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Original Article

Sequential Treatment Initiation with Timothy Grass and Ragweed Sublingual Immunotherapy Tablets Followed by Simultaneous Treatment Is Well Tolerated

Jennifer Maloney, MD[a], Gary Berman, MD[b], Remi Gagnon, MD[c], David I. Bernstein, MD[d], Harold S. Nelson, MD[e], Jörg Kleine-Tebbe, MD[f], Amarjot Kaur, PhD[a], Qing Li, PhD[a], and Hendrik Nolte, MD, PhD[a] *Kenilworth, NJ; Minneapolis, Minn; Québec, QC, Canada; Cincinnati, Ohio; Denver, Colo; Berlin, Germany*

What is already known about this topic? Many patients are allergic to both grass and ragweed, and dual administration of grass and ragweed sublingual immunotherapy (SLIT) tablets may be indicated for some of these patients.

What does this article add to our knowledge? In patients allergic to both grass and ragweed, following a 2-week period of sequential single SLIT-tablet treatment, simultaneous administration of grass and ragweed SLIT tablets within 5 minutes was well tolerated.

How does this study impact current management guidelines? This study found that after tolerability with single SLIT-tablet administration has been established, dual treatment with grass and ragweed SLIT tablets may be able to be followed by simultaneous tablet administration at home.

BACKGROUND: Dual treatment with grass and ragweed sublingual immunotherapy (SLIT) tablets has not been studied.
OBJECTIVE: To characterize the safety and tolerability of dual grass and ragweed SLIT-tablet administration.
METHODS: This open-label, multicenter trial (NCT02256553) enrolled North American adults (N = 102) allergic to grass and ragweed. The trial had 3 periods, each of 2 weeks duration. In period 1, subjects received once-daily timothy grass SLIT tablet (2800 bioequivalent allergen unit; Merck, Inc, Kenilworth, NJ/ALK, Hørsholm, Denmark). In period 2, subjects received a short ragweed SLIT tablet (12 *Ambrosia artemisiifolia* 1-U; Merck/ALK) every morning and a grass SLIT tablet every evening. In period 3, subjects received once-daily grass and ragweed SLIT tablets within 5 minutes (simultaneous intake). The primary end point was the proportion of subjects with 1 or more local swelling events in each period. Secondary end points were the proportion of subjects with 1 or more local adverse events (AEs), that discontinued the treatment because of AEs, and subjects with 1 or more local AEs requiring treatment.

[a]Merck & Co., Inc, Kenilworth, NJ
[b]Clinical Research Institute, Inc, Minneapolis, Minn
[c]Clinique Spécialisée en Allergie de la Capitale, Québec, QC, Canada
[d]Bernstein Clinical Research Center and Division of Immunology and Allergy, University of Cincinnati, Cincinnati, Ohio
[e]National Jewish Health, Denver, Colo
[f]Allergy & Asthma Center Westend, Berlin, Germany

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Conflicts of interest: J. Maloney was an employee of Merck Sharp & Dohme Corp. at the time of the trial. A. Kaur, Q. Li, and H. Nolte are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc, Kenilworth, NJ. G. Berman has received research grants from Shionogi, Circassia, Perrigo, Meda, Watson Laboratories, GlaxoSmithKline, Sunovion, TEVA, and Mylan; and received consultancy fees from Teva R. Gagnon has received consultancy fees as a Merck Canada advisory board member; received research grants from Merck; and received honorarium for conferences from Merck Canada, Pfizer Canada, AstraZeneca, and Mead Johnson. D. I. Bernstein is a member of the Joint Task Force Practice Parameters; has served on advisory boards for Merck & Co., Inc, and Circassia; has received consultancy fees from Merck and Ciracassia; has received research support from Merck, Circassia, Greer, and Stallergenes; has received lecture fees from Merck; has received payment for developing educational presentations from AstraZeneca; and is a member of the Immunotherapy Committee for the American Academy of Allergy, Asthma & Immunology (AAAAI). H. S. Nelson has served on advisory boards for Merck and Circassia; has received consultancy fees from Merck; has received grants/research support from Circassia; and is on the data safety monitoring boards for AstraZeneca and Pearl Therapeutics. J. Kleine-Tebbe is on the advisory boards for Merck, Allergy Therapeutics, Circassia, ALK-Abelló, Novartis, LETI, and Bencard; has received consultancy fees from Merck and Circassia; has received research support from Allergopharma, ALK-Abelló, Dr Fooke, DST, HAL Allergy, and Circassia; has received lecture fees from AstraZeneca, MEDA, Roxall, Allergopharma, ALK-Abelló, Bencard, HAL Allergy, LETI, Lofarma, Novartis, and Stallergenes; and is a member of the Immunotherapy Committee for the AAAAI and board member of the European Academy of Allergy and Clinical Immunology Immunotherapy Interest Group.

