; maximal daily score, 8), thus ranging from 0 to 20. Consequently, the TCS ranged from 0 to 38.

Mild and severe days. A *mild* day was defined as a day without intake of antihistamine tablets or eyedrops and with no single symptom score of greater than 1, and a severe day was defined as a day with a DSS of 6 or greater and 2 or more moderate symptoms or 1 severe symptom. Percentages of mild and severe days were calculated for each subject as the number of mild or severe days in the pollen season divided by the number of diary records in the season, where DSS could be calculated and where it had been registered whether symptom-relieving medication had been taken or not (and multiplied by 100).

Rhinoconjunctivitis quality of life. Rhinoconjunctivitis quality of life was assessed weekly by using the Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities (RQLQ[S]) for adults, and the RQLQ(S) + 12 for adolescents.[E1-E3] The RQLQ(S) comprised 28 questions in 7 domains (activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems, and emotional function), and the RQLQ(S) + 12 comprised 25 questions in 6 domains (nose symptoms, eye symptoms, practical problems, activity limitation, non-hay fever symptoms, and emotional function). Each question was scored on a scale from 0 to 6 (6 = worst). The overall RQLQ score for each time point was a mean of all 28 or 25 responses, with each domain weighed equally.

Asthma Control Test. Asthma control was assessed every 4 weeks and included 5 assessments (activity limitation, shortness of breath, nighttime symptoms, use of rescue medication, and overall asthma control), each of which was scored on a scale from 1 to 5 (1 = worst).

Safety assessments. AEs, whether reported by the subject and detected through physical examinations, laboratory tests, or other means, were recorded from when subjects provided informed consent until the last visit and were followed as appropriate. Only treatment-emergent AEs (ie, those occurring between first treatment and 1 week after the end of the trial) are presented. If the same type of AE (eg, itching in the mouth for 5-10 minutes after intake of treatment) occurred more than 1 day in a row, it was considered 1 AE. If the AE reappeared at a later time, it was considered a new AE. AEs were coded by the sponsor by using the Medical Dictionary for Regulatory Activities, version 19.0. Regulatory authorities and independent ethics committees/institutional review boards were informed of serious AEs in accordance with local requirements and ICH guidelines for Good Clinical Practice.[E4]

Statistical methodology

The full analysis set included all randomized subjects by assigned treatment according to the ICH intent-to-treat principle. The analyses were performed using all observed data, with no imputation for missing data. The per-protocol population was defined as subjects in the full analysis set with at least 70% treatment compliance, no major protocol violations assessed as having an effect on the primary end point, at least 50% diary records during the BPS, and at least 7 days with pollen counts of greater than 100 grains/m^3 and cumulative counts of greater than 1000 grains/m^3 during the BPS.

Statistical tests used a 5% significance level, and all tests and CIs were 2-sided. The null hypothesis was the hypothesis of no difference between the 2 treatments.

Sensitivity analyses of the primary and key secondary end points were conducted by repeating the analysis of these end points by (1) using the per-protocol population and (2) using all randomized subjects and 2 methods for multiple imputation.

In method 1 the square root average scores during the BPS/TPS were imputed for subjects who discontinued before the season and for subjects in whom the end point could not be calculated. Missing data in all treatment groups were sampled from the observed data of the end point in the placebo group by using the method of unrestricted random sampling with replacement. Thus all subjects with missing data in the BPS/TPS were included in the analysis as if no treatment effect was present.

In method 2 the square root average scores during the BPS/TPS were imputed for subjects who discontinued before the season and for subjects in whom the end point could not be calculated. For this sensitivity analysis, imputations were done as follows. First, missing data in the placebo group were sampled from observed data in the placebo group by using the method of unrestricted random sampling with replacement. Second, missing data in the SQ tree SLIT-tablet group for subjects who discontinued because of AEs were sampled from the observed data in the placebo group by using the method of unrestricted random sampling with replacement. Thus all subjects who discontinued because of AEs with missing data were included in the analysis as if no treatment effect was present. Third, missing data in the SQ tree SLIT-tablet group for subjects who discontinued for other reasons than AEs were sampled from the observed data in the SQ tree SLIT-tablet group by using the method of unrestricted random sampling with replacement. For both imputation methods, the Rubin multiple imputation strategy with 1000 imputations was used,[E5] in which each missing value was replaced with a set of plausible values that represent the uncertainty about the right value to impute.

The percentage of mild and severe days during the BPS and TPS were analyzed with a generalized logistic regression model, with treatment as a fixed effect and pollen region as a random effect.

The overall RQLQ score was analyzed with a repeated-measurements linear mixed model using a banded Toeplitz covariance structure. The model included treatment, time point, treatment group–time point interaction term, and pollen station as fixed factors and subject nested within pollen station as a random effect.

The total Asthma Control Test score for the pollen season was calculated as the average of the nonmissing scores in the given season and was analyzed by using a linear mixed-effects model similarly to the analyses of primary and key secondary end points.

