

Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen

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ABSTRACT

Specific immunotherapy is a well-established treatment for allergic rhinoconjunctivitis; conventional regimens are lengthy, however, reducing convenience and cost-effectiveness. This study evaluated the efficacy and safety of an ultrashort course (four doses) of the immunotherapy Grass Modified Allergen Tyrosine Adsorbate (Allergy Therapeutics, Worthing, U.K.) monophosphoryl lipid A (MATA MPL). Subjects were randomized to receive four injections of either Grass MATA MPL (n = 514; 300–2000 standardized units/injection) or placebo (n = 514) before the grass pollen season. They used electronic diaries to record allergy symptoms and medication use during the pollen season. The primary end point was the difference between the mean combined symptom and medication scores in the Grass MATA MPL and placebo groups during the 4 local peak pollen weeks. The injection course was completed by 95.3 and 97.7% of the Grass MATA MPL and placebo groups, respectively, and was well tolerated. Grass MATA MPL treatment afforded a 13.4% benefit over placebo in the 4 peak pollen weeks (p = 0.0038). The benefit in subjects with 28 complete diary entries during the 4 peak pollen weeks was 26.9% (p = 0.0031). Significant benefits over placebo were observed in subjects with severe symptoms (17.1%; p = 0.0023), in those who had a history of allergic rhinoconjunctivitis for up to 35 years (up to 37.2%; p = 0.0059) and at sites with a higher burden of disease (38.3%; p < 0.0001). The ultrashort course of Grass MATA MPL was well tolerated and provided a significant benefit over placebo in relieving allergy symptoms.

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Subcutaneous immunotherapy (SCIT) attenuates the symptoms of allergic rhinoconjunctivitis and alleviates the sensitization of subjects to causative allergens.¹ SCIT is administered conventionally every 4–8 weeks for 3–5 years.^{2–4} This protracted regimen is inconvenient for patients, lowers cost-

effectiveness, and may have an adverse impact on treatment adherence.^{5,6}

Grass MATA MPL (Pollinex Quattro, Pollinex Complete; Allergy Therapeutics, U.K.), is a SCIT vaccine of Modified Allergen Tyrosine Adsorbate (MATA) that consists of a mixture of modified pollen allergens from 13 grass species adsorbed onto tyrosine (modified allergen along with the immunologic adjuvant monophosphoryl lipid A [MPL]). Modification of the allergens by glutaraldehyde binding to ϵ -amino lysine groups reduces their IgE binding affinity, thereby diminishing the potential risk of systemic anaphylaxis, while maintaining immunogenicity, including the capacity to produce a vigorous allergen-specific IgG response. MPL, a detoxified endotoxin derivative, is a toll-like receptor 4 agonist that promotes sustained antigen-specific IgG responses to injected antigens.⁷ MPL promotes Th1 over Th2 responses in a monocyte-dependent, IL-12-dependent manner.^{7–9} The use of tyrosine as a carrier also biases the immune response more toward Th1 relative to Th2 and because tyrosine is more rapidly eliminated from the depot site than more conventional adjuvants, it is potentially safer as well as more efficacious.^{7,9} Previous studies have shown that four preseasonal injections of Grass MATA MPL are clinically effective in relieving allergic symptoms.^{10–13} This study evaluated the efficacy and

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safety of Grass MATA MPL in adults with seasonal allergic rhinoconjunctivitis associated with grass pollen.

METHODS

A randomized, double-blind, placebo-controlled study (NCT00414141; EudraCT trial 2005-004959-35) was conducted in 84 centers (United States, 58; Canada, 17, United Kingdom, 6; Austria, 3) during the 2007 grass pollen season according to the ethical principles of the Declaration of Helsinki and with Good Clinical Practice guidelines. Written informed consent was obtained and the protocol was approved by the relevant ethics and regulatory authorities.

Study Population

Adult subjects (aged 18–59 years) with a history of moderate-to-severe seasonal allergic rhinitis and/or conjunctivitis to grass pollen that required treatment with antihistamines, nasal steroids, and/or leukotriene modifiers were eligible. Disease severity was determined using the disease severity questionnaire (DSQ), which consisted of four questions each rated on a 4-point scale relating to the severity of allergy symptoms (0 = not at all to 3 = a lot) during the previous grass pollen season. Moderate-to-severe seasonal allergic rhinitis was defined as DSQ of ≥ 5 of a maximum of 12. Subjects had a positive skin-prick test to grass pollen mix using a lancet with a defined thorn length of 1 mm. To enhance the chance of including patients with moderate-to-severe allergy, the limit of wheal size diameter was 5 mm (compared with the usual 3 mm). Subjects also had to have a positive class of ≥ 2 specific sIgE (>0.71 U/mL).