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Corresponding author: Hendrik Nolte, MD, PhD, Merck Research Laboratories, RY34-A468, 126 E Lincoln Ave, PO Box 2000, Rahway, NJ 07065. E-mail: hendrik.nolte@merck.com.

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Abbreviations used
AE- adverse event
AR/C- Allergic rhinitis with or without conjunctivitis
SLIT- sublingual immunotherapy
TRAE- treatment-related adverse event
WAO- World Allergy Organization

RESULTS: No severe swellings, systemic allergic reactions, asthma attacks, or reactions requiring epinephrine were reported. Most (99%) AEs were graded mild to moderate. The proportions of subjects with 1 or more local swelling events were 14%, 22%, and 15% for periods 1, 2, and 3, respectively. For periods 1, 2, and 3, the proportions of subjects with 1 or more local AEs were 71%, 69%, and 56%, respectively; the proportions discontinuing the treatment because of treatment-related AEs were 5%, 1%, and 2%, and the proportions with 1 or more local AEs requiring treatment were 4%, 4%, and 1%. CONCLUSIONS: In this trial, a 4-week sequential SLIT-tablet dosing schedule followed by simultaneous intake of timothy grass and ragweed tablets was well tolerated. **© 2015 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).** **(J Allergy Clin Immunol Pract 2016;4:301-9)**

Key words: *Allergic rhinitis; Immunotherapy; Grass; Ragweed; Immunotherapy tablet; Safety; Sublingual; Simultaneous; Dual*

Ragweed and grass are prevalent allergens in North America, with an estimated 30% to 40% of the US population reporting current hay fever symptoms to each of these allergens.[1] In Canada, sensitivity to ragweed and grass is as high as 33% and 29%, respectively.[2] Furthermore, patients are often allergic to both grass and ragweed. In North American clinical trials of grass or ragweed sublingual immunotherapy (SLIT) tablets, approximately 65% of grass-allergic subjects were also sensitized to ragweed[3] and approximately 50% of ragweed-allergic subjects were also sensitized to grass.[4] Dual administration of SLIT tablets may be indicated for some patients allergic to both grass and ragweed. Indeed, treatment with multiple allergens is common practice with subcutaneous immunotherapy.

Grastek and Ragwitek (Merck & Co, Inc, Kenilworth, NJ/ALK, Hørsholm, Denmark) are SLIT tablets approved for use in the United States and Canada for the treatment of timothy grass (or cross-reactive grass) pollen- and short ragweed pollen-induced allergic rhinitis with or without conjunctivitis (AR/C). The prescribing information for the ragweed and timothy grass SLIT tablets recommends that treatment without uptitration be initiated at least 12 weeks before the expected onset of the respective pollen season[5,6]; in North America, this time period for ragweed would coincide with the grass pollen season when patients receiving grass SLIT tablets were still undergoing treatment. Therefore, simultaneous administration of grass and ragweed SLIT tablets would be required to treat AR/C associated with both allergens.

Although the tolerability of the individual grass and ragweed SLIT tablets has been demonstrated in double-blind, placebo-controlled, randomized clinical trials,[3,4,7,8] there are no available data on dual administration of these tablets. Furthermore, there is no guidance on dosing schedules introducing dual-tablet administration without uptitration. The primary objective of this phase 4 trial was to evaluate a sequential dosing schedule and characterize the safety and tolerability of dual grass and ragweed SLIT-tablet administration in adults with grass and ragweed pollen-induced AR/C.

METHODS

Study design and treatment

This was a phase 4, multicenter, open-label trial in adults with both ragweed and grass allergy conducted from October 13, 2014, to February 18, 2015, at 3 sites in the United States and Canada (P006; NCT02256553). Trial protocols were approved by the appropriate institutional review boards, and written informed consent from subjects was obtained before the start of the trial.

