Sublingual allergen immunotherapy with a liquid birch pollen product in patients with seasonal allergic rhinoconjunctivitis with or without asthma

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Background: Sublingual allergen immunotherapy (SLIT) has been demonstrated to be both clinically efficacious and safe. However, in line with the current regulatory guidance from the European Medicines Agency, allergen immunotherapy (AIT) products must demonstrate their efficacy and safety in pivotal phase III trials for registration.

Objective: We sought to investigate the efficacy and safety of sublingual high-dose liquid birch pollen extract (40,000 allergy units native [AUN]/mL) in adults with birch pollen allergy.

Methods: A randomized, double-blind, placebo-controlled, parallel-group multicenter trial was conducted in 406 adult patients with moderate-to-severe birch pollen-induced allergic rhinoconjunctivitis with or without mild-to-moderate controlled asthma. Treatment was started 3 to 6 months before the birch pollen season and continued during the season in 40 clinical study centers in 5 European countries. For primary end point assessment, the recommended combined symptom and medication score of the European Academy of Allergy and Clinical Immunology was used. Secondary end points included quality-of-life assessments, immunologic parameters, and safety.

Results: Primary efficacy results demonstrated a significant ($P < .0001$) and clinically relevant (32%) reduction in the combined symptom and medication score compared with placebo after 3 to 6 months of SLIT. Significantly better rhinoconjunctivitis quality-of-life scores ($P < .0001$) and the patient's own overall assessment of his or her health status, including the visual analog scale score (Euro Quality of Life Visual Analogue Scale; $P = .0025$), were also demonstrated. In total, a good safety profile of SLIT was observed.

Conclusion: This study confirmed both the clinical efficacy and safety of a sublingual liquid birch pollen extract in adults with birch pollen allergy in a pivotal phase III trial (EudraCT: 2013-005550-30; ClinicalTrials.gov: NCT02231307). (J Allergy Clin Immunol 2019;143:970-7.)

Key words: *Birch pollen allergy, allergic rhinoconjunctivitis, sublingual immunotherapy, allergen immunotherapy, efficacy, safety, combined symptom and medication score, pivotal phase III trial, quality of life*

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Abbreviations used
ACQ: Asthma Control Questionnaire
AE: Adverse event
AIT: Allergen immunotherapy
ARC: Allergic rhinoconjunctivitis
AUN: Allergy units native
CSMS: Combined symptom and medication score
dMS: Daily medication score
dSS: Daily symptom score
EAACI: European Academy of Allergy and Clinical Immunology
EMA: European Medicines Agency
EQ-VAS: Euro Quality of Life Visual Analogue Scale
ITT: Intention to treat
PP: Per protocol
RQLQ: Rhinitis Quality of Life Questionnaire
SLIT: Sublingual allergen immunotherapy
TEAE: Treatment-emergent adverse event

Allergic rhinoconjunctivitis (ARC) is a symptomatic disorder of the upper airways induced by an IgE-mediated inflammatory response in sensitized subjects after allergen exposure. Symptoms can be both nasal and ocular. ARC is estimated to affect 10% to 25% of the global population, with a considerable effect on quality of life.[1,2] If left untreated, ARC is considered one of the major risk factors for the development of asthma.[3-5] Treatment of ARC involves allergen avoidance, pharmacotherapy, and allergen immunotherapy (AIT).[1] Pharmacotherapy is intended for symptomatic treatment only. However, despite adequate pharmacotherapeutic treatment, up to every fifth patient still presents with uncontrolled nasal and/or ocular symptoms, with a high impairment of quality of life affecting work productivity, social interactions, and other aspects of life.[1,6]

AIT is the only disease-modifying treatment option available for patients with IgE-mediated allergic diseases, such as ARC, and can be administered through several routes.[7-10] With sublingual administration, the allergen preparation is held underneath the tongue to allow an immune-modulating effect through the sublingual mucous membrane.[11-13] Sublingual allergen immunotherapy (SLIT) appears to be safe and well tolerated.[13] The efficacy and safety of SLIT in patients with ARC induced by various inhalant allergens has been confirmed in multiple clinical trials and recent systematic reviews[14-17] and is considered a viable alternative to subcutaneous immunotherapy.[7-10] In line with the regulatory guidance of the European Medicines Agency (EMA),[18] individual products in AIT have to demonstrate their clinical efficacy in (pivotal) phase III trials subsequent to controlled clinical trials (phase II) of the investigational product for optimal dose determination.