Exclusion criteria included pregnancy, breast-feeding, asthma (if daily controller medication was required or if subject had attended the emergency room or was admitted to the hospital within 12 months of study initiation), emphysema, bronchiectasis, nasal polyps, or chronic sinusitis. Subjects treated previously with grass pollen immunotherapy were excluded unless this was discontinued at least 3 years before the start of the study with initial success but subsequent symptom recurrence.

Study Design

All investigational sites recorded the local pollen counts for trees, grasses, Bermuda grass, ragweed, and other regional allergy symptom-causing plants at least 3 days/wk from the time of the first subject being screened to the end of the study (*i.e.*, after the last subject has completed the study). The official start of the grass pollen season at the individual site was defined as a grass pollen count ≥ 5 grains/m³ for at least 2 of 7 days. The start of the pollen season triggered the

start of the e-diary entry. The end of the grass pollen season was defined as a grass pollen count of <5 grains/m³ for 2 consecutive weeks (approximately 10 weeks after the official start of the grass pollen season). The 4 weeks with the highest pollen count were used to define the peak weeks of the pollen season.

The study entailed nine visits. At visit 1, skin-prick tests were conducted and subjects completed the DSQ. Eligible subjects were randomized 1:1 (using an interactive voice randomization system) at visit 2 (7–14 days after visit 1) to either subcutaneous injections of Grass MATA MPL or placebo (Allergy Therapeutics U.K., Ltd, Worthing, U.K.). Randomization was performed in blocks at both study and site levels. Cetirizine (10 mg tablets) and prednisolone (5 mg tablets) were provided to treat intolerable allergy symptoms when required.

Grass MATA MPL dosages were 300 standardized units (SU) in injection 1 (visit 2), 800 SU in injection 2 (visit 3, 7–14 days after visit 2), 2000 SU in injection 3 (visit 4, 7–14 days after visit 3), and 2000 SU in injection 4 (visit 5, 7–28 days after visit 4). Each Grass MATA MPL injection (0.5 mL) included MPL (50 μ g) and 2% w/v L-tyrosine. The entire Grass MATA MPL course contained 21.5 μ g of Lol p1. Each placebo injection contained 2% w/v L-tyrosine. Subcutaneous injections were administered to the lateral/posterior aspects of the upper arms, alternating arms. Injections were completed at least 3 weeks before the start of the 2007 grass pollen season (grass pollen count, ≥ 5 grains/m³ for at least 2 of 7 days).¹⁴

Subjects were assessed 21 days after the final injection (visit 6) and middle (visit 7), at the end (visit 8), and 6–8 weeks after the end (visit 9) of the grass pollen season. Throughout the pollen season, subjects assessed and recorded average daily symptoms and medication use in an electronic diary.

Blood samples were collected at visits 2 and 6–9 for measurement of grass pollen-specific IgG (Timothy-specific IgG; solid phase radioimmunoassay; Dr. Hamilton, Baltimore, MD) and IgE (Immulite, Diagnostic Products Corp., U.K.). Adverse events (AEs) were recorded throughout the study. Treatment-emergent events were defined as AEs occurring during the treatment phase and at least possibly related to treatment.

Efficacy Assessments

Eight symptoms were assessed: itchy, burning, watery, and swollen eyes; nasal congestion; runny nose; nasal itching; and sneezing. Each was scored using a 4-point scale (0 = no symptoms to 3 = severe symptoms). The total symptom score (TSS) for the eight symptoms (maximum 24) was combined with a medication score during the 4 peak weeks of the grass pollen season to yield the combined symptom medica-

tion score (CSMS). The medication score for each 24-hour period was calculated by adding 5 points for every cetirizine tablet and 12 points for every prednisolone tablet to the TSS. Medication scoring was based on the assumed efficacy as reported in the literature and the combined scoring system concurred with the Food and Drug Administration. The daily CSMS was determined by calculating a 3-day rolling average (previous, current and following days).

Efficacy End Points

The primary efficacy end point was the difference in CSMS in the Grass MATA MPL- and placebo-treated groups during the locally measured 4 peak weeks of the grass pollen season. Secondary efficacy end points included the difference in CSMS during the entire grass pollen season in subjects with a history of severe symptoms (DSQ ≥ 7 with at least one symptom category of 3 [severe]) and in the European subgroup.

