Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy

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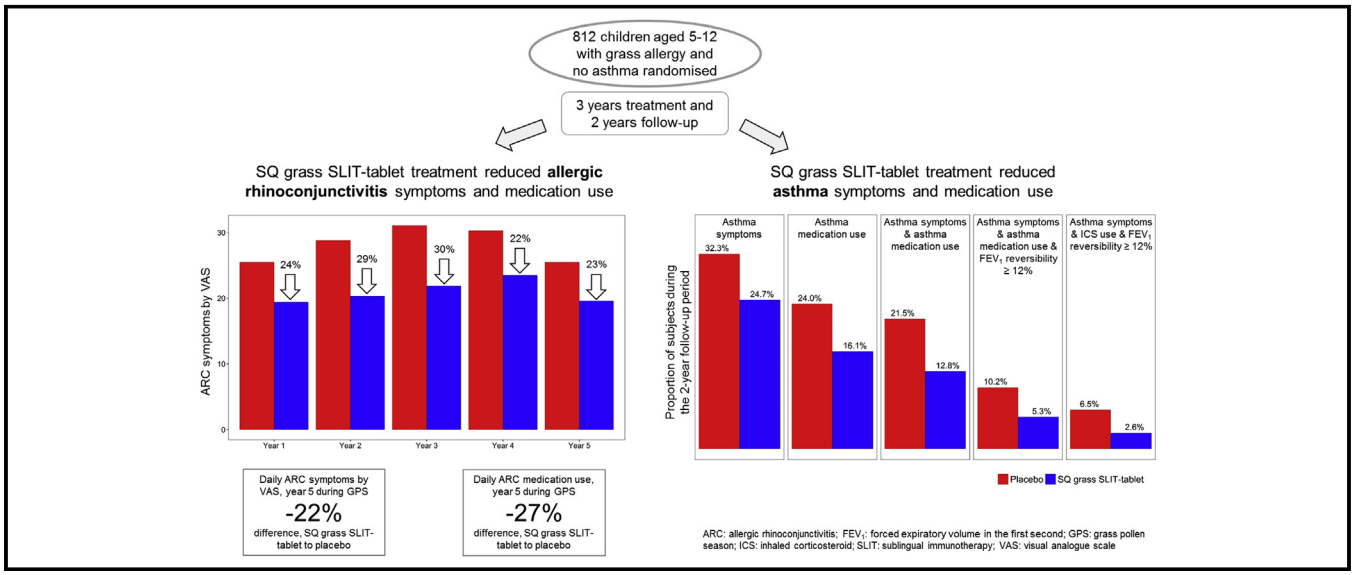
GRAPHICAL ABSTRACT



Background: Allergy immunotherapy targets the immunological cause of allergic rhinoconjunctivitis and allergic asthma and has the potential to alter the natural course of allergic disease.

Objective: The primary objective was to investigate the effect of the SQ grass sublingual immunotherapy tablet compared with placebo on the risk of developing asthma.

Methods: A total of 812 children (5-12 years), with a clinically relevant history of grass pollen allergic rhinoconjunctivitis and no medical history or signs of asthma, were included in the randomized, double-blind, placebo-controlled trial, comprising 3 years of treatment and 2 years of follow-up.

Results: There was no difference in time to onset of asthma, defined by prespecified asthma criteria relying on documented reversible impairment of lung function (primary endpoint). Treatment with the SQ grass sublingual immunotherapy tablet significantly reduced the risk of experiencing asthma symptoms or using asthma medication at the end of trial (odds ratio = 0.66, $P < .036$), during the 2-year posttreatment follow-up, and during the entire 5-year trial period. Also, grass allergic rhinoconjunctivitis symptoms were 22% to 30% reduced ($P < .005$ for all 5 years). At the end of the trial, the use of allergic rhinoconjunctivitis pharmacotherapy was significantly less (27% relative difference to placebo, $P < .001$).

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Total IgE, grass pollen–specific IgE, and skin prick test reactivity to grass pollen were all reduced compared to placebo. Conclusions: Treatment with the SQ grass sublingual immunotherapy tablet reduced the risk of experiencing asthma symptoms and using asthma medication, and had a positive, long-term clinical effect on rhinoconjunctivitis symptoms and medication use but did not show an effect on the time to onset of asthma. (J Allergy Clin Immunol 2018;141:529-38.)

Key words: *Allergy immunotherapy, asthma symptoms, children, disease-modifying treatment, long-term trial*

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Asthma affects an estimated 300 million individuals worldwide and is considered a serious global health problem affecting all age groups.[1,2] It is among the most frequent chronic diseases in childhood[3] and imposes a considerable burden on patients, their families, and health care systems. Allergic rhinoconjunctivitis (ARC) is a recognized risk factor for asthma development.[4-6]

Allergy immunotherapy (AIT) targets the immunologic cause of upper and lower respiratory IgE-mediated allergic symptoms by modulating the immunological response to allergen exposure. In addition to reducing ARC symptoms and the need for allergy pharmacotherapy, AIT has shown potential to alter the natural course and to prevent the progression of the allergic disease in children.[7,8] AIT treatment could therefore represent an attractive modality for the prevention of the development of asthma, as an added benefit in addition to the established effect on ARC. Results from a limited number of open trials with a low number of subjects included, suggest that AIT can reduce the risk of developing asthma symptoms in subjects with ARC.[9-13] The Grazax Asthma Prevention (GAP) trial is the first to evaluate this effect of AIT in a large, randomized, double-blind, and placebo-controlled trial.

The SQ grass sublingual immunotherapy (SLIT) tablet (GRAZAX 75,000 SQ-T/2,800 BAU, ALK, Hørsholm, Denmark) is a rapid-dissolving tablet-based allergy immunotherapy product.

The objective of the GAP trial was to investigate the effect of 3 consecutive years of treatment with the SQ grass SLIT tablet compared with placebo on the risk of developing asthma (defined by the fulfilment of a set of specific, predefined asthma diagnosis criteria) in children with grass pollen ARC but no existing signs or symptoms of asthma. The effect was investigated throughout the trial, which comprised a screening period, a 3-year treatment period, and a 2-year follow-up period. In addition, the asthma status at the end of trial was assessed. The trial also assessed the impact on ARC symptoms and medication use and immunological markers. The trial is the largest pediatric AIT trial conducted to date and is the first large, double-blind, placebo-controlled trial assessing prevention of asthma in a pediatric population. The results of the trial could potentially impact the medical purpose of the SQ grass SLIT tablet.

Abbreviations used

AE:	Adverse event
AIT:	Allergy immunotherapy
ARC:	Allergic rhinoconjunctivitis
FAS:	Full analysis set
GAP:	Grazax Asthma Prevention
GPS:	Grass pollen season
ICH:	International Conference on Harmonization
IMP:	Investigational medicinal product
NNT:	Number needed to treat
OR:	Odds ratio
SAE:	Serious adverse event
SLIT:	Sublingual immunotherapy
SPT:	Skin prick test
VAS:	Visual analog scale

METHODS

The trial was a 1:1 randomized, parallel-group, double-blind, placebo-controlled trial, designed and conducted in accordance with the principles of the Declaration of Helsinki[14] and in compliance with the Good Clinical Practice guidelines of the International Conference on Harmonization (ICH).[15] Relevant national ethics committees and regulatory authorities approved the trial protocol and amendments.

The trial (EudraCT: 2009-011235-12, NCT: NCT01061203) was conducted at 101 sites in 11 European countries and included 812 children.[16] Eligible children were 5 to 12 years old at randomization with a positive skin prick test (SPT) response (wheal diameter ≥3 mm) and specific IgE to *Phleum pratense* (≥IgE class 2; ≥0.70 kU/L); grass ARC requiring allergy pharmacotherapy during 2 grass pollen seasons (GPSs) prior to randomization; and no medical history of asthma and/or wheezing and no signs of asthma within the last 2 years or since the fifth birthday. Written informed consent was obtained from parents/guardians of the participants.

Randomization was performed by the sponsor in blocks of 6, using the SAS system for Windows (SAS Institute, Cary, NC). Randomized treatment assignment was stratified for trial site. The trial was an add-on trial, where all children, in addition to the investigational medicinal product, were offered allergy and asthma pharmacotherapy. Children randomized to both placebo and AIT received relevant pharmacotherapy during the 5-year trial period.[17,18]

The grass SLIT tablet contains *Phleum pratense* grass pollen allergen extract and is formulated as a rapidly dissolving oral lyophilisate for sublingual administration. The daily dose is 1 tablet for at-home administration, except first intake, which is to be administered under medical supervision. The placebo intervention was tablets identical to the grass SLIT tablets but without pollen extract.

The trial comprised a screening period, a 3-year treatment period, and a 2-year follow-up period (see Fig E1 in this article's Online Repository at www.jacionline.org). Details of the trial design[16] are found in the Methods section in the Online Repository (available at www.jacionline.org).