Here we report a randomized, double-blind, placebo-controlled, phase III study with an open-label safety extension period in adults with birch pollen allergy. For SLIT, a high-dose liquid birch pollen extract[19] or placebo was used. Clinical efficacy was analyzed by using primary and secondary end points, as recommended by the European Academy of Allergy and Clinical Immunology (EAACI).[20] This study is deemed pivotal regarding the investigational product, as well as the end points used for efficacy assessment.

METHODS

Study design

This was a multicenter (n = 40), randomized, double-blind, placebo-controlled, parallel-group study performed preseasonally over 3 to 6 months before the birch pollen season (September 2014 to May 2015) and continued coseasonally during the pollen season including 406 adult patients (18-65 years), followed by an open-label safety extension period over 6 months (June 2015 to February 2016) including 343 patients. All participants had confirmed moderate-to-severe persistent ARC according to the Allergic Rhinitis and its Impact on Allergy classification[1] for at least 2 consecutive years with or without mild-to-moderate (controlled) asthma caused by sensitization to birch pollen. Sensitization was confirmed based on positive skin prick test responses with a mean wheal diameter of 3 mm or greater compared with that elicited by the negative control (HAL Allergy B.V., Leiden, The Netherlands) and a positive serum specific anti-birch IgE test result (concentration, >0.7 U/mL; ImmunoCAP; Thermo Fischer, Phadia, Uppsala, Sweden) and clinical relevance based on positive nasal provocation test results to birch pollen (HAL Allergy B.V., Leiden, The Netherlands). All patients independent of evidence of concomitant asthma needed an FEV_1 of greater than 70% or a peak expiratory flow of greater than 80% of predicted value to be included in the study. Patients had to be willing and capable of completing an e-diary during the birch pollen season.

Patients were excluded if they were sensitized and symptomatic to pets when regularly exposed, subject to any subcutaneous immunotherapy or SLIT with the investigational or a cross-reacting allergen within 5 years before the start of this study, or had uncontrolled asthma or other respiratory diseases. Treatment duration for patients in the double-blind part of the study was 6 to 9 months.

All patients provided written informed consent. The study protocol, including all accompanying material, was approved by ethics committees and competent authorities of the 5 participating countries (Germany, Belgium, Poland, Czech Republic, and Slovakia). The trial was registered in the EudraCT database as no. 2013-005550-30 and in the register of ClinicalTrials.gov with identifier NCT02231307.

AIT

Eligible patients were randomly assigned to active/placebo treatment in a 1:1 manner stratified by the study site by using an Interactive Web Response System.

For SLIT, a biologically standardized liquid allergen extract of birch pollen *(Betula verrucosa)* in a glycerinated phosphate buffer was used and stabilized with ε-aminocaproic acid in water for injection at a concentration of 40,000 allergy units native [AUN]/mL (active product; HAL Allergy B.V.). The Bet v 1 content of the product is 0.4 mg/mL, as measured in comparison to the EDQM–Bet v 1 reference preparation. Unlike the active preparation, placebo did not contain any allergen. Regarding the excipient's composition, active and placebo preparations were the same, except for the caramel colorant (E150c) added to placebo to ensure color blinding for the 2 treatments (placebo product; HAL Allergy B.V.).

Both study medications were taken sublingually once daily. After a daily increase of 1 drop, the maintenance dose was reached at 5 drops per day. Drops were held for 2 to 3 minutes underneath the tongue and then swallowed. The first dose (drop) of study medication was taken under the supervision of the respective investigator.

Patient treatment compliance was checked based on the daily study medication use entered into the e-diary and on returned used/unused bottles or bottles claimed to be lost at the end of study site visits. In case of 25% or more of the missing doses reported or absenteeism for greater than 7 days during the actual pollen season, patients were considered protocol violators.

Assessment of efficacy

An overview of all assessments comprising the primary, secondary and safety parameters and their timing is presented in Table I.