A series of additional efficacy analyses included differences in CSMS in the Grass MATA MPL- and placebo-treated groups according to overall duration of allergic disease and in subjects with more severe symptoms (DSQ ≥ 9). Well days—days without medication intake and low TSS—were calculated based on TSS ≤ 2 , ≤ 3 , or ≤ 4 . Bad days were defined as days when the CSMS was ≥ 8 or ≥ 10 . Subjects with an overall median CSMS ≤ 2 during the 4 peak weeks of the grass pollen season were defined as “well subjects.”

The median CSMS during the 4 peak pollen weeks in the placebo groups (all study sites) was 7.06. Sites with CSMS > 7.06 during the 4 peak pollen weeks were assumed to have high allergen exposure and/or include more severely affected patients and a subanalysis was conducted in subjects at these sites.

Statistical Analysis

The intention-to-treat (ITT; all randomized patients) population was used for the primary analysis and all analyses involving the CSMS for the 4 peak pollen weeks. For the primary efficacy analysis, missing data for subjects who did not submit valid diary data for at least 2 of the 4 peak pollen weeks were imputed using a matched-pair technique. Categories were age, sex, DSQ, specific IgE, and skin-prick test scores. This methodology was not used in secondary analyses. A sensitivity analysis required by the Food and Drug Administration included subjects with 28 complete diary entries for the 4 peak pollen weeks (complete data population). The full analysis set—all randomized subjects with valid diary records for at least 1 week during the entire grass pollen season—was used to analyze efficacy end points during the entire pollen season. The records for a week were considered valid if the CSMS could be calculated on ≥ 4 of 7 days. Safety was ana-

lyzed in all randomized subjects who received at least one dose of study medication. Patients who stopped treatment prematurely but remained in the study were defined as discontinuations and those subjects who left the study at any time were defined as withdrawals.

Treatment group differences were assessed by analysis of covariance with CSMS as the dependent variable, treatment group, sex, and region as factors, and age and average pollen count (per center) during the 4 peak weeks as covariates. Because data were not normally distributed, data were expressed as median $\pm$ SD. Efficacy data were log-transformed before the analysis of covariance to achieve a normal distribution. Two-sided tests were performed at the 5% level. Least-squares means for group and intergroup differences were calculated with the corresponding 95% confidence intervals.

RESULTS

Subjects were randomized to Grass MATA MPL ($n = 514$) or placebo ($n = 514$). One subject in the placebo group withdrew before treatment, so 1027 subjects were included in the safety analysis. Subject disposition is shown in Fig. 1. Demographic and baseline characteristics were similar in both treatment groups (Table 1). The mean $\pm$ SD (median) wheal size after the skin-prick test to grass pollen was 11.4 ± 5.8 mm (10.0 mm) and 11.6 ± 5.5 mm (10.0 mm) for Grass MATA MPL and placebo groups, respectively. Only 69 and 65 subjects in the Grass MATA MPL and placebo groups, respectively, were monosensitized to grass pollen. The majority (87%) had concomitant sensitizations to other allergens. Most subjects completed the treatment course, 97.7% (501/513) of the placebo group and 95.3% (490/514) of the Grass MATA MPL group in a median period of 25 days.

Efficacy Assessments

Median CSMS during the 4 peak weeks of the grass pollen season was 6.00 ± 5.57 in Grass MATA MPL-treated subjects and 7.06 ± 5.57 in placebo-treated subjects. In the ITT analysis ($n = 1028$), the least-squares mean CSMS was reduced by 13.4% with Grass MATA MPL compared with placebo ($p = 0.0038$; Fig. 2). In the complete data population ($n = 343$), a 26.9% benefit over placebo was achieved by the Grass MATA MPL group ($p = 0.0031$) with a greater difference between groups in European subjects than in the overall population (32.1%; $p = 0.0341$) although the number of European subjects was small ($n = 94$). Similar differences were seen during the entire pollen season as during the 4 peak pollen weeks (Fig. 2). In subjects with a history of severe rhinoconjunctivitis a relative benefit of 17.1% was achieved by the Grass MATA