To evaluate whether asthma developed since the previous visit, the following were assessed at each trial visit: Asthma physical examination—child presenting at the visit with present wheezing during normal breathing or presenting with prolonged phase of forced exhalation. Assessment of asthma medical history in the period since the last visit, which included presence of the following asthma symptoms: (1) wheezing, (2) cough lasting for more than 10 consecutive days, (3) shortness of breath, and (4) chest tightness. In addition, the children were asked whether they had used any asthma medication to treat respiratory or pulmonary symptoms since the last visit. Asthma medications included: β_2-agonists, systemic corticosteroid, inhaled corticosteroids, leukotriene receptor antagonists, long-acting β_2-agonist, sustained-release theophylline, and cromolyn sodium. Assessment of lung function (FEV_1 reversibility).

The primary endpoint was time to onset of asthma measured in days from randomization. Asthma was defined as the fulfillment of 1 or more of the following 3 criteria, which were evaluated at each trial visit for each time period "since last visit": (1) At least 1 episode of wheeze, cough, shortness of breath or chest tightness, and a change in FEV_1 ≥12% after β_2-agonist administration.

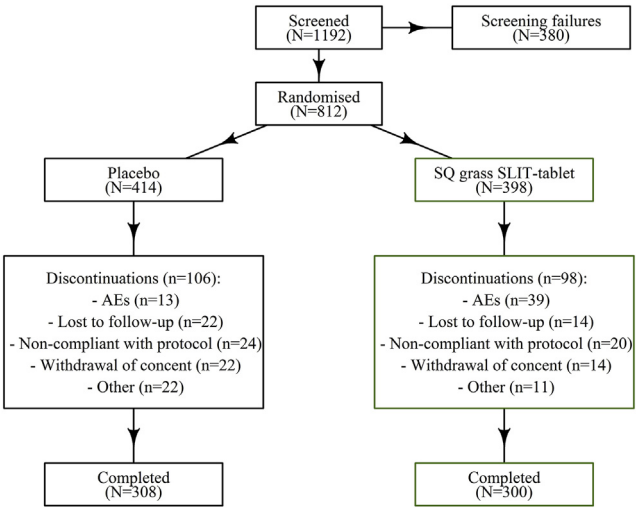

FIG 1. Flow diagram of subject disposition.

(2) Wheezing with or without prolonged phase of forced exhalation observed at physical examination and an intake of asthma medication, which resulted in a clinically relevant effect. (3) Wheezing with or without prolonged phase of forced exhalation observed at physical examination and a change in FEV_1 ≥12% after β_2-agonist administration. According to the trial protocol, the onset of asthma was considered a binary event (asthma yes/no) that only could occur once per subject. Thus, the children were only classified as having asthma if the criteria were met at a single given visit, and clinical information from previous or subsequent visits was not taken into consideration when this classification was made. Children with frequent reporting of asthma symptoms but no observable reversible impairment of lung function at trial visits were not classified as having asthma. Likewise reclassification was not done if a child, once classified as having asthma, reported no asthma symptoms or asthma medication use at subsequent visits.

Asthma symptom and asthma medication status at end of trial (in the period from winter visit in year 5 to GPS visit in year 5) was a predefined secondary asthma endpoint. The proportion of children with asthma symptoms and/or asthma medication use during the course of the trial was further characterized *post hoc* and analyzed for the entire trial and the follow-up period. In addition, the number of children needed to treat (NNT) to prevent 1 additional child from having asthma symptoms and using asthma medication was analyzed *post hoc* for the 2-year follow-up period.

Secondary rhinoconjunctivitis endpoints included visual analog scale (VAS) score of ARC symptoms (yearly at the GPS visit), VAS score of ARC symptoms (daily for 2 weeks prior to GPS visit in year 5), ARC medication score (daily for 2 weeks prior to GPS visit in year 5), and immunology (IgE and IgG_4). Safety assessments included recording of adverse events (AEs), events of special interest (including discontinuations due to AEs), serious AEs (SAEs) (according to ICH Harmonized Tripartite Guideline E2A, Step 5)[19] and physical examinations. AEs were coded using Medical Dictionary for Regulatory Activities (ICH) version 18.0.

The statistical software used was SAS version 9.4 and R version 3.2.2 (R Foundation, Vienna, Austria). Details of the sample size calculation and statistical methodology are provided in the Methods section in the Online Repository. All statistical analyses were carried out by the sponsor.

RESULTS

Subject disposition is shown in Fig 1. The total analysis set included 1192 children. Of these, 380 (32%) were screening failures. The full analysis set (FAS) (and the identical safety analysis set) included 812 randomized children; 414 on placebo and 398 on the SQ grass SLIT tablet. Of all randomized children, 608 children (75%) completed the trial. There was no overall difference in discontinuations between treatment groups but a higher proportion of children discontinued due to AEs in the active group (n = 39) compared with in the placebo group (n = 13). No children were excluded from the analysis data sets.

TABLE I. Asthma endpoints

Primary endpoint: time to onset of asthma by protocol definition (FAS)						
		Diagnosed with asthma				
Group	n	n	Proportion	HR*	95% CI	*P* value
Placebo	414	39	9.42	0.9	0.57-1.43	.667
SQ grass SLIT tablet	398	34	8.54			

Secondary endpoint: asthma symptom and medication status since last visit at end of trial (assessed at GPS visit in year 5)†						
		With asthma symptoms or asthma medication use				
Group	n	n	Proportion	OR‡	95% CI	*P* value
Placebo	398	81	20.35	0.66	0.45-0.97	.036
SQ grass SLIT tablet	377	59	15.65			

*Hazard ratio SQ grass SLIT tablet versus placebo.
†For subjects withdrawn prior to winter visit in year 5, the last observation carried forward of "asthma medical history" and "asthma medication history" was applied. If no data were available, no imputation was performed for the subject.
‡Odds ratio SQ grass SLIT tablet versus placebo.

The treatment groups were similar with regard to baseline demographics (see Table E1 in this article's Online Repository at www.jacinonline.org).

The primary efficacy analysis of time to onset of asthma as defined by the prespecified asthma diagnosis criteria showed no difference between SQ grass SLIT tablet and placebo (Table I). Seventy-three children fulfilled the asthma diagnosis criteria, but some of these children had no signs or symptoms of asthma at the subsequent visits during the 2-year follow-up period. Of the 73 children fulfilling the criteria, 51 reported asthma symptoms or use of asthma medication during the 2-year follow-up period, and only 43 of those (29 children on placebo and 14 children on SQ grass SLIT tablet) reported both asthma symptoms and asthma medication use during that period. Of the 739 children not diagnosed with asthma according to protocol criteria, 147 children reported asthma symptoms or use of asthma medication during the 2-year follow-up period, and 66 of those children (41 children on placebo and 25 children on SQ grass SLIT tablet) reported both asthma symptoms and medication use during that period.

The predefined efficacy analysis of asthma symptom and medication status at the end of the trial (assessed at GPS visit in year 5) showed that fewer children on SQ grass SLIT tablet treatment compared with placebo-treated children experienced asthma symptoms or used asthma medication; odds ratio (OR) = 0.66; $P = .036$, corresponding to a relative risk reduction of 29.4% (Table I).

The proportion of children experiencing asthma symptoms or using asthma medication was further characterized *post hoc* each year of the 5-year trial period. The OR for experiencing asthma symptoms or using asthma medication on SQ grass SLIT tablet versus placebo treatment was in favor of the SQ grass SLIT tablet each year, with statistical significance (P value < .05) from year 2 onward (see Fig E2 in this article's Online Repository at www.jacionline.org); the corresponding relative risk reductions ranged from 36.2% to 50.7%.

When the analysis was repeated for the winter visits alone or the GPS visits alone (Fig 2), the pattern was similar, with