The primary end point was defined as the difference in mean combined symptom and medication score (CSMS) between the active and placebo treatment groups, as assessed during the birch pollen season. The CSMS is the EAACI-recommended end point for pivotal studies, described in detail in the

TABLE I. Overview of assessments of the primary, secondary, and safety parameters

Visits (timing) / Assessments	Visit 1, −7 d	Visit 2, day 1	Visit 3, day 14	Visit 4, day 42	Visit 5, day 84	Visit 6, February 2015	Visit 7, April 2015	Visit 8, Jun 2015	Visit 9, 14 days after visit 8	Visit 10, 26 wk after visit 9
Symptom score + allergy-related medications (e-diary)	X	X				X	X	X		
Quality-of-life questionnaires*		X					X	X		
Serum immunoglobulins (IgE, IgG, IgG_4)	X				X			X		
Vital signs and weight†	X	X						X	X	X
Physical examination	X	X						X	X	X
Blood sampling safety	X				X			X		
Urinalysis safety	X				X			X		
Lung function	X	X					X	X		
Electrocardiography	X							X		
AE/concomitant medication documentation eCRF	X	X	X	X	X	X	X	X	X	X

eCRF, Electronic Case Report Form.
*Quality-of-life questionnaires were assessed twice during the pollen season on the e-diary on April 15 and 30; ACQ questionnaires were assessed at visits 2, 7, and 8.
†Weight was only assessed during the visit 1 screening; at the other visits, only blood pressure was measured.

position paper of the EAACI.[20] Briefly, CSMS is the sum of the daily symptom score (dSS) plus daily medication score (dMS). The dSS is comprised of 6 individual symptom scores: 4 nasal symptoms (itchy nose, sneezing, runny nose, and blocked nose) and 2 ocular symptoms (itchy/red eyes and watery eyes), all rated on a scale of 0 to 3. The dSS was calculated as a mean of all nonmissing dSS during the pollen season (range, 0-18) divided by the number of individual symptoms (6 symptoms). Hence, the mean dSS can range from 0 to 3. The dMS is based on the following scores: 0, no rescue medication; 1, antihistamines; 2, nasal corticosteroids; and 3, oral corticosteroids. This score was again calculated as the average of the dMS during the pollen season. Consequently, the mean dMS has a range of 0 to 3. The CSMS, which is equal to the dSS plus dMS, has a range of 0 to 6 (see Appendix E1 in this article's Online Repository at www.jacionline.org).[20]

The mean CSMS was calculated from the sum of all daily CSMS during the birch pollen season divided by the number of days in the birch pollen season. For efficacy assessment, the respective mean CSMS of the active and placebo groups were compared. A minimum clinically important CSMS difference of 23% was predefined in the study protocol and justified by using both clinical and statistical considerations (data on file).

Each clinical site was allocated to a pollen station in the region/country, which reported the pollen load daily. Determination of pollen counts was done with volumetric pollen traps (Burkard Scientific, Uxbridge, United Kingdom). The birch pollen season was predefined to start if birch pollen counts were 80 grains/m^3 or greater per 24 hours on 3 of 5 consecutive days, with the first of such days taken as the start day of the birch pollen season. The season ended when birch pollen counts were less than 80 grains/m^3 per 24 hours on 3 of 5 consecutive days, and the last of such days was the actual end day of the birch pollen season.[21] The total season could consist of several separate periods that comply with this definition. The birch peak pollen season was defined as all days with birch pollen counts of 500 grains/m^3 or greater per 24 hours.

Secondary end points[20] were mean CSMS during the birch peak pollen season; mean dSS and dMS separately during both the birch pollen and birch peak pollen seasons; serum specific IgE, IgG, and IgG_4 levels; and quality of life during the birch pollen season and at the end of treatment. The latter was assessed by using the (validated) disease-specific Rhinitis Quality of Life Questionnaires (RQLQ-S)[22] for all patients, an Asthma Control Questionnaire (ACQ)[23] for patients with concomitant asthma, and a visual analog scale (EQ-VAS)[24] at baseline during the pollen season and at the end of treatment (see Table I for details). Serum specific IgE, IgG, and IgG_4 levels to birch pollen extract (t3) and Bet v 1 major allergen (t215) were determined by using ImmunoCAP assays.

Safety data

The safety and tolerability of active versus placebo treatment was assessed based on the number and severity of local and systemic reactions; adverse events (AEs); laboratory parameters, such as hematology and blood chemistry; urinalysis; vital signs; physical examination; electrocardiography; lung function testing; and use of concomitant medication.