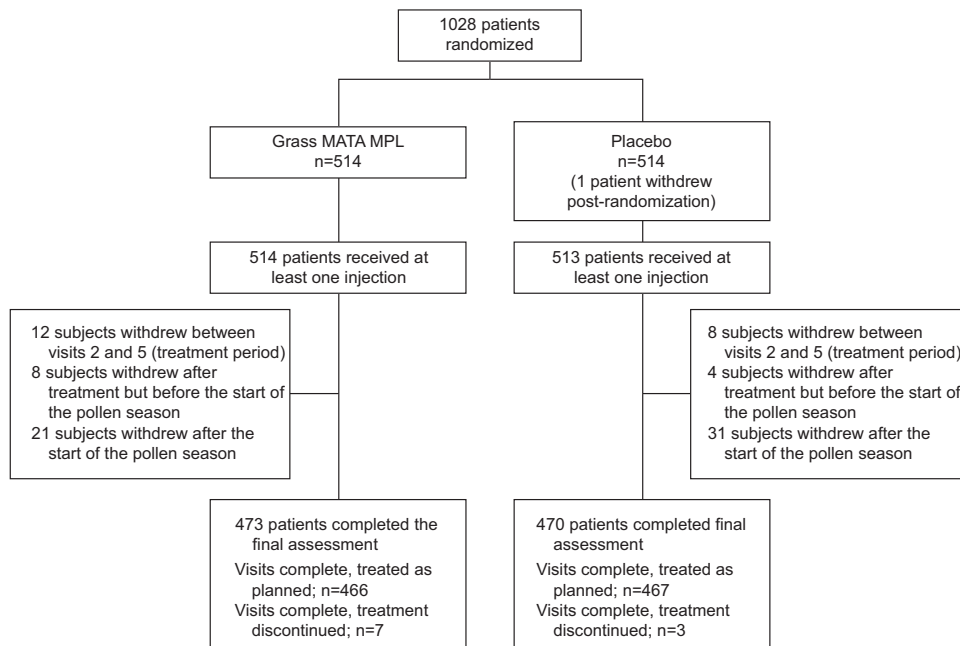


Figure 1. Subject disposition.

MPL group compared with those receiving placebo ($p = 0.0023$).

The mean duration of disease was 21.7 years in the Grass MATA MPL group and 21.3 years in the placebo group; a majority of subjects in the ITT population (951/1028; 93%) had suffered from allergy symptoms for >5 years. Grass MATA MPL was associated with significant benefit in CSMS compared with placebo, even in subjects having experienced symptoms for up to 35 years (37%; $p = 0.0059$; Table 2).

Overall, 55.4% of subjects had $DSQ \geq 9$ at baseline (570/1028)—using a scale that had a maximum severity score of 12. These subjects with a history of more severe allergy symptoms achieved a 13.4% benefit in CSMS with Grass MATA MPL compared with placebo ($p = 0.04$), similar to the overall population.

Significantly more “well days” and fewer “bad days” were experienced by Grass MATA MPL-treated subjects compared with the placebo-treated subjects. Subjects receiving Grass MATA MPL had 86% fewer bad days than placebo-treated subjects. The number of well subjects in the Grass MATA MPL group was 85% higher than in the placebo group ($p = 0.0005$; Fig. 3).

The overall median CSMS in the placebo-treated group during the 4 peak pollen weeks was 7.06. Study sites that may have had higher allergen exposure and/or more severely affected subjects were identified by median CSMS > 7.06 during the 4 peak pollen weeks in the placebo group. In total, 492 subjects were enrolled in this subanalysis. There was an even greater degree of improvement in the Grass MATA MPL-treated group than in the placebo-treated group (me-

dian CSMS, 5.99 ± 6.23 and 9.09 ± 5.93 , respectively). The difference between these treatment groups was 38.3% ($p < 0.0001$). The CSMS scores reflected the change in pollen count during the pollen season (Fig. 4).

Immunologic Changes in Grass-Specific IgE and IgG

Pretreatment median serum grass-specific IgE concentrations were similar in Grass MATA MPL (16.2 ± 30.15 kU/L)—and placebo (16.2 ± 32.4 kU/L)—treated groups. There was a slight increase in IgE level after active treatment, but levels remained stable throughout the pollen season; the expected seasonal increase in IgE levels was observed in subjects in the placebo group.

Pretreatment median serum grass-specific IgG concentrations were similar in the Grass MATA MPL (200.0 ± 968.4 mg/L)—and placebo (423.0 ± 949.0 mg/L)—treated groups. Median serum grass-specific IgG concentrations increased 6.5-fold from baseline to the start of the pollen season (posttreatment) in the Grass MATA MPL-treated group, but only increased slightly in the placebo group toward the end of the pollen season (Fig. 5). This difference in IgG concentration was statistically significant ($p < 0.001$) at all time points after treatment.