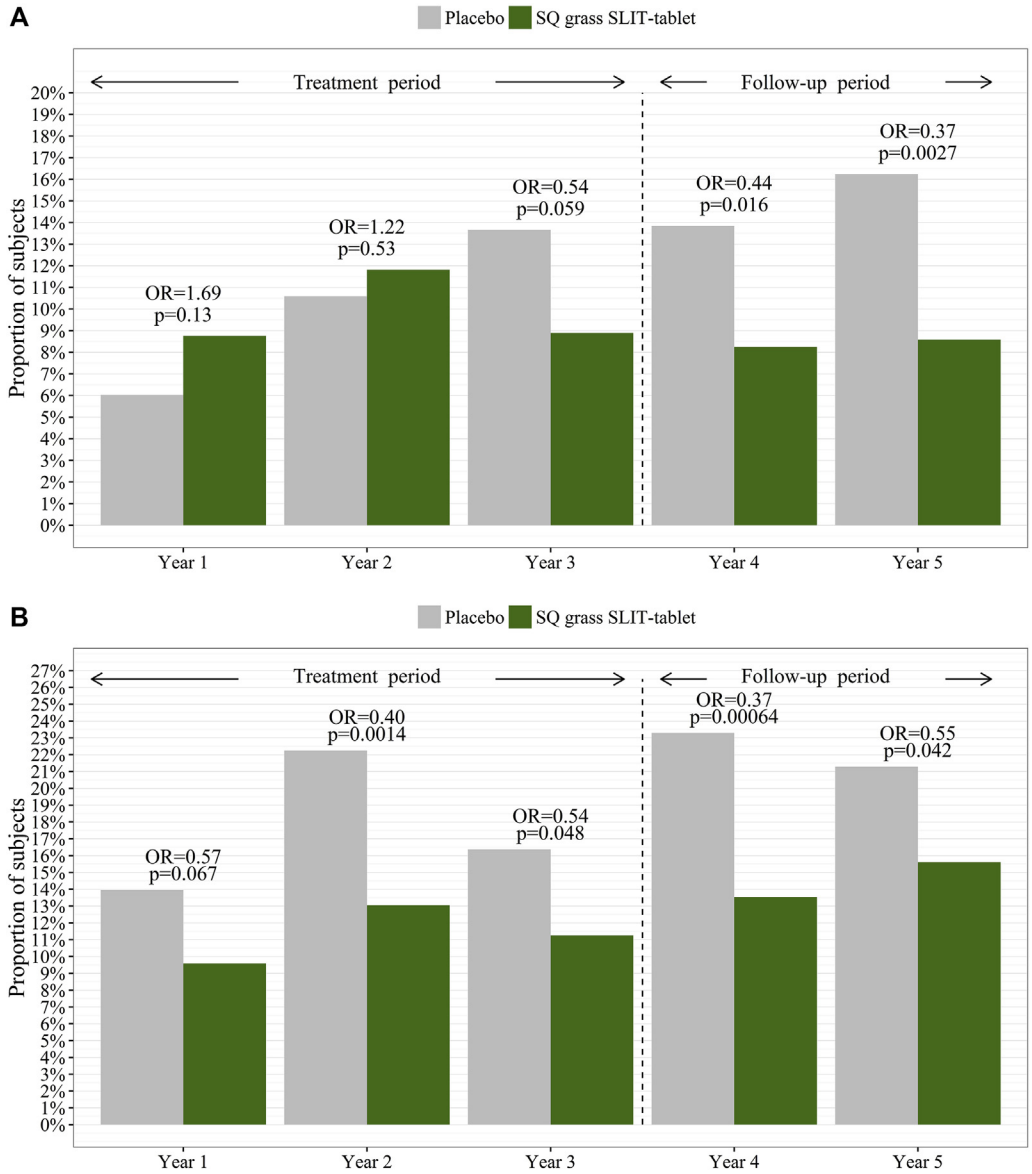

FIG 2. Proportion of subjects experiencing asthma symptoms or asthma medication use reported at winter visits **(A)** and summer visits **(B)**.

differences in favor of SQ grass SLIT tablet treatment. Thus, the treatment effect was year round. The difference between the 2 treatment groups became more pronounced with time.

The treatment effect on asthma symptoms (see Fig E3 in this article's Online Repository at www.jacionline.org) was primarily due to a reduction in wheeze, chest tightness, and shortness of breath. The treatment effect on asthma medication use (see Fig E4 in this article's Online Repository at www.jacionline.org) was primarily due to a reduction in β_2-agonist use.

Children treated with the SQ grass SLIT tablet also had a reduced risk of experiencing asthma symptoms and/or using asthma medication when longer time periods were analyzed. This was the case both when assessing the entire 5-year trial period (asthma symptoms: OR = 0.71, P = .025; asthma medication: OR = 0.72, P = .047; asthma symptoms and asthma medication use: OR = 0.67, P = .028) and even more pronounced when assessing the 2-year follow-up period (asthma symptoms: OR = 0.55, P = .017; asthma medication: OR = 0.34, P = .002; asthma symptoms and asthma medication use: OR = 0.28, P = .0004, relative risk reduction of 71%) (Fig 3).

The SQ grass SLIT tablet reduced the proportion of children experiencing asthma symptoms and/or using asthma medication during the follow-up period. Also, when including documented FEV_1 reversibility ≥12% in the clinical characterization of the children, the proportion fulfilling the criteria was lower when treated with the SQ grass SLIT tablet than with placebo (P = .028) (Fig 4).

The NNT to prevent 1 additional child in having asthma symptoms, using asthma medication as well as having both asthma symptoms and asthma medication use during the 2-year follow-up was analyzed. For asthma symptoms, NNT = 12; for asthma medication use, NNT = 11; and for both asthma

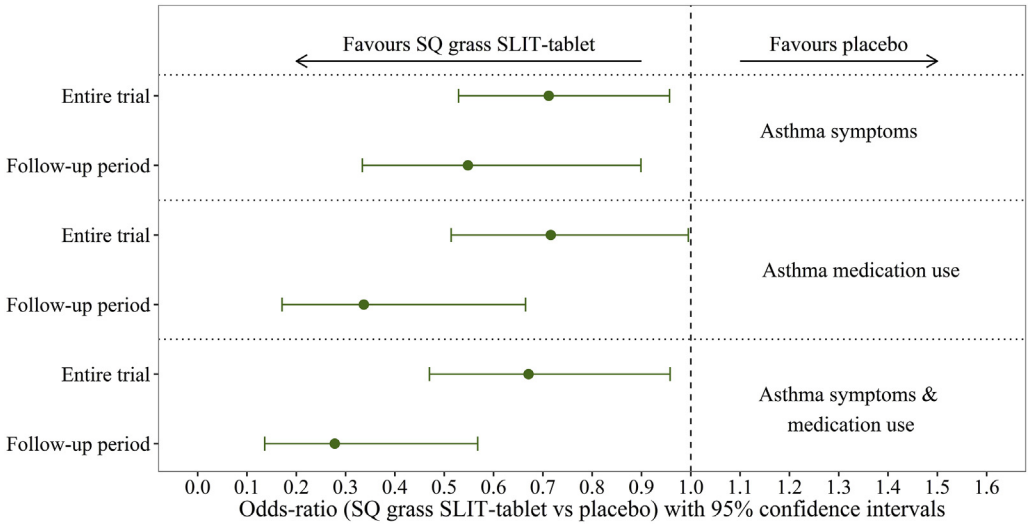

FIG 3. OR for experiencing asthma symptoms, using asthma medication, and both, shown for the entire trial period and for the 2-year follow-up period.

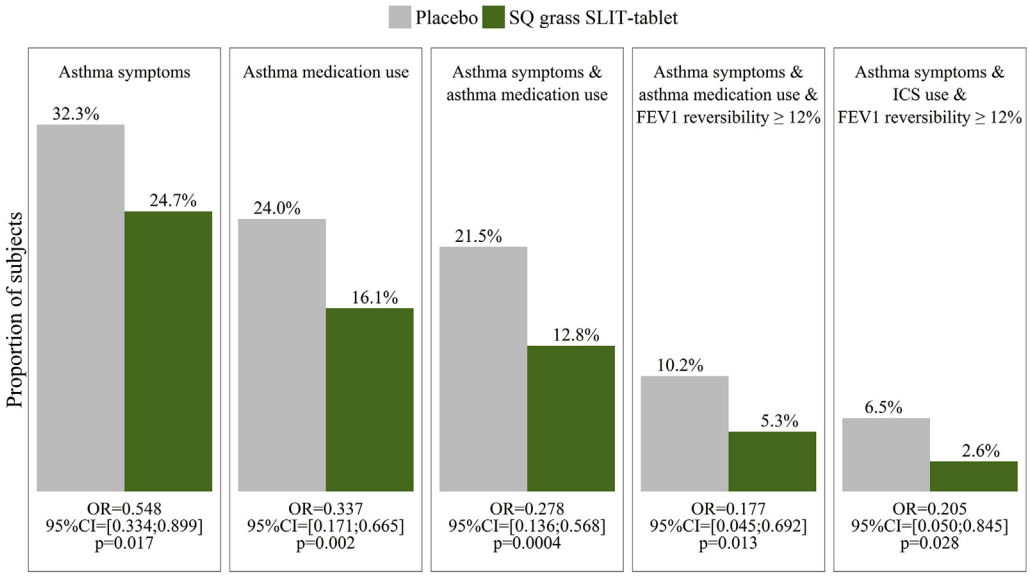

FIG 4. Proportion of subjects experiencing asthma symptoms, asthma medication use, asthma symptoms and asthma medication use, asthma symptoms and asthma medication use, and having a documented FEV_1 reversibility ≥12%, asthma symptoms and inhaled corticosteroids use, and documented FEV_1 reversibility ≥12% during the 2-year follow-up period.

symptoms and asthma medication use, NNT = 10. The treatment effect (OR for SQ grass SLIT tablet vs placebo) was independent of age. However, younger children had a higher predicted probability of developing asthma symptoms and using asthma medication than older children had. Thus, the younger the children were at treatment start, the greater the percentage was prevented from having asthma symptoms and using asthma medication during the follow-up period. Consequently, the NNT to prevent 1 additional child from having asthma symptoms and asthma medication use during the 2-year follow-up period increased with age, with NNT = 6 for children 5 years of age and NNT = 20 for children 12 years of age (see Table E2 in this article's Online Repository at www.jacionline.org).

The ARC symptoms were evaluated yearly at the GPS visits by individual rating on a VAS of how the children had perceived their symptoms during the preceding week. The VAS score was evaluated on a scale from 0 (no symptoms) to 100 mm (severe symptoms). For all 3 treatment years and the 2 follow-up years, the adjusted mean for the ARC VAS score was statistically significantly lower (ie, lower severity of symptoms) in the SQ grass SLIT tablet group compared with the placebo group (relative differences of 22% to 30%) (Table II).