Local reactions of oromucosal, ear, and gastrointestinal tract origin were graded by severity (mild = no disruption of normal daily activities, moderate = affect normal daily activities, and severe = inability to perform daily activities), and systemic reactions graded according to EAACI criteria[25] were assessed per treatment group. All serious AEs were coded by using the Medical Dictionary for Regulatory Activities version, which was considered current at the start of the trial (ie, Medical Dictionary for Regulatory Activities 17.0). Further differentiation of "drug-related" or "non–drug-related" and treatment-emergent adverse events (TEAEs) was carried out. FEV_1 was measured 3 times with a spirometer or a universal range peak flow meter. Concomitant medication was classified according to the World Health Organization Drug Dictionary (March 2014) and assigned to anatomic therapeutic class.

Statistical analysis

A sample size of 170 patients per group was determined to provide a power of 90% to detect a decrease of 25% in the active versus placebo groups, assuming a mean CSMS of 1.30 in the placebo group and SD of 0.92 at a significance level of .05 (2-sided). Based on an expected dropout rate of 15%, a total of 200 patients per group were planned to be randomized.

Primary outcome analysis was carried out in the intention-to-treat (ITT) population by using a mixed model with mean CSMS as a dependent variable. It included treatment (active vs placebo) as a fixed factor and sites pooled according to their assigned pollen station as a random factor. All tests were 2-sided ($\alpha = .05$). Analogously, this primary end point was also analyzed in the per-protocol (PP) population. All secondary and exploratory end points were analyzed based on mean estimates and 95% CIs of the respective mean parameter for each treatment group, as well as for the treatment difference. For percentages of *well days* and *severe days*, a responder analysis using the ANOVA model with treatment as a fixed factor was carried out. Well days were defined as days with no rescue medication and a symptom score of no greater than 2,[26] and severe days were defined as days with a symptom score of 3 in any of the 6 rhinoconjunctivitis symptoms.[27] Statistical analyses were conducted with SAS software (version 9.3; SAS Institute, Cary, NC).

RESULTS

Patients

Four hundred six patients were enrolled in one of the 2 treatment groups (208 to the active treatment and 198 to the