Safety

During the treatment period, 13 subjects (2.5%) in the Grass MATA MPL group and 2 subjects (0.4%) in the placebo group experienced AEs leading to study

Table 1 Demographic and baseline characteristics of subjects

Variable	ITT Population		Complete Data Population	
	Grass MATA MPL (n = 514)	Placebo (n = 514)	Grass MATA MPL (n = 177)	Placebo (n = 166)
Age, yr (mean ± SD)	36 ± 11	35 ± 11	40 ± 111	38 ± 10
Male sex, n (%)	261 (50.8)	261 (50.8)	81 (45.8)	78 (47.0)
Race, n (%)				
White	452 (87.9)	460 (89.5)	160 (90.4)	155 (93.4)
Black/African American	27 (5.3)	25 (4.9)	5 (2.8)	8 (4.8)
Asian	22 (4.3)	21 (4.1)	6 (3.4)	3 (1.8)
Other	13 (2.5)	8 (1.6)	6 (3.4)	0 (0)
Disease duration, yr (mean ± SD)	22 ± 11.6	21 ± 11.7	24 ± 12.7	23 ± 11.0
Allergy symptoms, n (%)				
Rhinitis	513 (99.8)	514 (100)	177 (100)	166 (100)
Conjunctivitis	487 (94.7)	484 (94.2)	168 (94.9)	149 (89.8)
Cough	177 (34.4)	153 (29.8)	56 (31.6)	50 (30.1)
Urticaria	104 (20.2)	104 (20.2)	35 (19.8)	29 (17.5)
Bronchial asthma	70 (13.6)	74 (14.4)	27 (15.3)	20 (12.0)
Other*	148 (28.8)	158 (30.7)	52 (29.4)	56 (33.7)
Grass pollen-induced asthma, n (%)				
Yes	70 (13.6)	74 (14.4)	27 (15.3)	20 (12.0)
No	444 (86.4)	440 (85.6)	150 (84.7)	146 (88.0)
Rhinoconjunctivitis severity, n (%)				
Severe	358 (69.6)	355 (69.1)	127 (71.8)	118 (71.1)
Moderate	156 (30.4)	159 (30.9)	50 (28.2)	48 (28.9)

*Itching throat, itching skin, headache, fatigue.

ITT = intention to treat; MATA = Modified Allergen Tyrosine Adsorbate; MPL = monophosphoryl lipid A.

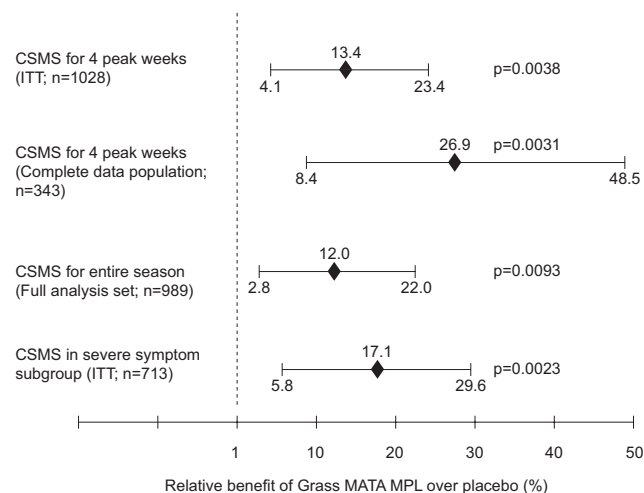


Figure 2. Relative benefit (%) of Grass Modified Allergen Tyrosine Adsorbate monophosphoryl lipid A (MATA MPL) over placebo during the 4 peak weeks of the pollen season and the entire pollen season and in subjects with severe symptoms (disease severity questionnaire [DSQ], ≥ 7 with at least one symptom category = 3).

drug discontinuation. In general, these patients continued to keep symptom diaries during the study period; however, four subjects in the Grass MATA MPL group and one patient in the placebo group

were eventually withdrawn from the study because of AEs. The reasons for withdrawal in the Grass MATA MPL group were injection site erythema (definitely related to therapy), rhinitis (probably related to therapy), chest discomfort (probably related to therapy), and bilateral deafness (unlikely to be related to therapy). In the placebo group one patient was withdrawn because of pregnancy (unrelated to therapy).

During treatment, 70.2% of Grass MATA MPL-treated subjects and 47.0% of placebo-treated subjects experienced one or more AE ($p < 0.001$) with injection site reactions being the most common AE with Grass MATA MPL (Table 3). For each injection, 62.9–70.2% of Grass MATA MPL-treated patients and 83.6–91.2% of placebo-treated patients did not report AEs. Most AEs (97.8%) were mild or moderate in severity. No major differences were seen between the two treatment groups with regard to systemic AEs.