In addition to the yearly rating on a VAS at the GPS visits, the ARC symptoms were also rated daily in a diary during 14 days prior to the GPS visit in year 5 (2015). The adjusted mean was statistically significantly lower in the SQ grass SLIT tablet group

TABLE II. Rhinoconjunctivitis endpoints

Secondary endpoint: yearly ARC VAS score during the GPS in years 1-5 (FAS)					
	Adjusted mean (95% CI)				
	Placebo	SQ grass SLIT tablet	Absolute difference (95% CI)	Relative difference*	*P* value
Year 1	25.5 (21.9-29.1)	19.4 (15.9-22.9)	6.1 (2.7-9.4)	24	<.001
Year 2	28.8 (25.1-32.5)	20.3 (16.8-23.9)	8.4 (5.0-11.9)	29	<.001
Year 3	31.1 (27.4-34.8)	21.9 (18.3-25.5)	9.23 (5.7-12.8)	30	<.001
Year 4	30.3 (26.5-34.0)	23.5 (19.9-27.1)	6.7 (3.1-10.3)	22	<.001
Year 5	25.5 (21.7-29.3)	19.6 (16.0-23.3)	5.8 (2.2-9.4)	23	.002
Secondary endpoint: daily VAS score during the GPS 2015 (FAS)					
	Adjusted mean (95% CI)				
	Placebo	SQ grass SLIT tablet	Absolute difference (95% CI)	Relative difference*	*P* value
GPS 2015	19.5 (16.9-22.4)	15.2 (12.7-17.9)	4.37 (1.35-7.40)	22	.005
Secondary endpoint: daily ARC medication score during the GPS 2015 (FAS)					
	Adjusted mean (95% CI)				
	Placebo	SQ grass SLIT tablet	Absolute difference (95% CI)	Relative difference*	*P* value
GPS 2015	6.7 (5.6-7.9)	4.9 (3.9-6.0)	1.8 (0.9-2.7)	27	<.001

*Percentage of reduction in Grazax relative to placebo.

than in the placebo group with a relative difference of 22% in favor of SQ grass SLIT tablet ($P = .005$) (Table II).

The use of ARC medication was recorded daily in a diary during 14 days prior to the GPS visit in year 5 (2015) and the medication score was calculated (see Table E3 and the Methods section in this article's Online Repository at www.jacionline.org). The adjusted mean of the daily ARC medication score in the GPS of year 5 was statistically significantly lower in the SQ grass SLIT tablet group than in the placebo group; relative reduction SQ grass SLIT tablet versus placebo was 27% (Table II).

The mean levels of grass pollen–specific IgE were similar at baseline for the 2 treatment groups. Specific IgE levels increased during the 5-year trial period. The mean increase from baseline in $\log_{10}$-transformed–specific IgE (see Fig E5 in this article's Online Repository at www.jacionline.org) was significantly lower for SQ grass SLIT tablet–treated children than for placebo-treated children after 3 years of treatment and after the 2-year follow-up period ($P < .001$). The same pattern was seen for serum total IgE (see Fig E6 in this article's Online Repository at www.jacionline.org). The treatment effect on grass pollen–specific IgE levels was paralleled by a reduced SPT response to grass pollen allergens in SQ grass SLIT tablet–treated children at the study's end ($P < .05$), which was 2 years after completion of the SQ grass SLIT tablet treatment (see Fig E7 in this article's Online Repository at www.jacionline.org).

The mean levels of grass pollen–specific IgG_4 were similar at baseline for SQ grass SLIT tablet and placebo. The mean changes from baseline in $\log_{10}$-transformed–specific IgG_4 (see Fig E8 in this article's Online Repository at www.jacionline.org) showed a statistically significant increase with SQ grass SLIT tablet compared with placebo both after 3 years of treatment and after the 2-year follow-up ($P < .001$).

The already established safety profile of the SQ grass SLIT tablet was confirmed. Overall, 765 children (94%) reported a total of 7797 AEs during the trial. A similar proportion of the children in the SQ grass SLIT tablet group and placebo group reported AEs (95% vs 93%). Most of the reported AEs (88%) did not lead to investigational medicinal product (IMP) interruptions or discontinuations, and the vast majority of AEs (97%) were resolved. This pattern applied to both treatment groups (Table III). Of the overall trial population, 73 children (9%) reported a total of 98 SAEs. More children in the SQ grass SLIT tablet group (11%) reported SAEs than did children from the placebo group (7%) (Table III). Fifty-two children (6%) discontinued the trial due to a total of 89 AEs. More children in the SQ grass SLIT tablet group (10%) discontinued the trial due to AEs than did children in the placebo group (3%). The most frequently reported AEs (AEs reported in ≥5% of the children in the SQ grass SLIT tablet group) were nasopharyngitis, allergic conjunctivitis, oral pruritus, cough, and gastroenteritis (Fig 5).

The proportion of the AEs assessed as possibly related to the IMP was 15% in the SQ grass SLIT tablet group and 4% in the placebo group (Table III). The most frequently reported IMP-related AEs were oral pruritus, throat irritation, tongue pruritus, and ear pruritus. A greater proportion of children in the SQ grass SLIT tablet group (n = 244, 61%) reported IMP-related AEs than children in the placebo group did (n = 95, 23%). The majority of all IMP-related AEs were mild (74%) or moderate (23%) in severity. This pattern applied to both treatment groups.

For the 2 most frequently reported IMP-related AEs (oral pruritus and throat irritation), the overall median onset was 1 day (on the day of first IMP intake). The median number of days from start of the AE until the event no longer occurred was 14.5 days for oral pruritus and 5 days for throat irritation for SQ grass SLIT tablet–treated children.

No deaths occurred during the trial. No events were reported as serious systemic allergic reactions. Seven of the SAEs were assessed as possibly related to the IMP; 1 placebo-treated child: type 1 diabetes; 6 SQ grass SLIT tablet–treated children: dyspnea, generalized tonic-clonic seizure, asthma, immune thrombocytopenic purpura, anemia, abdominal pain (see the Online Repository for details).

TABLE III. Overview of AEs

	Placebo group n = 414		SQ grass SLIT tablet group n = 398		Overall n = 812	
Treatment group	**n (%)**	**e (%)**	**n (%)**	**e (%)**	**n (%)**	**e (%)**
All AEs	385 (93)	3772 (100)	380 (95)	4025 (100)	765 (94)	7797 (100)
Causality						
Unlikely	378 (91)	3612 (96)	354 (89)	4313 (85)	732 (90)	7025 (90)
Possible	95 (23)	160 (4)	244 (61)	612 (15)	339 (42)	772 (10)
Severity of all AEs						
Mild	369 (89)	2834 (75)	367 (92)	3090 (77)	736 (91)	5924 (76)
Moderate	262 (63)	837 (22)	248 (62)	834 (21)	510 (63)	1671 (21)
Severe	50 (12)	101 (3)	59 (15)	101 (3)	109 (13)	202 (3)
By worst case*						
Mild	114 (28)		122 (31)		236 (29)	
Moderate	221 (53)		199 (50)		420 (52)	
Severe	50 (12)		59 (15)		109 (13)	
Seriousness						
Serious	30 (7)	36 (<1)	43 (11)	62 (2)	73 (9)	98 (1)
Nonserious	385 (93)	3736 (>99)	380 (95)	3963 (98)	765 (94)	7699 (99)
Action taken						
NA†	24 (6)	68 (2)	27 (7)	62 (2)	51 (6)	130 (2)
None	376 (91)	3354 (89)	362 (91)	3470 (86)	738 (91)	6824 (88)
Temporarily interrupted	148 (36)	333 (9)	155 (39)	423 (11)	303 (37)	756 (10)
IMP discontinued	12 (3)	17 (<1)	38 (10)	70 (2)	50 (6)	87 (1)
Outcome						
Recovering	12 (3)	19 (<1)	16 (4)	18 (<1)	28 (3)	37 (<1)
Recovered	385 (93)	3657 (97)	379 (95)	3916 (97)	764 (94)	7573 (97)
Not recovered	73 (18)	88 (2)	68 (17)	86 (2)	141 (17)	174 (2)
Unknown	6 (1)	8 (<1)	4 (1)	5 (1)	10 (1)	13 (<1)
Leading to trial discontinuation						
Yes	13 (3)	18 (<1)	39 (10)	71 (2)	52 (6)	89 (1)
No	383 (93)	3754 (>99)	369 (93)	3954 (98)	752 (93)	7708 (99)

e, Number of events; *NA*, not applicable.
*By worst case implies that each subject was only counted once by the AE of the worst severity experienced throughout the trial; when summarizing AEs by worst case, e and %e are not applicable.
†Action taken was not filled in for AEs occurring after the end of treatment (ie, during the follow-up period).

DISCUSSION

ARC is a well-established risk factor for the development of asthma.[20-22] Treating the underlying cause of allergic rhinitis could potentially represent an attractive modality for the prevention of asthma in allergic children.