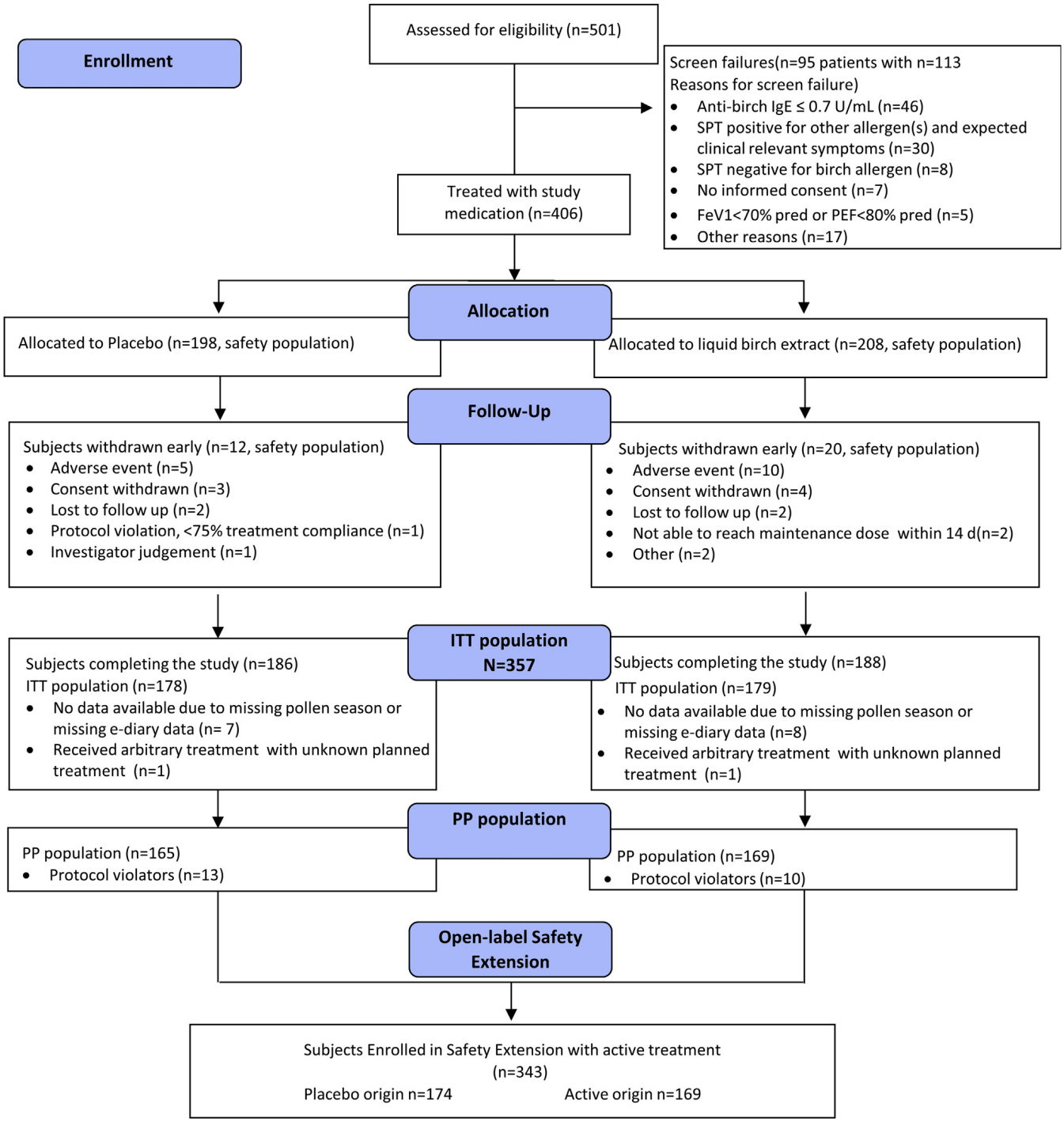

FIG 1. CONSORT flow diagram: overview of patient disposition in the double-blind part of the study and the safety extension study. *SAF,* Safety population.

placebo group, see Fig 1, CONSORT flow diagram). Demographics and baseline characteristics of the study population are depicted in Table II. Demographic and baseline characteristics did not show notable differences between placebo and active treatment.

Thirty-two patients terminated the study prematurely (Fig 1). The main reason for early termination was the development of AEs. The ITT population for primary efficacy evaluation consisted of 357 patients. As specified in the study protocol, the ITT population includes all patients who are randomized and received at least 1 dose of study medication and for whom at least 1 postbaseline (postscreening) measurement for the primary efficacy parameter is available.

A total of 343 patients who completed the double-blind phase of the study were included in the open-label safety extension period and treated with the active product exclusively.

Demographic and baseline characteristics (Table II) did not show notable differences between active and placebo treatment nor were any relevant differences between treatment groups identified in relation to (1) allergy medical history, (2) asthma

TABLE II. Summary statistics of demographics and baseline characteristics (safety population)

Parameter name	Placebo (n = 198)	Active (40,000 AUN/mL [n = 208])	All (n = 406)
Sex, no. (%)			
Female	118 (59.6)	106 (51.0)	224 (55.2)
Male	80 (40.4)	102 (49.0)	182 (44.8)
Race, no. (%)			
Black	1 (0.5)		1 (0.2)
White	195 (98.5)	207 (99.5)	402 (99.0)
Hispanic	1 (0.5)	1 (0.5)	2 (0.5)
Other	1 (0.5)		1 (0.2)
Age (y)			
No.	198	208	406
Mean (SD)	36.69 (10.77)	37.48 (11.43)	37.10 (11.11)
Median (minimum-maximum)	36.00 (18.0-61.0)	37.00 (18.0-65.0)	36.00 (18.0-65.0)
BMI (kg/m^2)			
No.	198	208	406
Mean (SD)	25.02 (4.01)	25.32 (4.14)	25.18 (4.07)
Median (minimum-maximum)	24.54 (17.0-39.2)	24.84 (17.9-37.7)	24.71 (17.0-39.2)
Other allergies			
No	108 (54.5)	103 (49.5)	211 (52.0)
Yes	90 (45.5)	105 (50.5)	195 (48.0)

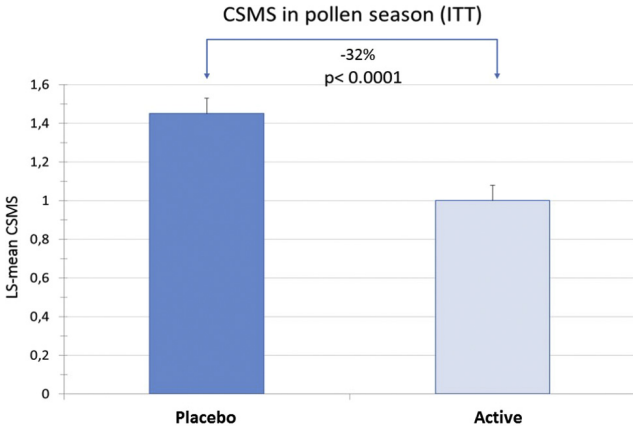

FIG 2. Mean CSMS during the birch pollen season for patients in the placebo and active treatment groups (ITT).

medical history, (3) serum specific IgE levels, (4) lung function and nasal provocation test results, (5) physical examination results and concomitant medication, and (6) compliance (data not shown).