Only one severe systemic reaction (generalized erythema) was reported by a subject receiving Grass MATA MPL during the treatment period. This patient continued and finished treatment as planned. No major differences between the treatment groups were observed in clinical laboratory tests, vital signs, or electro-

Table 2 Difference between combined symptom medication score during the 4 peak pollen weeks in the Grass Modified Allergen Tyrosine Adsorbate monophosphoryl lipid A (MATA MPL) and placebo groups stratified by the subjects' disease duration

Disease Duration (years)	Relative Benefit of Grass MATA MPL over Placebo (%)	LS Means (95% CI)	Two-Sided <i>p</i> Value
>5 (<i>n</i> = 901)	14.8	1.148 (1.048, 1.257)	0.003
>10 (<i>n</i> = 773)	13.8	1.138 (1.033, 1.255)	0.009
>15 (<i>n</i> = 642)	13.1	1.131 (1.017, 1.257)	0.023
>20 (<i>n</i> = 490)	15.7	1.157 (1.026, 1.304)	0.017
>25 (<i>n</i> = 343)	20.8	1.208 (1.051, 1.387)	0.0078
>30 (<i>n</i> = 232)	19.6	1.196 (1.005, 1.422)	0.0435
>35 (<i>n</i> = 137)	37.2	1.372 (1.097, 1.715)	0.0059
>40 (<i>n</i> = 64)	30.4	1.304 (0.962, 1.766)	0.086

Only patients with CSMS data were analyzed.

LS = least square.

cardiograph assessments, and there were no instances of anaphylaxis or death.

The rate of AEs during posttreatment follow-up was similar for the Grass MATA MPL and placebo groups. During the posttreatment period, two patients withdrew from the study in the Grass MATA MPL group, one because of pregnancy, the other reported a case of transverse myelitis >4 weeks after the final injection. In the placebo group, three subjects withdrew, one as a result of pregnancy, the others resulting from severe sinusitis and lung cancer.

DISCUSSION

This study is the largest controlled study of allergen-specific immunotherapy conducted to date. Subjects receiving Grass MATA MPL achieved a significant 13.4% benefit during the peak weeks of the pollen season—an outcome that was supported by key secondary outcomes, such as treatment benefit in the complete data population (26.9%). The relatively small number of subjects from Europe experienced a greater benefit than the overall population, although our understanding of the pathophysiology and natural history of allergic rhinitis is increasing,^{15,16} the reason for this difference remains obscure. It is interesting to speculate that this may result from differences in lifestyle and environmental conditions such as air-conditioning, but this requires further investigation.

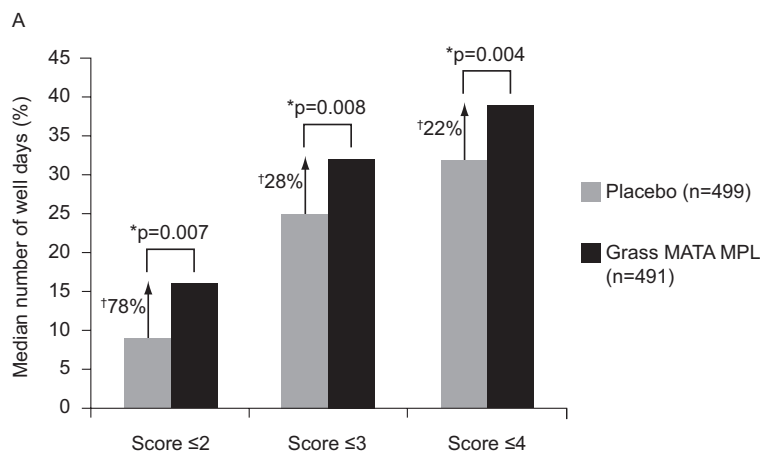
In 2007, a World Allergy Organization task force published recommendations on the design of studies of specific immunotherapy in allergic rhinitis.¹⁷ Despite this study being initiated before these recommendations were published, the current study fulfills the requirements defined: it was a randomized, double-blind placebo-controlled study where efficacy was assessed using a CSMS throughout the entire pollen season and described in all randomized patients. Par-

adoxically, this makes it difficult to compare the results with those from previous studies where only subjects with nearly complete monitoring data—usually ~75%—were included in the efficacy analyses, as opposed to the present study where all randomized subjects were assessed for the primary outcome. The subgroup of subjects in the present study for whom complete data were available is similar to that studied in the earlier trials and the outcome in this subgroup may, therefore, be the most appropriate for comparison purposes. The benefit of Grass MATA MPL over placebo observed in this group (26.9%) was higher than that found in the overall study population, possibly because precise documentation leads to more reliable data.