The GAP trial is the first large, randomized, double-blind, placebo-controlled trial to investigate asthma prevention with AIT. When the trial was initiated, there was (and still is) no consensus regarding an appropriate and generally applicable diagnostic algorithm for the identification of asthmatic children in the early stage of the disease. The asthma diagnosis criteria used in the GAP trial relied to a large degree on the demonstration of reversible impairment of lung function assessed in different ways: reported asthma symptoms and a FEV_1 change ≥12% after β_2-agonist administration, observed wheezing that improved with asthma medication, or observed wheezing and a FEV_1 change ≥12% after β_2-agonist administration.

In the GAP trial, 73 children were diagnosed with asthma according to the prespecified criteria but not all had signs or symptoms of asthma when evaluated during the 2-year follow-up period or at the end of the trial. The data obtained in the trial indicate that onset of asthma may not be a dichotomous "yes/no" event but rather a dynamic process of symptoms and medication patterns. The data showed that some children diagnosed with asthma did not show signs of asthma later in the trial, and that many children not diagnosed with asthma did show signs suggestive of asthma. The data obtained in the trial indicate that an appropriate asthma diagnosis in this particular population should not be based on a single time point evaluation with emphasis on the demonstration of reversible lung function impairment but rather should rely on a combined clinical assessment obtained over a longer observation period, which is normally done in daily practice.[23]

The trial did not show an effect of SQ grass SLIT tablet treatment on the time to onset of asthma as defined by the fulfilment of the prespecified asthma diagnosis criteria. However, when looking at asthma symptoms or asthma medication use, the trial showed a clear and consistent effect of SQ grass SLIT tablet treatment. The effect was apparent both during the GPS and during winter, with wheeze, chest tightness, and shortness of breath being most important for the observed differences in asthma symptoms between SQ grass SLIT tablet– and placebo-treated children.

The observed treatment effect on asthma medication use increased with time due to a continuous increase over time in the proportion of children with asthma medication use in the placebo group.

The SQ grass SLIT tablet treatment reduced the proportion of children with asthma symptoms or use of asthma medication when evaluated at the end of trial. SQ grass SLIT tablet treatment also reduced the proportion of children reporting any asthma symptoms during the entire 5-year trial period and during the

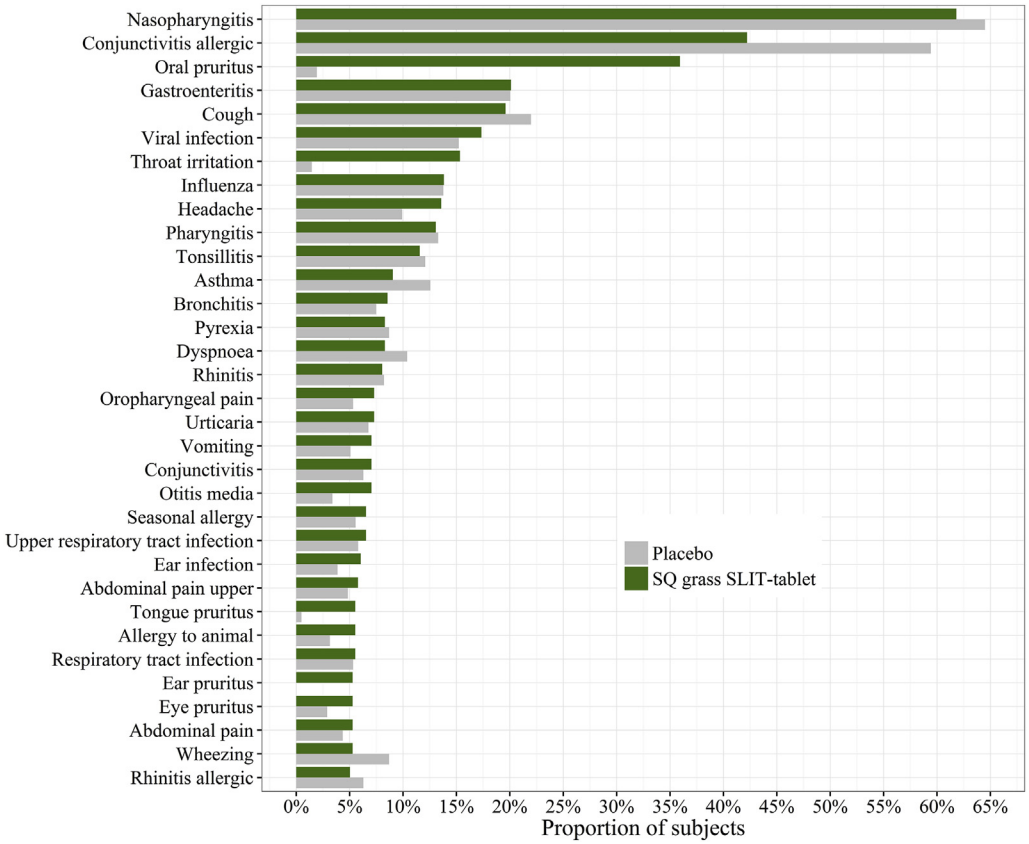

FIG 5. Percentage of subjects with the most frequently reported AEs (≥5% of the subjects in the active group).

2-year posttreatment period. Thus, SQ grass SLIT tablet treatment prevented asthma symptoms in the trial population, as an added benefit to the treatment effect on ARC. This was apparent when assessed during the entire 5-year trial period, during the 2-year follow-up period, and at the trial's end.

The importance of starting SQ grass SLIT tablet treatment early in life was evident, as the NNT increased with age as younger children had a higher risk of developing asthma symptoms and asthma medication use.

The effectiveness of SQ grass SLIT tablet on prevention of asthma symptoms in allergic children is indirectly supported by a large retrospective cohort study of patients with allergic rhinitis but without asthma (n = 118,754).[24] This study found that in patients treated with AIT (n = 2,431), the risk of "incident asthma" (defined by symptoms and 2 or more prescriptions of inhaled corticosteroids) was lower than in patients who did not receive AIT (risk ratio = 0.60, 95% CI: 0.42-0.84) after a follow-up period of 5 years. The AIT group was primarily treated with subcutaneous immunotherapy with only 10 patients in the analysis being treated with SQ grass SLIT tablets (conducted shortly after regulatory approval); however, none of these 10 patients had asthma in the follow-up period from 2007 to 2012. The investigators suggested that AIT use in routine care may provide a 40% risk reduction for the development of asthma in patients with AR.

The SQ grass SLIT tablet provided statistically significant reductions of the ARC symptoms of 22% to 30% when compared with placebo ($P < .002$) during the 3 treatment years and the 2 follow-up years. The VAS diary score on ARC symptoms confirmed the fifth year result with a 22% reduction in the SQ grass SLIT tablet group relative to that in the placebo group ($P = .005$). In addition to a reduction of symptoms, children in the SQ grass SLIT tablet group also had reduced use of ARC medications by 27% relative to the placebo group ($P < .001$).

In a previous trial investigating the long-term and disease-modifying effect of the SQ grass SLIT tablet in adults, the mean ARC symptom score was reduced by 25% to 36% in the active group relative to the placebo group over the 5 years of the trial.[25] During the 3 years of treatment and the 2-year follow-up, the analysis of ARC symptoms by VAS scores in that trial also showed statistically significantly lower scores for the SQ grass SLIT tablet group of 25% to 37% when compared with the placebo group ($P \leq .01$).[26] Thus, the posttreatment sustained effect demonstrated in the GAP trial confirms the disease-modifying property of the SQ grass SLIT tablet in children and is in line with previous trial results from adults.

In conclusion, SQ grass SLIT tablet treatment prevented asthma symptoms and asthma medication use in children with grass pollen ARC and no preexisting asthma. This disease-modifying effect was greatest in the follow-up period and was apparent both during GPS and during winter. SQ grass SLIT tablet treatment also significantly reduced ARC symptoms and medication use. The effect persisted 2 years posttreatment and was comparable to what has previously been established in an adult population. The clinical findings were paralleled by the immunological findings showing that at the trial's end, SQ grass

SLIT tablet–treated children had lower total IgE, lower grass pollen–specific IgE, and reduced SPT reactivity to grass pollen than did placebo-treated children.

The SQ grass SLIT tablet had no effect on the time to onset of asthma (primary endpoint) when diagnosed according to the predefined criteria; few children fulfilled these criteria and clinical phenotypes were not stable over the course of the trial.

No new safety signals were identified, and the safety data confirmed the already known safety profile.

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Clinical implications: The data presented in this article demonstrate that treatment with the SQ grass SLIT tablet modifies the grass pollen allergic disease. The disease modification is expressed by preventing progression from allergic rhinoconjunctivitis symptoms to development of asthma symptoms and reducing rhinoconjunctivitis symptoms and medication use during and after treatment termination.

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METHODS

Details of the trial design

The trial was initiated during the fourth quarter of 2009 with recruitment and screening activities until after the GPS of 2010. To rule out asthma before randomization, 2 screening visits took place: 1 outside the pollen season (V1) and 1 during the pollen season (V2). The purpose of screening V1 was to investigate the subject eligibility in terms of all inclusion and exclusion criteria. At the screening V2 (placed in the GPS), all subjects were examined according to the prespecified asthma diagnosis criteria. Between screening V2 and the randomization visit, diurnal peak expiratory flow was assessed for 2 weeks. Subjects diagnosed with asthma were per definition screening failures. After the end of the GPS of 2010, eligible subjects were randomized to grass SLIT tablet or placebo for 3 consecutive years. The trial continued with double-blinded follow-up for an additional 2 years. The trial included "winter visits" (V4, V6, V8, V11, and V13) and "GPS visits" (V5, V7, V9, V12, and V14) each of the 5 years, where asthma status was assessed. In addition there was an "end of treatment visit" (V10) and a telephone contact prior to V14 informing about ARC home monitoring during the GPS of 2015. All randomized subjects were to continue in the trial for 5 years. Subjects experiencing asthma symptoms during the trial were instructed to call the investigator for an unscheduled visit. The end of trial visit (V15) took place after the GPS of 2015.