Treatment was initiated shortly after the ragweed season. There were 3 periods to the trial (Figure 1) and 5 clinic visits. At clinic visit 2, subjects received the full maintenance dose of the grass SLIT tablet (Grastek/Grazax; MK-7243, 2800 bioequivalent allergen unit; Merck & Co, Inc/ALK) with no uptitration and under supervision at the clinic followed by a 30-minute observation. For the remainder of period 1, subjects self-administered 1 grass SLIT tablet every evening. At clinic visit 3, subjects received 1 maintenance dose of the ragweed SLIT tablet (Ragwitek; MK-3641, 12 *Ambrosia artemisiifolia* 1-U; Merck & Co, Inc/ALK) under supervision in the morning, followed by a 30-minute observation. That same evening subjects self-administered 1 grass SLIT tablet. For the remainder of period 2, subjects self-administered 1 ragweed SLIT tablet every morning and 1 grass SLIT tablet every evening. At clinic visit 4, subjects received both ragweed SLIT tablet and grass SLIT tablet within 5 minutes (referred to as simultaneous administration) under supervision, followed by a 30-minute observation. For the remainder of period 3, subjects self-administered 1 ragweed SLIT tablet and 1 grass SLIT tablet within 5 minutes each day. The timing of at-home dosing during period 3 was at the discretion of the subject, but was to be at approximately the same time each day. Subjects were instructed not to place both tablets under the tongue at the same time, but to take the ragweed SLIT tablet first, followed by the grass SLIT tablet once the ragweed SLIT tablet had dissolved (dissolution time is typically <10 seconds). Subjects were reminded by telephone the day before clinic visit 3 and clinic visit 4 not to take their study medication(s) the next day before coming to the clinic. Compliance was assessed by subject interview during clinic visits and was calculated as the number of days on therapy/number of days should be on therapy $\times$ 100%.

Subjects were instructed not to swallow during the first minute after SLIT-tablet administration. A washout period of 7 days before visit 2 was required for antihistamines. The use of medications as a pretreatment to prevent adverse events (AEs) was not allowed during the trial, but medications (except antihistamines) were allowed to treat AR/C symptoms. Subjects using low- or medium-dose inhaled corticosteroids were allowed to continue during the trial, as long as they were on a stable regimen for at least 2 weeks before screening. Self-injectable epinephrine was provided to each subject in the event of a systemic reaction, and subjects were instructed on its use.

Key inclusion and exclusion criteria

Subjects eligible for the trial were men or women aged 18 to 65 years, with a clinical history of physician-diagnosed ragweed and grass pollen-induced AR/C of at least 1 year duration, with or without asthma. A positive skin prick test response from the Duotip device (Lincoln Diagnostics, Inc, Decatur, Ill), defined as an average wheal diameter 5 mm or larger than that of the saline control to both

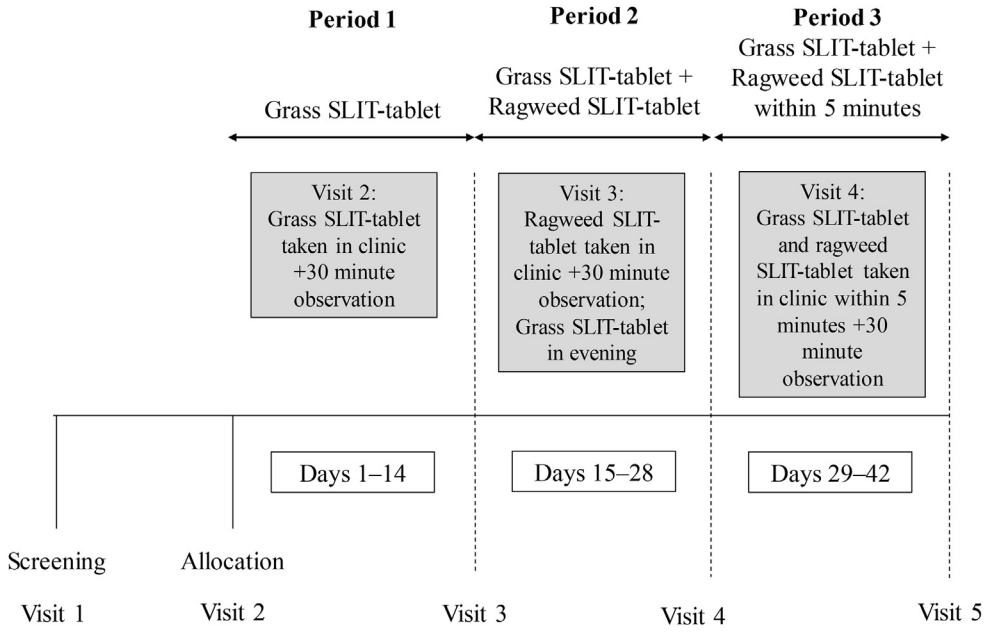


FIGURE 1. Trial design.