Efficacy

Primary end point. The primary end point analysis showed a statistically significant ($P < .0001$) difference of 32% for the CSMS during the pollen season in the active group compared with that in the placebo group in the ITT population (Fig 2 and Table III). Supportive of this result was a CSMS reduction in the PP population, also decreasing by 32% ($P < .0001$) in the active versus placebo treatment groups during birch pollen exposure. Additional sensitivity analysis with all randomized subjects with multiple imputation of missing values by using the method of unrestricted random sampling with replacement (ie, missing data of the placebo group were replaced by observed data of the placebo group and *vice versa*) showed consistent results ($P < .0001$). The same was true for the 2 worst-case scenarios like "all patients with missing values got data of the placebo effect" and "patients from active group with missing values got data of the placebo effect, patients from placebo group with missing values got data of the effect of active treatment" ($P < .0001$ and $P < .001$, respectively). The differences were still greater than the predefined minimal clinically relevant difference and did not change the conclusion for the treatment effect.

Secondary end points. During the peak pollen season, a statistically significant reduction in CSMS of 38% ($P < .0001$) for the active group (ITT population) could be detected and was almost identical to the decrease in CSMS, as determined in the PP set of patients (39%; $P < .0001$). Also, evaluation of CSMS subcategories (ie symptom, medication, and nasal and ocular symptom scores) showed a statistically significant reduction in the active patient set during both the pollen season and the peak pollen season (Fig 3 for the pollen season in the ITT population).

Also, the percentage of well days and severe days showed consistent statistically significant improvement in the actively treated group, with 15% more well days and 5% less severe days during the pollen season. The result of this analysis was similar irrespective of whether the PP or ITT populations were assessed.

Baseline RQLQ-S scores were similar for both treatment groups (mean value: placebo = 0.41 vs active = 0.47). During the pollen season, RQLQ-S scores increased in both groups, corresponding to a reduced quality of life caused by increased rhinitis burden. However, after active treatment, the mean RQLQ-S score increase from a baseline of 0.55 (SE, 0.09) was less pronounced compared with the RQLQ-S score increase of 1.10 (SE, 0.09) observed after placebo. This corresponds to a significantly ($P < .0001$) improved rhinoconjunctivitis quality of life in actively treated patients of the ITT population (difference, −0.55; 95% CI, −0.77 to −0.33). Analysis of RQLQ-S scores for the PP population yielded similar statistically significant results. At the end of treatment (after the end of the pollen season), RQLQ-S scores in both treatment groups returned to similar values (mean RQLQ-S score: active, 0.42 [SE, 0.08]; placebo, 0.50 [SE 0.08]).

A treatment effect on general health-related quality of life could also be shown. During the pollen season, a statistically significant improvement in change from baseline EQ-VAS scores between active and placebo group patients (ITT population) was apparent (mean EQ-VAS score active, −3.95 [SE, 1.27]; placebo, −8.72 [SE, 1.27]; difference, 4.77 [95% CI, 1.68-7.86]; $P = .0025$). Assessment of the PP population demonstrated comparable results. At baseline and at the end of the study (ie, outside the pollen season), general health status was not different between the groups. Assessment of ACQ scores in patients with birch pollen–induced concomitant asthma (subgroup of 27% of all patients) did not show statistically significant differences between treatment groups, irrespective of whether the ITT or PP populations were considered, which can be explained by the relatively mild asthma symptoms, as demonstrated by the relatively low mean ACQ score at baseline (0.42 [SD, 0.58]) and by the fact that asthma had to be controlled during the trial.