Details of sample size calculation

The sample size calculations were based on 3 years of observation, because the original protocol defined an interim analysis after the 3 treatment years. This was amended to a final analysis after 5 years. Because randomization was completed at the time of the amendment (February 27, 2012), the amendment had no influence on the sample size.

Sample size calculation was entirely based on the preventive allergy treatment (PAT) trial.[E1] In the PAT trial, 71% (60 of 85) of children in the active group were without asthma after 3 years of immunotherapy and 51% (40 of 78) were without asthma in the open control group (in-house data).

With a sample size in each group of 158, with a total number of 114 asthma events required (36%), a 0.05 level 2-sided log-rank test for equality of survival curves would have 95% power to detect a difference between a proportion of 71% without asthma in the grass SLIT tablet group and 51% without asthma in the placebo group after 3 years.

Assuming a 20% dropout per year, a total of 618 ($158 \times 2/0.8^3$) subjects were required to be randomized.

Details of statistical methodology

Demography and baseline characteristics. Demographic and baseline characteristics were summarized by treatment group displaying number of subjects, mean ± SD, median, 5% quantile, 25% quantile, 75% quantile, 95% quantile, minimum and maximum for continuous variables, and frequency tables for categorical variables.

Extent of exposure and definition of GPS. Number of daily IMP doses used was calculated as the difference between the number of daily doses dispensed and the number of daily doses returned.

IMP compliance percentage was calculated as the number of daily doses used divided by the duration of IMP treatment period in days (number of days from IMP treatment start to IMP treatment stop) and multiplied with 100.

Exposure in treatment years was calculated as the number of daily doses used divided by 365.

Duration of IMP treatment period, number of tablets used per subject, IMP compliance, and treatment years were displayed in summary tables by treatment group.

The GPS was defined for each pollen region as starting on the first day of 3 consecutive days with grass pollen count ≥10 grains/m^3 and ending on the last day of the last occurrence of 3 consecutive days with grass pollen count ≥10 grains/m^3. Start and stop dates of each GPS for each pollen region were determined and described in the statistical analysis plan before unblinding.

The defined GPS was used to assess whether the date of onset of asthma or suspicion of asthma was within the GPS.

Endpoints. The primary efficacy analysis of the primary endpoint "time to onset of asthma" as defined by the protocol criteria (1) to (3) was performed with a Cox proportional hazards regression analysis. The model included treatment group as a fixed effect. Age at randomization was included as a covariate. Country was included as a random effect assumed to follow a gamma distribution. Thus this was a shared Cox gamma frailty model. Based on this model, the estimated adjusted hazard ratio for time to onset of asthma for grass SLIT tablet compared with placebo was presented together with the 2-sided 95% CI and a *P* value. All subjects provided data to the primary analysis.

The proportion of subjects having no asthma symptoms and no asthma medication use since last visit at the end of the trial (V13 to V14) was summarized by treatment group and visit without imputation.

The analysis of the odds of not having any asthma symptoms and any asthma medication use between V13 and V14 was performed with a generalized logistic regression analysis. Treatment was included as a fixed effect, age as a covariate, and country as a random effect. The adjusted OR for having an asthma symptom– and asthma medication–free period (V13 to V14) at the end of trial visit was estimated and the 2-sided 95% CI presented. For subjects discontinued before the end of the trial (V13 to V14), asthma symptoms and asthma medication use was imputed by last observation being carried forward. No imputation was done for subjects discontinued before first assessment of asthma symptoms and asthma medication use (V4 or an unscheduled visit).

The proportion of subjects with asthma symptoms and asthma medication use since last visit was calculated by treatment group without imputation for each visit, each year, the follow-up period, and the entire trial period. Odds for each binary outcome (yes/no) were analyzed by visit, by year, by period, and for the entire trial.

The analysis by visit and by year was done with a repeated measurement generalized linear mixed model (GLMM) with a logit link function. The dependent variable was binary (yes/no). The explanatory variables included as fixed effects were age at randomization, treatment, visit/year, and treatment–visit/year interaction. Subject and country were included as random effects. The integral over the random effects space was approximated by the Laplace approximation.

The by-period analysis was done with a repeated measurement GLMM with a logit link function. The dependent variable was binary (yes/no). The explanatory variables included as fixed effects were age at randomization, treatment, period, and treatment-period interaction. Subject was included as a random effect. The estimated OR for grass SLIT tablet versus placebo was reported along with 95% CI and a *P* value. The estimate was subject-specific. The multivariate *t* distribution was used for CI and *P* value.

The analysis for the entire trial was done with a GLMM with a logit link function. The dependent variable was binary (yes/no). The explanatory variables included as fixed effects were age at randomization and treatment. Country was included as a random effect. The estimated OR for grass SLIT tablet versus placebo was reported along with 95% CI and a *P* value. The estimate was subject-specific. The multivariate *t* distribution was used for CI and *P* value.

The relative risk (RR) and relative risk reduction (RRR) of grass SLIT tablet versus placebo are calculated based on the estimated coefficients (coef) in the GLMM:

$$RRR = 1 - RR = \frac{e^{coef_Grazax}/1+e^{coef_Grazax}}{e^{coef_Placebo}/1+e^{coef_Placebo}}$$

The yearly VAS scoring of ARC symptoms at the GPS visits was evaluated with a repeated measures analysis. Treatment, visit, and treatment by visit were included as fixed effects; baseline VAS as a covariate; and country as a random effect. Between-group differences in adjusted means with 95% CI and *P* value were presented for each visit.

The average daily VAS scoring of ARC symptoms prior to the 2015 GPS visit (V14) was evaluated with a linear mixed effect (LME) model. The

average VAS was the response variable, treatment was a fixed class effect, and country was a random class variable. Different residual errors for each treatment group were specified in the LME model. The LME model was estimated using the method of restricted maximum likelihood.

The average daily ARC medication score prior to the 2015 GPS visit (V14) was evaluated with a LME model. The average ARC medication score was the response variable, treatment was a fixed class effect, and country was a random class variable. Different residual errors for each treatment group were specified in the LME model. The LME model was estimated using the method of restricted maximum likelihood.

The NNT was calculated as 1/[difference in predicted probability of having asthma symptoms and asthma medication use] placebo – SQ grass SLIT tablet using a population based model (generalized estimation equation).

Difference between groups in SPT diameter was analyzed by Wilcoxon rank sum test.

AEs were summarized by treatment group, system organ class and preferred term displaying the number of subjects in treatment group, number and percentage of subjects having the AE, as well as number of events. Furthermore, AEs were summarized according to severity, relationship, outcome, and seriousness. Physical examinations/asthma physical examinations were summarized by examination and treatment group via shift tables displaying change in normal/abnormal from pretreatment visits to posttreatment visits.

Calculation of ARC medication score

The total daily ARC medication score was calculated as the sum of the total daily scores for each medication (see Table E3). The average ARC medication score was calculated as the average of total daily ARC medication score based on observed data during the 14 days of recording.

Details on the 7 IMP-related SAEs

The case of dyspnea occurred in a subject treated with the first dose of SQ grass SLIT tablet. The subject swallowed the tablet and had a sense of difficulty breathing. No action was taken with regard to the IMP in response to the event.

The case of generalized tonic-clonic seizure occurred while the subject was playing football, 8 months after first dose of SQ grass SLIT tablet. The subject was hospitalized but did not receive any medicinal treatment for the event. During hospitalization, an electroencephalogram revealed possibly epileptic activity. The subject fully recovered from the event a few hours after admission. IMP was discontinued 4 days after the event.

The case of asthma occurred after 10 months on SQ grass SLIT tablet treatment. The subject was spending time in the garden shortly after the lawn was mowed and experienced hoarseness and cough throughout the day. The following evening, the subject had a relapse and was hospitalized and treated with β_2-agonist and recovered. No action was taken with IMP due to the event.

The case of immune thrombocytopenic purpura was reported in a subject on SQ grass SLIT tablet, 13 days after first IMP intake, when the subject was admitted to hospital due to a small sports incidence. The subject presented with multiple hematomas and petechiae. The IMP was permanently discontinued due to the event.

The case of anemia occurred in a subject treated with SQ grass SLIT tablet for 2 years. The subject had a sister with anemia and was therefore tested when experiencing tiredness for several months. The subject was diagnosed with anemia due to iron deficiency. The subject discontinued IMP due to the event and was discontinued from the trial.

The case of abdominal pain occurred in a SQ grass SLIT tablet–treated subject 2 weeks after treatment initiation. The subject also experienced fever simultaneously. The IMP was temporarily interrupted due to the event.