A artemisiifolia and *Phleum pratense*, was required. Subjects were required to have an FEV_1 of 70% or more of predicted at both screening and visit 2 following at least a 6-hour washout period of short-acting β_2-agonists. Subjects with unstable, uncontrolled, or severe asthma or with asthma treated with long-acting β_2-agonists at screening were excluded. Other key exclusion criteria were a history of anaphylaxis with cardiorespiratory symptoms due to previous immunotherapy or inhalant allergens, a diagnosis of eosinophilic esophagitis, history of severe systemic allergic reaction or severe local reaction to SLIT, allergen immunotherapy within the past month, receipt of maintenance doses of ragweed and/or grass subcutaneous immunotherapy for 1 month or more within the last 5 years, previous exposure to grass or ragweed SLIT, or pregnancy. Discontinuation criteria included any life-threatening treatment-related adverse event (TRAE), persistent and escalating AEs in the mouth or throat, severe or persistent symptoms of esophagitis, severe treatment-related anaphylactic reaction, or difficulty controlling asthma.

Assessments

The primary end points of the trial were the proportion of subjects with 1 or more event of local swelling (ie, pharyngeal edema, laryngeal edema, mouth edema, oropharyngeal swelling, palatal edema, tongue swelling/edema, or throat tightness) during each of the periods 1, 2, and 3. Secondary end points were the proportion of subjects with 1 or more event of a local AE (ie, local swellings as listed for the primary end point, as well as lip swelling/edema, ear pruritus, dysphagia, oral discomfort, glossodynia, oral pruritus, oral hypoesthesia, throat irritation, oral paresthesia, or stomatitis), the proportion of subjects with 1 or more AE that led to study discontinuation, and the proportion of subjects with 1 or more local AE that required symptomatic treatment during each trial period. Other safety assessments included monitoring of vital signs, oropharyngeal examination, and pulmonary function tests at each clinic visit.

An exploratory end point was the subject's overall perception of tolerability for the study medications over the previous 7 days before clinic visits 3, 4, and 5. This assessment was measured by a questionnaire that asked how willing the subject would be to take the medication every day if asked to do so by his or her doctor. Possible answers were "Definitely," "Probably," "Neutral," "Probably not," and "Definitely not."

A Side Effect Report Card was developed by the study sponsor and used as a method to actively capture AEs by a list of closed-ended questions in real time on a daily basis from each subject. The card collected information on AEs identified by the World Allergy Organization (WAO) as local AEs of SLIT (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).[9] Each day subjects captured any events that occurred within 60 minutes of SLIT-tablet administration. During periods 1 and 3, subjects captured events once daily after SLIT-tablet administration. During period 2, subjects captured events twice daily, once after each SLIT-tablet administration. AEs were also monitored during in-clinic visits and by interviewing of subjects.

The intensity and relatedness to treatment of all AEs reported by the subjects were assessed by the investigators. Per protocol, intensity was assessed as mild (easily tolerated), moderate (discomfort enough to interfere with daily activity), or severe (incapacitating with inability to do work or usual activity). A modified WAO grading system was applied programmatically as a secondary method for grading the intensity. The WAO grading defines severity as follows: Mild (grade 1): not troublesome and no symptomatic treatment required and no discontinuation of SLIT because of local side effects; moderate (grade 2): troublesome or requires symptomatic treatment and no discontinuation of SLIT because of local side effects; severe (grade 3): grade 2 and SLIT discontinued because of local side effects.[9] To grade severity in a more objective way, the "troublesome" component was not included in the modified version of the WAO grading system.

Any AE considered possibly related to treatment was considered a TRAE. Serious AEs were defined as any AE that was life-threatening or resulted in death, persistent or significant disability, resulted in hospitalization or prolonged an existing hospitalization, congenital anomaly/birth defect, cancer, or other medically important event.

There was 1 accidental overdose of 2 ragweed SLIT tablets with subsequent development of mild throat irritation that was considered a serious AE per the study protocol, but did not meet the regulatory requirement for seriousness. For this analysis, the event was not considered a serious AE.

Statistical analyses

All safety analyses were conducted on all treated subjects. Approximately 100 subjects were planned for the trial. With 100 subjects, the half-width of the 95% CI for an AE rate of 20% was 8.3. For the primary and secondary end points, the 95% CI was calculated using the Clopper-Pearson method. AEs captured via subject interview and monitoring, as well as AEs captured on the Side Effect Report Card, were all collected in the same database to determine the incidence of AEs. Analyses were conducted using SAS version 9.3 (Cary, NC).

RESULTS

Subjects

A total of 102 subjects were enrolled in the study and included in the analysis; 91 (89%) completed the study. Discontinuations were due to AEs (n = 9), protocol violation (n = 1), and subject withdrawal not related to treatment (n = 1). The subjects' demographic characteristics are presented in Table I. No subject reported having previously received allergen immunotherapy.