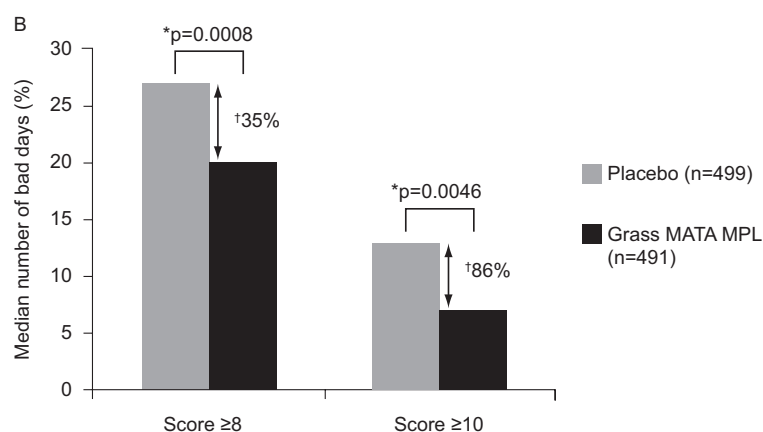
The population studied had a median disease duration of >20 years and symptom scores higher than those reported in other recent multicenter studies.^{18,19} Importantly, the benefits of Grass MATA MPL over placebo were evident in subjects with severe disease and in subjects who had suffered from symptoms for decades.

The concept of well days was introduced by Dahl and colleagues.¹⁸ They reported that subjects receiving sublingual immunotherapy had 53% well days versus 44% with placebo—a 20% relative difference. In the present study, Grass MATA MPL treatment was associated with a 78% relative increase in well days compared with placebo. Moreover, Grass MATA MPL-treated subjects experienced 86% fewer bad days than the placebo-treated group and 85% more of them were defined as well subjects who were not substantially inconvenienced by their symptoms.

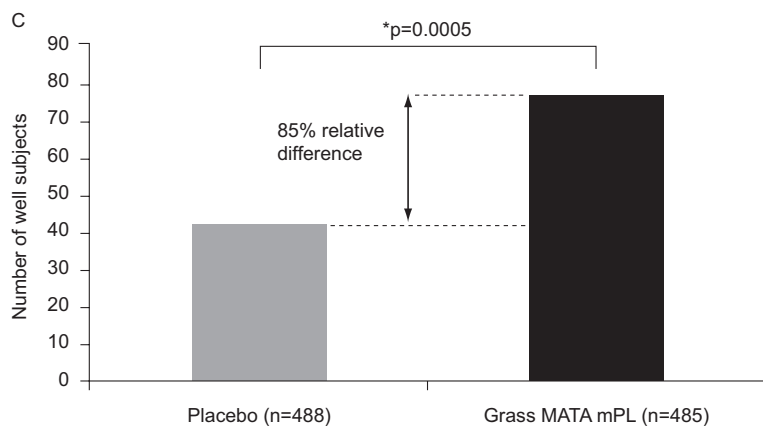
Based on the relatively low use of relief medication and small increase in IgE in the placebo group it appears that the grass pollen exposure in 2007 was relatively mild, which may also have obscured the thera-



* Wilcoxon 2-sample test; †Relative superiority of Grass MATA MPL over placebo
n=number of patients with at least one diary entry during the pollen season



* Wilcoxon 2-sample test; †Relative difference between treatment groups
n=number of patients with at least one diary entry during the pollen season



* p value based on a Chi-Square-test with significance at the 5% level
n=number of subjects with data available

Figure 3. Median number of (A) well days and (B) bad days in the placebo and Grass Modified Allergen Tyrosine Adsorbate monophosphoryl lipid A (MATA MPL) groups as a percentage of the entire observation period. (C) Proportion of well subjects in each treatment group.

peutic response.²⁰ Consequently, one of the additional analyses studied the clinical response in those areas where the allergen exposure may have been particularly high or the patients had a more severe disease (as judged by high median CSMS in placebo subjects). In

these areas the difference between treatment groups was 38.3%, indicating that Grass MATA MPL was beneficial even under these more-demanding conditions, and perhaps giving a more accurate estimate of the benefit.