The case of type 1 diabetes occurred in a subject on placebo 859 days after first IMP treatment in the trial. The subject discontinued IMP due to the event.

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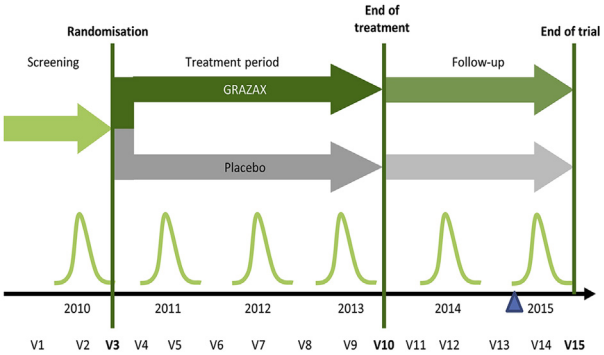

Visit	Time schedule
Screening V1	From approximately November 2009 until anticipated end of GPS 2010. If V1 was performed in peak GPS, and overlapping with the visit window for V2, V1 and V2 could be completed as one visit
Screening V2	From anticipated peak GPS until anticipated end of GPS 2010 (+/- 2 weeks). If V1 was performed in peak GPS, and overlapping the visit window for V2, V2 should not be scheduled since all planned V2 assessments could be done at V1
Randomisation V3	After anticipated end of GPS 2010 and approximately 2-8 weeks after screening V2
Grass pollen season visits; V5, V7, V9, V12, and V14	From anticipated peak GPS until anticipated end of GPS (+/- 2 weeks)
Winter visits; V4, V6, V8, V11, and V13	6 months after GPS visit (+/- 1 month)
End of treatment, V10	After anticipated end of GPS and approximately 2-6 weeks after GPS V9 (year 2013)
Telephone Contact (▲)	No later than 3 weeks prior to V14
End of trial, V15	After anticipated end of GPS and approximately 2-6 weeks after the last GPS visit (year 2015)
Unscheduled visit, At any time from V3 to V15	Unscheduled visit: if scheduled within a month from a scheduled visit, the unscheduled will become the scheduled visit

FIG E1. Trial design including time schedule for trial visits and telephone contact.

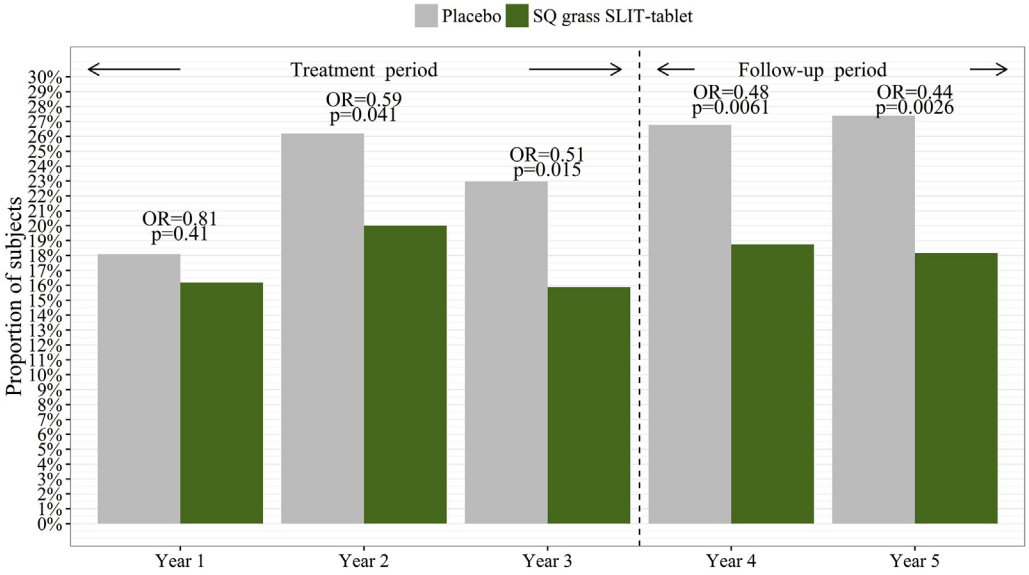

FIG E2. Proportion of subjects experiencing asthma symptoms or using asthma medication.

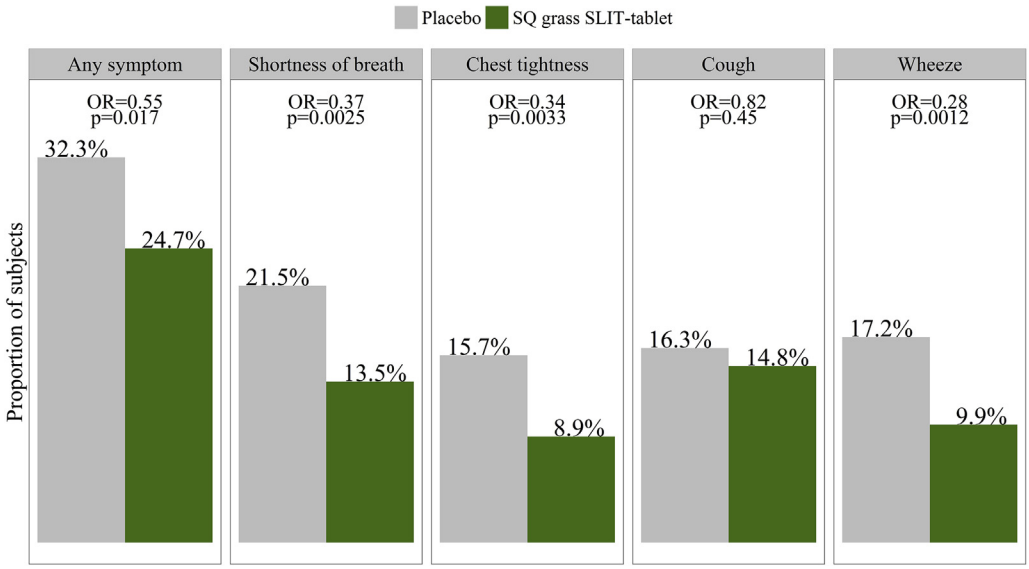

FIG E3. Proportion of subjects having asthma symptoms during the 2-year follow-up period – by symptom.

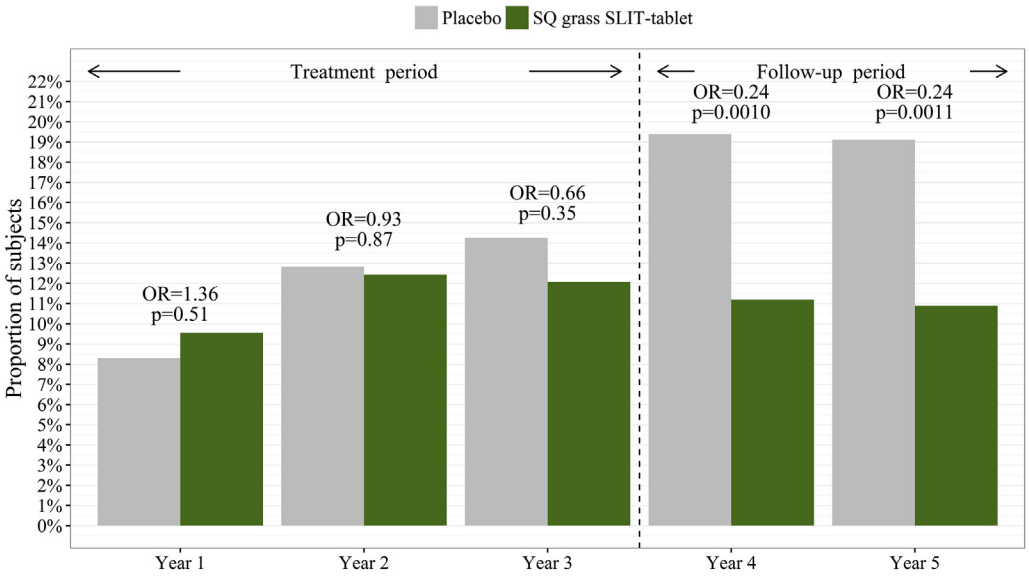

FIG E4. Proportion of subjects using asthma medication.

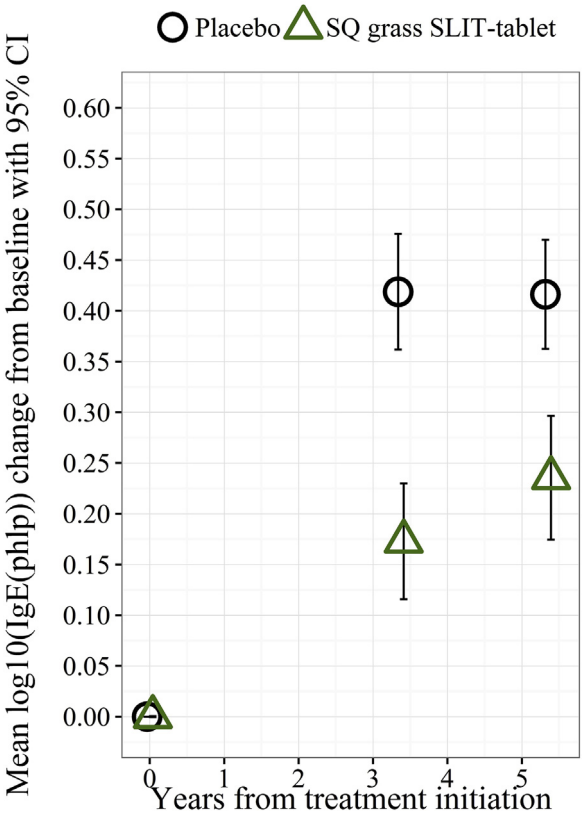

FIG E5. Change from baseline in grass pollen-specific IgE.