Overall safety

Overall compliance with the study medication was 96.1%. Single and dual administrations of the SLIT tablets were well tolerated. There were no reported severe swellings, systemic allergic reactions, asthma exacerbations, events that met the regulatory definition of serious, or reactions treated with epinephrine during the trial. One subject accidentally took more than 1 ragweed SLIT tablet during period 2 and developed mild throat irritation. Overall, 95 subjects (93%) reported any treatment-emergent AE, and 93 subjects (91%) experienced any TRAE (Table II). There was a trend toward a declining proportion of subjects with treatment-emergent AEs and TRAEs over the course of the trial (Table II). In the last week of the trial, 54 subjects (53%) experienced TRAEs, and on the last day of the trial, 7 subjects (7%) experienced TRAEs. The most commonly reported TRAEs (≥5% of the subjects) overall and during each treatment period were throat irritation, oral pruritus, and ear pruritus (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Most (99%) AEs were graded mild to moderate. Tongue and mouth ulcerations assessed as treatment-related were reported at an overall incidence of 12% and 17%, respectively (see Table E2), and recurred for a median of 1 day and 3 days, respectively. Investigators visually confirmed ulcers in only 1 subject. All tongue and mouth ulcerations were assessed as mild and did not contribute to any treatment discontinuations.

Assessment of local swellings

There were no local swellings in the mouth assessed as severe in intensity. The proportions of subjects experiencing at least 1 event of local swelling were 14%, 22%, and 15% for periods 1, 2, and 3, respectively. For period 2, the proportion of subjects experiencing local swellings was 17% with the ragweed SLIT tablet and 14% with the grass SLIT tablet. Figure 2 shows the onset and recurrence of all reported treatment-related local swellings of any type or intensity (n = 103). Most subjects experienced local swellings that were assessed as mild; a few (n = 12) had swellings that were considered by the investigators to be of moderate intensity. Overall, there were more events of local swelling in period 2 due to the introduction of the ragweed tablet and the onset of new local swellings associated with the grass tablet. In period 3, the frequency of new-onset local swellings decreased compared with period 2 (4% vs 17%, respectively). Most swellings recurred for less than 15 days, suggesting resolution of side effects.

TABLE I. Demographics and baseline characteristics of all enrolled subjects

Characteristic	Subjects allocated to ragweed 12 *Amb a* 1-U and grass 2800 BAU SLIT-tablet treatment (N = 102)
Age (y), mean ± SD	40.0 ± 12.0
Male, n (%)	49 (48.0)
White, n (%)	97 (95.1)
Subjects with asthma, n (%)	24 (23.5)
Using ICS at baseline, n (%)*	3 (12.5)
Percent predicted FEV_1, mean*	93%
Duration of AR/C (y), mean ± SD	26.0 ± 14.7
Phleum pratense wheal diameter (mm), mean ± SD	11.6 ± 3.7
Ambrosia artemisiifolia wheal diameter (mm), mean ± SD	10.3 ± 3.6

Amb a, *Ambrosia artemisiifolia*; *BAU*, bioequivalent allergen unit; *ICS*, inhaled corticosteroid.
*Among subjects with asthma.

Proportion of subjects with AEs

The proportions of subjects experiencing at least 1 local AE were 71%, 69%, and 56% for periods 1, 2, and 3, respectively. Except for 1 event of throat irritation in period 3 that was assessed as severe, all other local AEs were assessed as mild or moderate in intensity (Figure 3). In period 3, the frequency of new-onset local AEs decreased compared with that during period 2 (7% vs 50%, respectively). In the last week of the trial, 52 subjects (51%) experienced local AEs, and on the last day of the trial, 5 subjects (5%) experienced local AEs.

The proportions of subjects who discontinued because of AEs were 5%, 1%, and 3% for periods 1, 2, and 3, respectively. Of the 9 discontinuations due to AEs, 8 were considered related to treatment by the investigator (Table II). In general, the subjects who discontinued often had multiple, persistent local AEs that escalated in intensity over time. The 1 subject who discontinued in period 2 experienced local AEs of mild intensity in period 1, which escalated to moderate local AEs and upper abdominal pain/nausea in period 2. The TRAEs (mild mouth edema and moderate edema under the tongue) that led 2 subjects to discontinue in period 3 were newly-onset in period 3.

The proportions of subjects who experienced at least 1 local AE that required symptomatic treatment were 4%, 4%, and 1% for periods 1, 2, and 3, respectively. Out of the total 9 subjects who required symptomatic treatment, 3 (3%) discontinued the trial (n = 2 in period 1, and n = 1 in period 2); these AEs would be graded as severe according to the WAO grading system. The medications used to treat the local AEs included diphenhydramine, cetirizine, loratadine, and pantoprazole.