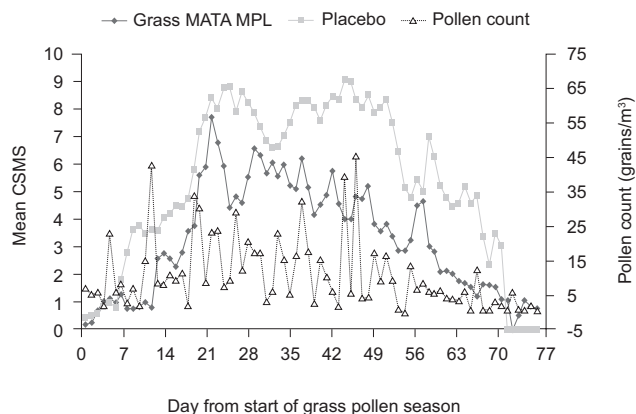


Figure 4. Combined symptom medication score (CSMS) in placebo and Grass Modified Allergen Tyrosine Adsorbate monophosphoryl lipid A (MATA MPL) groups and pollen count at a representative investigational site.

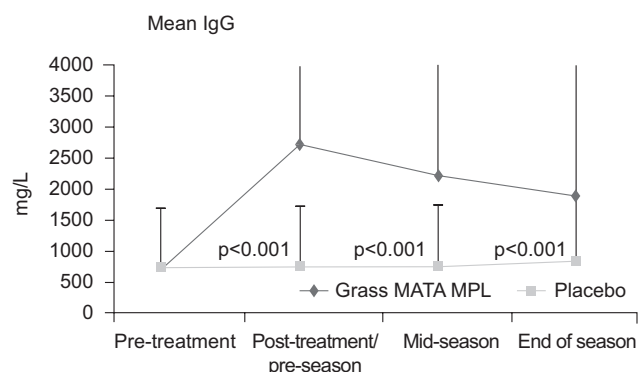


Figure 5. Median IgG level in the Grass Modified Allergen Tyrosine Adsorbate monophosphoryl lipid A (MATA MPL) and placebo groups (two-side *p* values, placebo versus Grass MATA MPL).

Treatment adherence is a frequent concern with specific immunotherapy.²¹ Both SCIT and sublingual immunotherapy have traditionally been administered for 3–5 years to achieve long-term suppression of allergy symptoms and to modify the natural history of house-dust mite and pollen allergy.^{22–25} The need for such prolonged administration is likely to affect treatment adherence. Encouragingly, 95% of subjects in the current study completed the treatment course; however, the adherence to therapy and additional benefit during additional treatment courses is still to be established.

Grass MATA MPL had a favorable AE profile with most AEs being mild to moderate in severity. The most commonly reported AEs were injection site reactions, but these were generally well tolerated because overall rates of treatment discontinuation and study withdrawal were low. Although more patients in the Grass MATA MPL group experienced AEs than in the placebo group they did not result in high rates of treatment withdrawal. Overall, only 2.5% (*n* = 13) of Grass MATA MPL had to discontinue from the study as a result of AEs and of those only 4 ultimately withdrew

Table 3 Summary of adverse events (reported in >5% of any one group) during the treatment period

Event	Grass MATA MPL (<i>n</i> = 514)	Placebo (<i>n</i> = 513)
Injection site conditions, (%)		
Pain	166 (32)	84 (16)
Pruritus	154 (30)	17 (3)
Swelling	129 (25)	9 (2)
Erythema	97 (19)	7 (1)
Warmth	26 (5)	2 (0)
Headache, <i>n</i> (%)	35 (7)	26 (5)
Nasopharyngitis, <i>n</i> (%)	30 (6)	31 (6)
Upper respiratory tract infection, <i>n</i> (%)	26 (5)	23 (4)

MATA = Modified Allergen Tyrosine Adsorbate; MPL = monophosphoryl lipid A.

from the study permanently. The significant benefit of Grass MATA MPL over placebo even in subjects with long-standing and severe allergic disease combined with its rapid immunologic effect and favorable AE profile suggests that it should be considered an effective treatment for seasonal allergic rhinoconjunctivitis.

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Erratum

Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen

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The analysis of symptom/medication score data employed ANCOVA which requires normally distributed data. Logarithmic transform of the data was performed and then ANCOVA conducted. The original subtraction of placebo minus active became a ratio of placebo to active with the difference calculated as *placebo- relative- to- active* and not as is customary assessing *active- relative- to- placebo*. All results have now been recalculated as *active- relative- to- placebo*. No changes in statistical significances of any data including p-values were subsequently noted consequent to this change in reference from *placebo- relative- to- active* to *active- relative- to- placebo*.

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