TABLE III. Primary end point analysis: CSMSs during the pollen season (ITT population)

Parameter	Placebo (n = 178), mean (SE)	Active (n = 179), mean (SE)	Active − placebo difference (95% CI), mean (SE)	*P* value
CSMS	1.45 (0.08)	1.00 (0.08)	−0.46 (−0.66 to −0.26)	<.0001

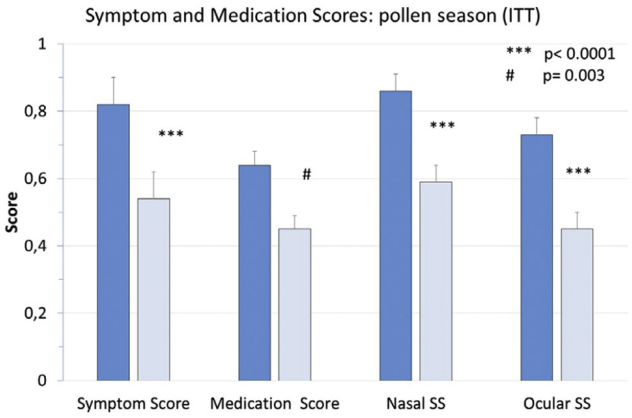

FIG 3. Mean Individual symptom, medication, and nasal and ocular symptom scores during the birch pollen season for patients in the placebo (dark blue) and active (light blue; ITT population) treatment groups. *SS*, Symptom score.

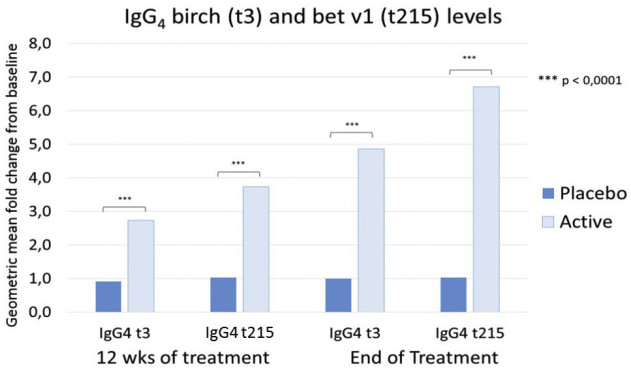

FIG 4. Mean fold change from baseline in serum specific IgG_4 (birch pollen, t3; Bet v 1, t215) levels for placebo and active treatment (ITT population).

Immunologic parameters, such as levels of specific IgE, IgG, and IgG_4 to both the birch pollen extract and Bet v 1, were found to increase significantly only in the active group. No significant changes were observed in the placebo group. Levels of specific IgE increased significantly after 12 weeks (2.3-fold change from baseline, $P < .0001$) in the active treatment group and decreased to a level just above the screening value at the end of the study. Levels of specific IgG and IgG_4 (Fig 4 for IgG_4) increased significantly after 12 weeks of treatment (3.7-fold change from baseline for specific IgG_4, $P < .0001$) and further increased at the end of the study (6.7-fold change from baseline for specific IgG_4, $P < .0001$). These results were similar whether analyzed in the ITT or PP populations.

Safety

The safety population included all patients who received study medication at least once.

Exposure to the study medication during the double-blind period of the study did not differ between the placebo and active groups. Compliance for the total period was high (about 99%), as indicated by the number of reported days without intake of study medication (ie, 2.7 ± 7.2 days for the active group and 2.1 ± 4.5 days for the placebo group).

During the open-label extension period of the study, exposure to the study medication was 174.9 ± 41.7 days for formerly placebo-treated patients and 187.3 ± 13.2 days for patients continuing active treatment.

Local and systemic TEAEs for the double-blind period of the study. In total, 342 local reactions occurred in 165 (40.6%) patients. One hundred twenty-three (59.6%) patients of the active group reported a total of 271 local reactions compared with 42 (21.2%) patients of the placebo group reporting 71 local reactions. In total, 83.0% of all reactions were of mild intensity. Four (1.9%) patients of the active treatment group experienced at least 1 severe local reaction (Table IV).

A total of 92 systemic reactions were reported by 51 (12.6%) patients. Of these, 73 reactions occurred in the active group (in 37 [17.8%] patients) compared with 19 reactions (in 14 [7.1%] patients) for the placebo group. The TEAEs in the active group were of grade 0 in 2 (1%) patients, grade I in 31 (14.9%) patients, grade II in 3 (1.4%) patients, and grade III in 1 (0.5%) patients; in the placebo group, TEAEs were of grade 0 in 1 (0.5%) patient, grade I in 12 (6.1%) patients, and grade II in 1 (0.5%) patient. Two patients receiving active treatment reported a drug-related serious AE: 1 angioedema (grade III) and 1 throat edema (grade II). Both resolved immediately after treatment. The patient with angioedema was withdrawn from the study. In the patient experiencing throat edema, a temporary dose adaptation was deemed necessary.