TABLE II. AE summary overall and by treatment period

		Ragweed 12 *Amb a* 1-U and grass 2800 BAU SLIT tablet (N = 102)				
		Period 1	Period 2			Period 3
n (%) of subjects reporting	Overall*	Grass SLIT tablet	Ragweed SLIT-tablet AM	Grass SLIT-tablet PM	Both SLIT tablets†	Grass SLIT tablet and ragweed SLIT tablet
Any TRAE	93 (91)	81 (79)	55 (54)	48 (47)	14 (14)	61 (60)
Any serious TRAE	0‡	0	0‡	0	0	0
Any TRAE leading to study discontinuation	8 (8)	5 (5)	0	1 (1)	0	2 (2)

AM, Morning; *Amb a*, *Ambrosia artemisiifolia*; *BAU*, bioequivalent allergen unit; *PM*, evening.
*Subjects reporting at least 1 event at any time during the trial.
†Both tablets attributed as the cause of the AE, or the investigator was not sure which tablet attributed to the AE.
‡One accidental overdose of 2 ragweed SLIT tablets with subsequent development of mild throat irritation was considered a serious AE per the study protocol, but did not meet regulatory criteria for seriousness.

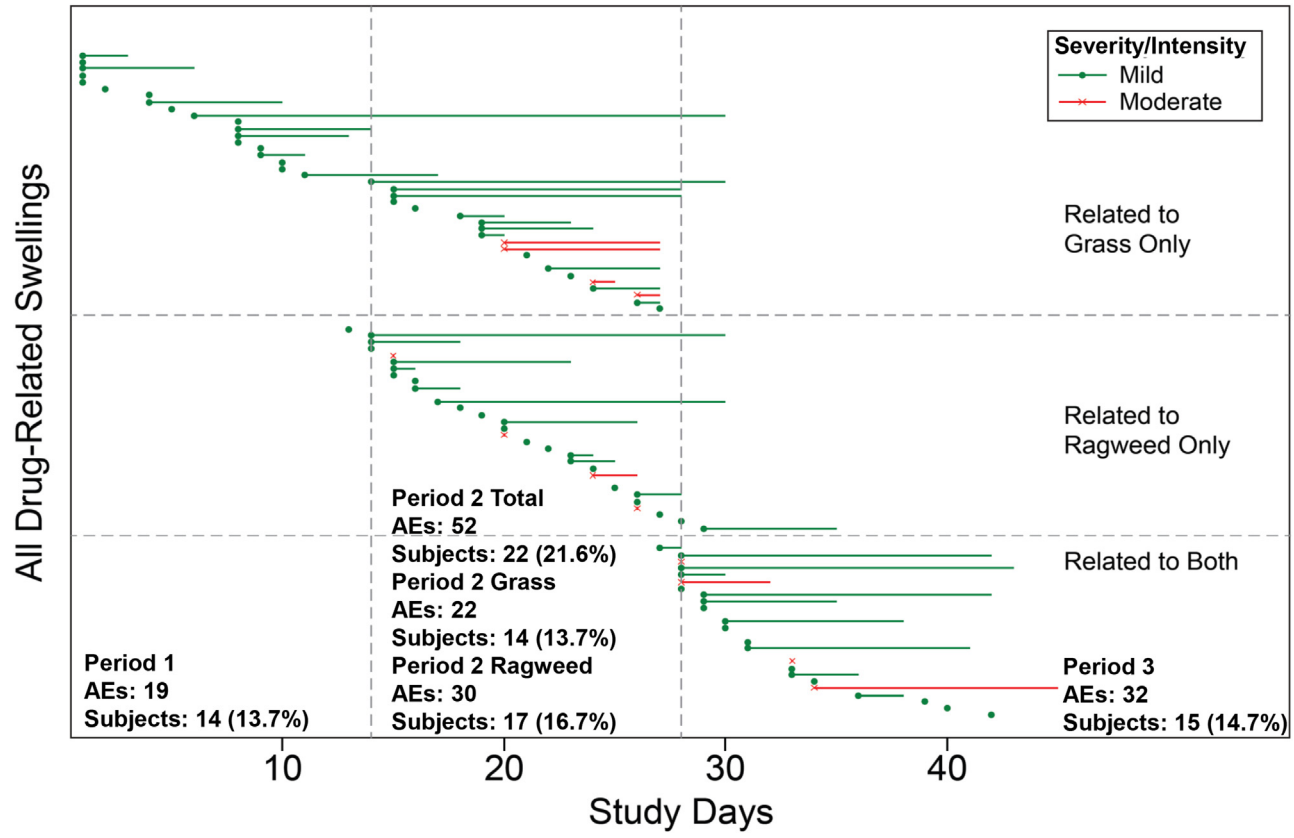


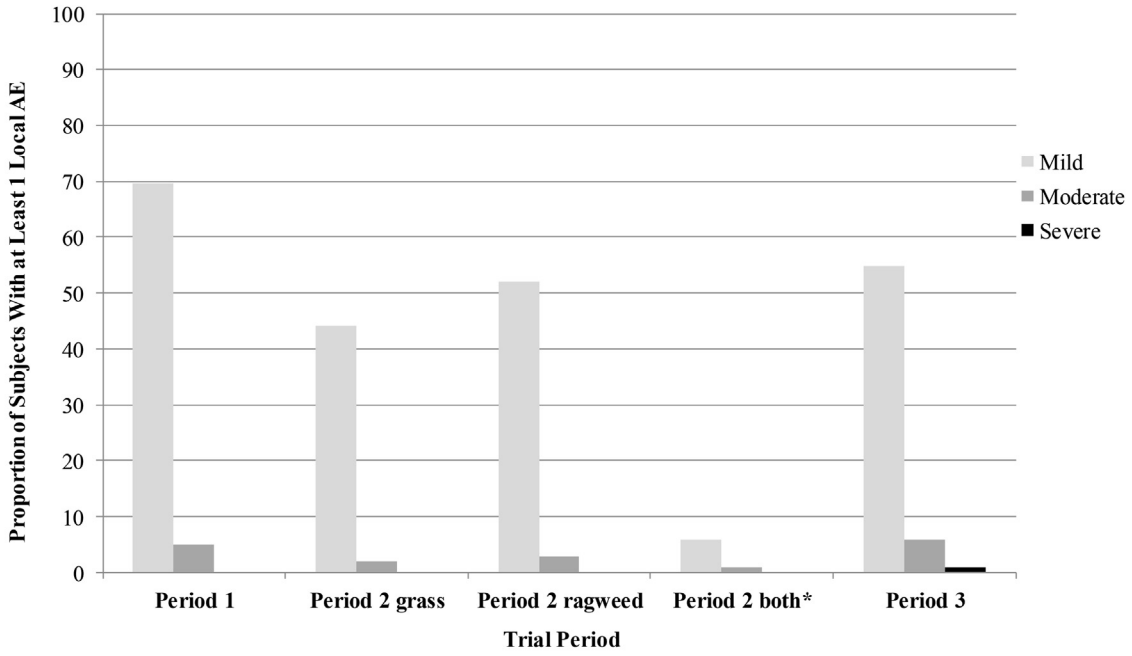
FIGURE 2. Onset and recurrence of local swelling events by treatment period and intensity. For better data visualization, outliers have been removed from the plot (2 subjects). Seven subjects started period 2 treatment on day 13.

Recurrence, duration, and onset of local AEs

In general, most local AEs that were reported by more than 1 subject recurred by medians of 1 to 3 days (Table III). The recurrence of mouth edema and tongue edema tended to be slightly longer than that of other local AEs. During observed doses at the clinic visits, the median durations of local AEs that were reported by more than 1 subject generally ranged from 15 to 25 minutes (Table IV). Overall, the median onset of local AEs that were reported by more than 1 subject in each treatment period was generally within a week of treatment initiation (Table V).

Patient satisfaction

Approximately 90% (89%, 91%, and 88% in periods 1, 2, and 3, respectively) of the subjects throughout all the 3 periods responded that they would definitely/probably take the medication if asked to do so by their doctor.



	Period 1	Period 2	Period 3
Total proportion of subjects, (95% CI)	71 (61, 79)	69 (59, 78)	56 (46, 66)

FIGURE 3. Proportion of subjects with at least 1 local AE by treatment period and intensity. Subjects could be counted more than once (ie, if a subject experienced both a moderate and a mild reaction, the subject was counted twice). The denominator used was all treated subjects (n = 102). *Both tablets attributed as the cause of the AE, or the investigator was not sure which tablet attributed to the AE.