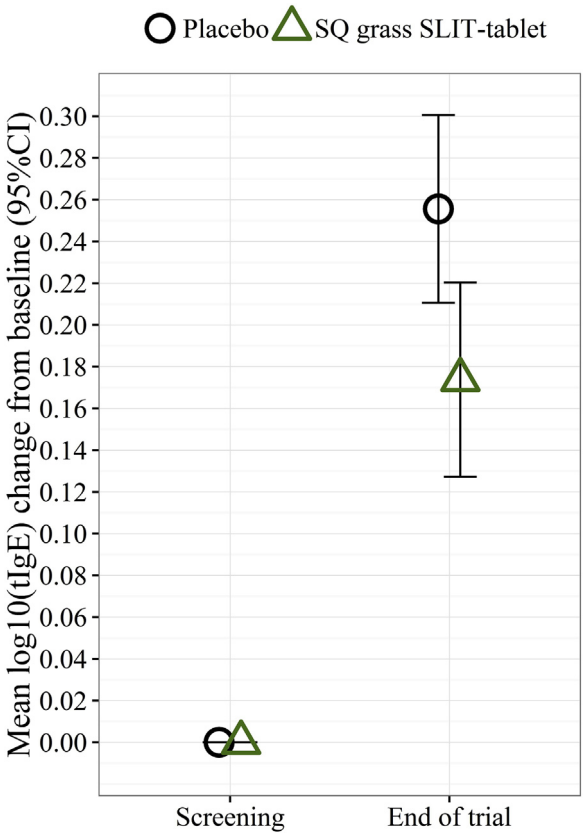

FIG E6. Change from baseline in total IgE.

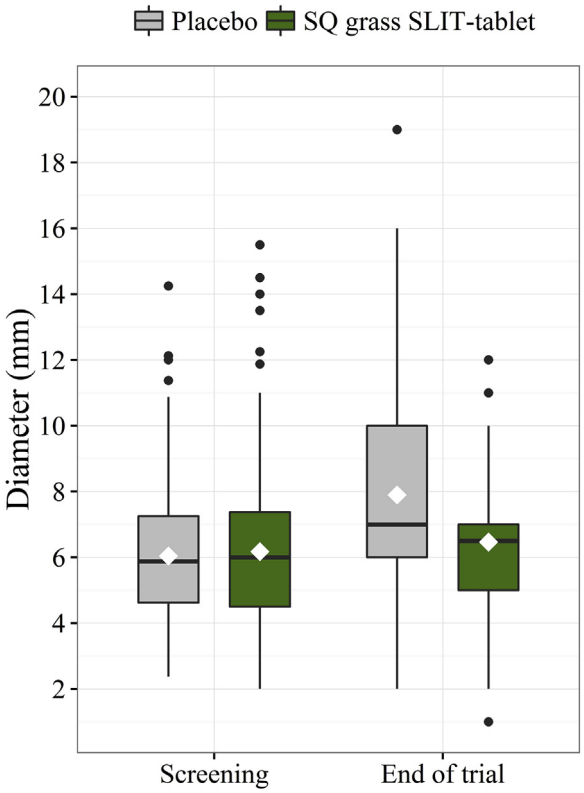

FIG E7. Skin prick test diameter.

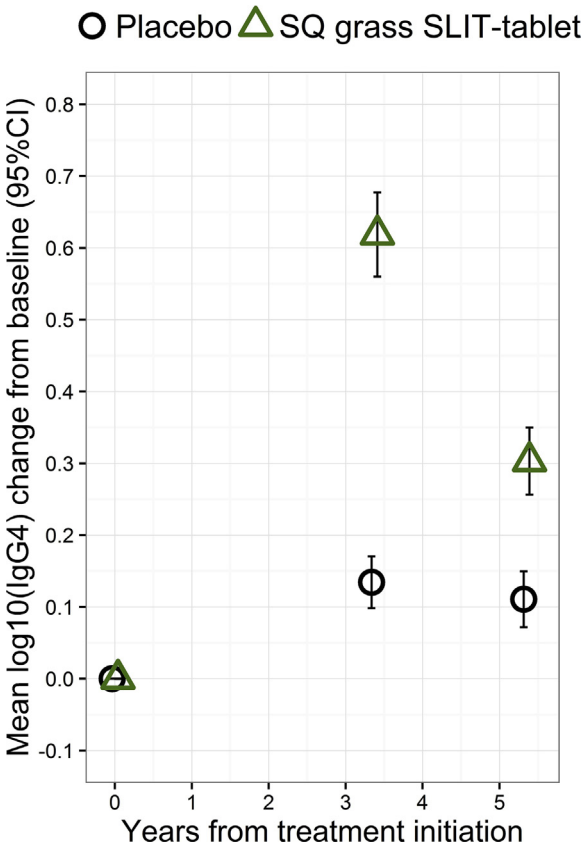

FIG E8. Change from baseline in grass pollen-specific IgG_4.

TABLE E1. Baseline demographics (FAS)

Treatment group	Placebo n = 414	SQ grass SLIT tablet n = 398	Overall n = 812
Sex			
Male	256 (62)	255 (64)	511 (63)
Female	158 (38)	143 (36)	301 (37)
Age (y)			
Mean ± SD	8.7 ± 2.1	8.5 ± 2.1	8.6 ± 2.1
Median	9.0	9.0	9.0
P25% to P75%	7.0-10.0	7.0-10.0	7.0-10.0
P5% to P95%	5.0-12.0	5.0-12.0	5.0-12.0
Ethnic origin			
Caucasian	403 (97)	378 (95)	781 (96)
Asian	2 (<1)	6 (2)	8 (<1)
African	2 (<1)	2 (<1)	4 (<1)
Hispanic	3 (<1)	6 (2)	9 (1)
Other	4 (<1)	6 (2)	10 (1)
Family smoking history			
Mother previous smoker	60 (14)	63 (16)	123 (15)
Mother smoker	63 (15)	61 (15)	124 (15)
Father previous smoker	62 (15)	56 (14)	118 (15)
Father smoker	81 (20)	84 (21)	165 (20)
Country			
Austria	12 (3)	13 (3)	25 (3)
Denmark	63 (15)	54 (14)	117 (14)
Finland	21 (5)	23 (6)	44 (5)
France	58 (14)	54 (14)	112 (14)
Germany	54 (13)	56 (14)	110 (14)
Norway	17 (4)	19 (5)	36 (4)
Poland	55 (13)	48 (12)	103 (13)
Spain	52 (13)	54 (14)	106 (13)
Sweden	61 (15)	58 (15)	119 (15)
Switzerland	8 (2)	8 (2)	16 (2)
United Kingdom	13 (3)	11 (3)	24 (3)
History of comorbidity			
Eczema	48 (12)	60 (15)	108 (13)
Food allergy	51 (12)	55 (14)	106 (13)
Years with grass ARC, mean [min; max]	3.4 [0.3; 10]	3.5 [0.2; 10]	3.4 [0.2; 10]
Baseline SPT positive, (house dust mites) *Dermatophagoides pteronyssimus*	70 (17)	60 (15)	130 (16)
Baseline SPT, positive, (birch) *Betula verrucosa*	142 (34)	134 (34)	276 (34)
Polysensitized	265 (64)	266 (67)	531 (65)

Values are n (%) unless otherwise indicated.
Px%, x% Percentile.

TABLE E2. Prevention of asthma symptoms and asthma medication use in children, analyzed by NNT

***Post hoc* defined endpoints: NNT* during the 2-year follow-up period**									
	Age at randomization (y)								
	5	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Mean age (8.6)**
NNT,* asthma symptoms† (subjects)	10	10	11	11	12	13	14	15	12
NNT,* asthma medication‡ use (subjects)	7	7	8	10	11	14	17	21	11
NNT,* asthma symptoms,† and asthma medication‡ use (subjects)	6	7	8	9	11	13	16	20	10

*NNT: (1/[predicted probability placebo – predicted probability Grazax]). The predicted probability is derived from a generalized estimation equation model.
†Asthma symptoms: any episodes of wheeze, cough for 10 consecutive days, shortness of breath, or chest tightness.
‡Asthma medication: β_2-agonists, systemic corticosteroid, inhaled corticosteroids, leukotriene receptor antagonists, long-acting β_2-agonist, sustained-release theophylline, and cromolyn sodium.

TABLE E3. Calculation of daily ARC medication score

ARC medication	Unit score	Score
Antihistamine tablet	6 per tablet	6 × no. of tablets
Eye drop	1.5 per drop	1.5 × no. of drops
Nasal spray	1 per puff	1 × no. of puffs
Total daily ARC score		Sum of scores