Local and systemic TEAEs for the open-label extension period of the study. In total, 123 of 343 patients included in the open-label extension period of the study reported a local reaction, 88 of whom belonged to the former placebo group. Most local reactions were of mild-to-moderate intensity (>97%). Fifteen patients reported mild systemic reactions. No grade IV systemic TEAEs occurred, and no suspected unexpected serious adverse reactions have been reported. Regarding clinical and laboratory safety parameters, no safety issues were observed.

DISCUSSION

To our knowledge, this is the first report of a SLIT product for patients with birch pollen allergy undergoing the full development program, including the current pivotal phase III study, according to the EMA's recommendations.[18] In a preceding dose-range finding and tolerability (phase II) study, the dose of 40,000 AUN/mL was determined to be optimal for this birch SLIT product.[19] Moreover, this is the first report of a phase III trial on clinical efficacy of an AIT product using the CSMS recommended by the EAACI.[20]

For this birch SLIT product, unequivocal evidence for significant and clinically relevant efficacy was shown. This effect could

TABLE IV. Summary of local and systemic TEAEs during the double-blind period (safety population)

		Placebo (n = 198)		Active (40,000 AUN/mL [n = 208])		All (n = 406)	
		No.	%	No.	%	No.	%
Patients with ≥1 drug-related local TEAE	Total	41	20.7	123	59.1	164	40.4
Strongest intensity	Mild	33	16.7	97	46.6	130	32.0
	Moderate	8	4.0	22	10.6	30	7.4
	Severe	0	0.0	4	1.9	4	1.0
Patients with ≥1 systemic TEAE	Total	14	7.1	37	17.8	51	12.6
Strongest intensity	Mild	10	5.1	25	12.0	35	8.6
	Moderate	4	2.0	10	4.8	14	3.4
	Severe	0	0.0	2	1.0	2	0.5

be demonstrated after only 3 to 6 months of preseasonal followed by 3 months of coseasonal treatment. Results of the primary end point analysis were consistently supported by results obtained for all secondary end points, irrespective of whether analysis occurred during the whole pollen season or the peak pollen season or considering the ITT or PP population. The observed treatment effect size of 32% exceeds the recommendations of the World Allergy Organization regarding the minimal clinically relevant efficacy of 20%.[28] This decrease in CSMS in the active group was accompanied by a significantly improved quality of life (expressed by both RQLQ-S and EQ-VAS) compared with that seen in placebo-treated patients.

Immunologic changes during AIT, which are clearly indicative of efficacy, are titers of specific IgG and IgG_4 antibodies to birch pollen extract and Bet v 1. Both were significantly increased in the active group and remained unchanged in the placebo group. IgG_4 production has recently been shown to be confined to IL-10–secreting regulatory B cells, which are believed to be essentially involved in the development of allergen tolerance,[29] and has also been emphasized as a valuable biomarker of adherence to AIT.[30,31] Local and systemic adverse reactions were mainly of mild intensity and well controlled. Results of recent systemic reviews on high-dose SLIT[16,17,32] confirm our finding that local reactions are common and much more frequent in the active compared with placebo groups and that the frequency and severity of TEAEs decrease with ongoing treatment.

Direct comparison of clinical trial results with different AIT products in general and for SLIT products especially has been hampered greatly by the remarkable heterogeneity in outcome parameters for efficacy used in such studies, let alone the divergent study designs.[33,34] In the EMA guidelines,[18] which came into effect in 2009, recommendations were published on how to build primary end points based on combined symptom medication scores. These recommendations were taken up by an EAACI task force and transformed into a CSMS based on equal weight, respectively.[20] Data presented here with this new scoring system verify its ease of use, its responsiveness over time, and its fitness for the purpose of measuring disease-influencing elements deemed associated with ARC. Therefore it can be recommended as a standard in future clinical trials on AIT products for the treatment of ARC.

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Clinical implications: Data presented in this article demonstrate the efficacy and safety of this liquid SLIT product in patients with birch allergy with rhinoconjunctivitis with or without asthma based on EAACI recommended end points.

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