Immunologic parameters (birch-specific IgE and IgG_4) were analyzed as change from baseline by using a linear mixed-effects model. Change from baseline of the log_{10}-transformed immunologic parameter was the response variable; treatment, visit, and their 2-factor interaction were included as fixed effects; the log-transformed immunologic parameter at baseline was included as a regression variable; and subject was included as a random variable. Different residual errors for each treatment group were specified in the linear mixed-effects model. When log_{10} transforming data, values of 0 or greater for IgE and IgG_4 were given the minimum value measured of greater than 0 for IgE and IgG_4.

RESULTS

Population

Six hundred thirty-four subjects were randomized, 320 to SQ tree SLIT-tablet and 314 to placebo. There were 40 premature trial discontinuations in the SQ tree SLIT-tablet group and 22 in the placebo group. Of these, 26 and 8 discontinuations, respectively, were caused by AEs. Nine subjects in the SQ tree SLIT-tablet group and 4 subjects in the placebo group discontinued the trial prematurely, with "withdrawal of consent" as the reason. Subjects were informed that participation in the trial was voluntary and that withdrawal of consent could be done at any time without affecting subsequent medical treatment. The protocol clearly described that if an AE was involved in a trial discontinuation, this was to be recorded as the primary reason. Furthermore, 5 discontinuations in the SQ tree SLIT-tablet group were for other reasons (not specified), and in the placebo group 1 subject was lost to follow-up, 3 became pregnant, and 4 provided other reasons (not specified), and 2 subjects discontinued because of protocol deviations (they were not able to comply with the protocol). Ninety percent of the randomized subjects completed the trial.

Efficacy

Results of the statistical analyses of ARC symptoms and medication use during the BPS and TPS are shown in Table E1 for all subjects in the full analysis set with diary data during the BPS. Furthermore, sensitivity analyses of the primary end point, including per-protocol analyses and intent-to-treat analyses with multiple imputation of missing data (all randomized subjects), are available in Table E1.

Safety

Sixteen (5%) subjects treated with the SQ tree SLIT-tablet reported 44 severe treatment-related AEs, whereas 2 (<1%) subjects in the placebo group reported 13 severe treatment-related AEs. The most common severe treatment-related AEs in the SQ tree SLIT-tablet group were throat irritation, oral pruritus, and oral hypoesthesia, all of which were reported by 1% or more of the subjects. Twenty-five (8%) subjects in the SQ tree SLIT-tablet group discontinued the trial because of 98 AEs. These were mainly characterized as irritation or swelling in the mouth or throat. Most of these subjects discontinued treatment within the first month, and for a majority, symptoms resolved the same day as treatment was discontinued.

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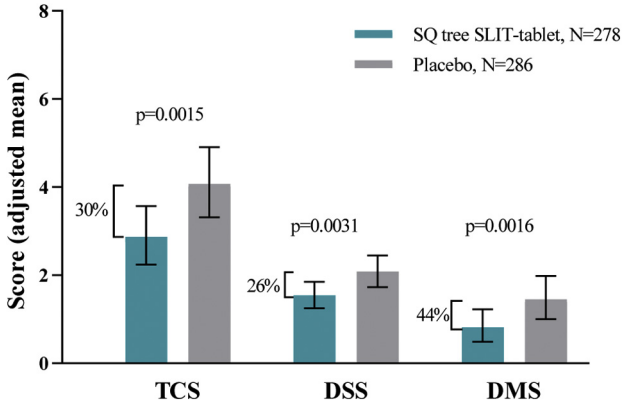

FIG E1. *Post hoc* analysis of average TCS, DMS, and DSS during the alder and hazel seasons.

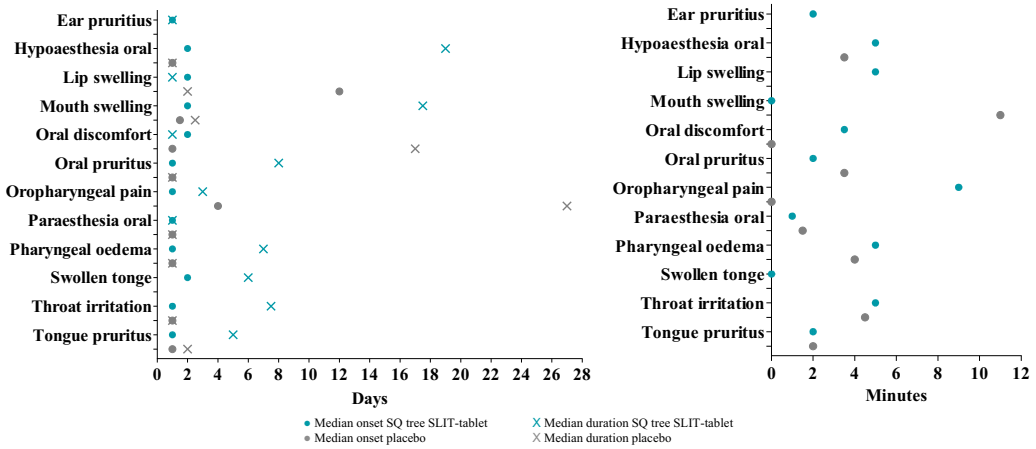

FIG E2. Median onset and duration of most frequent treatment-related AEs (experienced by ≥5% of subjects treated with SQ tree SLIT-tablet). *Left,* Median onset and duration of AE. Duration is given as time from onset until resolution (reoccurring AEs given from first to last day of appearance). *Overlapping symbols* indicate resolution on same day of occurrence. *Right,* Median onset of AE for AEs starting on the first day of treatment.

TABLE E1. Primary end point, sensitivity analyses of the primary end point, and secondary end points

		No. observed (no. Imputed)	Adjusted mean	Absolute difference (placebo-SQ tree SLIT-tablet [95% CI])	Percentage relative to placebo (95% CI)	*P* value
Primary analysis						
TCS during BPS (FASBPS)	Placebo	292	7.62	—	—	—
	SQ tree SLIT-tablet	283	4.61	3.02 (1.99-4.05)	39.59 (28.24-49.51)	<.0001
Sensitivity analyses						
TCS during BPS (PP)	Placebo	247	7.63	—	—	—
	SQ tree SLIT-tablet	235	4.35	3.27 (2.17-4.38)	42.90 (31.11-53.12)	<.0001
TCS during BPS (FAS), multiple imputation method 1	Placebo	292 (22)	7.67	—	—	—
	SQ tree SLIT-tablet	283 (37)	4.93	2.74 (1.69-3.78)	35.69 (24.25-46.20)	<.0001
TCS during BPS (FAS), multiple imputation method 2	Placebo	292 (22)	7.66	—	—	—
	SQ tree SLIT-tablet	283 (37)	4.86	2.80 (1.76-3.84)	36.55 (25.22-46.95)	<.0001
Secondary analyses						
TCS during TPS (FASBPS)	Placebo	292	6.22	—	—	—
	SQ tree SLIT-tablet	283	3.95	2.27 (1.44-3.11)	36.54 (24.99-46.62)	<.0001
DSS during BPS (FASBPS)	Placebo	292	3.60	—	—	—
	SQ tree SLIT-tablet	283	2.28	1.32 (0.84-1.81)	36.75 (25.29-46.70)	<.0001
DSS during TPS (FASBPS)	Placebo	292	3.02	—	—	—
	SQ tree SLIT-tablet	283	2.03	0.99 (0.60-1.38)	32.73 (21.45-42.56)	<.0001
DMS during BPS (FASBPS)	Placebo	292	3.21	—	—	—
	SQ tree SLIT-tablet	283	1.63	1.58 (0.94-2.22)	49.20 (33.38-62.41)	<.0001
DMS during TPS (FASBPS)	Placebo	292	2.58	—	—	—
	SQ tree SLIT-tablet	283	1.37	1.20 (0.69-1.72)	46.71 (30.47-60.29)	<.0001

FAS, Full analysis set; *FASBPS*, all subjects in the full analysis set with at least 1 diary entry during the BPS; *PP*, per protocol.

TABLE E2. Birch-specific immunologic parameters

		IgE (kU/L)		IgG_4 (mg_A/L)	
		SQ tree SLIT-tablet (n = 283)	Placebo (n = 292)	SQ tree SLIT-tablet (n = 283)	Placebo (n = 292)
Randomization	Mean (SD)	37.14 (49.92)	43.68 (73.11)	0.67 (0.82)	0.86 (1.45)
	Median	18.07	20.14	0.36	0.41
	Minimum-maximum	0.05-393.93	0.00-890.42	0.00-5.17	0.00-17.04
Off season	Mean (SD)	116.28 (198.79)	42.20 (73.15)	1.54 (1.97)	0.84 (1.51)
	Median	56.40	18.38	0.88	0.37
	Minimum-maximum	0.28-2529.2	0.00-894.49	0.00-11.63	0.00-18.64
Pre-TPS	Mean (SD)	83.67 (114.64)	34.06 (58.69)	2.53 (3.75)	0.79 (1.59)
	Median	43.66	14.07	1.23	0.30
	Minimum-maximum	0.30-1116.6	0.00-668.06	0.00-24.06	0.00-20.12
Pre-BPS	Mean (SD)	73.90 (100.03)	32.48 (52.86)	2.97 (4.40)	0.76 (1.50)
	Median	37.25	15.15	1.47	0.31
	Minimum-maximum	0.22-970.83	0.00-563.28	0.00-29.72	0.00-19.29
End of trial	Mean (SD)	67.83 (88.22)	44.97 (76.03)	3.53 (5.26)	0.84 (1.47)
	Median	33.81	19.32	1.65	0.31
	Minimum-maximum	0.16-578.65	0.00-688.40	0.00-36.75	0.00-15.00

Means are unadjusted.