DISCUSSION

Many patients are allergic to both grass and ragweed, and simultaneous treatment of AR/C related to these allergens using SLIT tablets would require dual-tablet administration. This trial is the first to demonstrate a simple and well-tolerated method for introducing dual and simultaneous administration of SLIT tablets. The end points for this trial were selected on the basis of AEs of the most clinical concern and with a frequency high enough to detect a potential safety signal. The primary end point was the proportion of subjects experiencing AEs with the potential to compromise the upper airway (local swellings). It is encouraging that there were no reported severe swellings in the mouth or throat, and all swellings of any type were of mild or moderate intensity and of short duration and recurrence. As expected, there were overall more reports of local swellings during the period when the subjects were introduced to the second allergen SLIT tablet (period 2) compared with the period when subjects received the first allergen SLIT tablet (period 1). It is of interest to note that the introduction of ragweed allergen appears to influence new-onset swellings related to grass SLIT tablet. This may be due to increased tissue hyperreactivity related to ragweed allergen administered in the morning. However, there was no increase in local swelling when comparing the 2 tablets during period 2 separately, and the intensity of local swellings did not worsen (no local swellings assessed as severe were reported during the trial). It still raises the question whether there would be an increased risk of AEs or more severe AEs if 2 tablets are introduced simultaneously from the start. The trial shows that if a subject experiences a swelling it may occur later than the first day of administration, and will typically be noticeable for approximately 20 minutes and reoccur for less than 15 days. Only 1 subject discontinued because of AEs during period 2, indicating that the AEs were tolerable for most subjects and local swellings were noticeable but not bothersome. During the period when both tablets were administered simultaneously (period 3), the proportion of subjects experiencing local swelling was similar compared with the period when subjects received only 1 SLIT tablet. In addition, simultaneous administration was well tolerated. Only 1 subject experienced a severe AE (throat irritation), and simultaneous administration did not increase the proportion of subjects experiencing any local AE, discontinuations due to AEs, or the proportion of subjects using symptomatic medications to treat AEs when compared with single SLIT-tablet administration.

The overall AE profile was similar to that observed with pivotal trials of grass and ragweed SLIT tablets alone.[3,4,7,8] The overall incidence of treatment-emergent AE and TRAEs was higher than that observed in pivotal trials, although, as in the pivotal trials, most of the TRAEs in the present trial were not severe. By period 3, the incidence of TRAEs and most of the individual AEs was similar to that in pivotal trials. There are several reasons that may explain the overall higher incidence of AEs in this trial. One possibility is due to the use of the modified WAO Side Effect Report Card. The solicitation of specific local AEs with every tablet intake may have prompted subjects to be more aware of perceived AEs, as opposed to retrospective recollection at clinic visits. This phenomenon was demonstrated in an analysis of 3 clinical trials, where the percentage of subjects experiencing AEs was higher using solicited methods versus unsolicited AE reporting.[10] In the present trial, the lack of a

TABLE III. Number of days of recurrence (d) of prespecified local AEs* by treatment period†

	Ragweed 12 *Amb a* 1-U and grass 2800 BAU SLIT tablet (N = 102)				
	Period 1	Period 2			Period 3
AE	Grass SLIT tablet	Ragweed SLIT-tablet AM	Grass SLIT-tablet PM	Both SLIT tablets‡	Grass SLIT tablet and ragweed SLIT tablet
Throat irritation, n	54	35	27	1	29
Median (range) (d)	1 (1-26)	1 (1-31)	4 (1-26)	6 (6-6)	2 (1-15)
Oral pruritus, n	51	32	33	2	35
Median (range) (d)	1 (1-42)	2 (1-28)	3.5 (1-42)	8 (1-15)	3 (1-42)
Ear pruritus, n	34	20	20	3	21
Median (range) (d)	1 (1-26)	2 (1-15)	2 (1-26)	10 (1-15)	1.5 (1-29)
Lip swelling, n	12	7	8	0	10
Median (range) (d)	1 (1-13)	1 (1-8)	1 (1-12)	—	2 (1-14)
Glossodynia, n	8	3	6	1	7
Median (range) (d)	1 (1-12)	1.5 (1-3)	2 (1-9)	10 (10-10)	1 (1-9)
Mouth edema, n	4	4	4	0	9
Median (range) (d)	6 (1-7)	4 (1-13)	4 (2-6)	—	2 (1-12)
Oral paresthesia, n	6	3	0	0	1
Median (range) (d)	1 (1-14)	1 (1-13)	—	—	7 (1-13)
Pharyngeal edema, n	5	6	5	0	3
Median (range) (d)	1 (1-3)	1 (1-9)	6 (1-14)	—	14 (3-15)
Swollen tongue, n	5	5	7	0	3
Median (range) (d)	1 (1-25)	1 (1-14)	2 (1-25)	—	3 (1-4)
Lip edema, n	3	2	2	0	1
Median (range) (d)	1 (1-4)	4 (1-7)	3 (1-5)	—	1.5 (1-2)
Palatal edema, n	3	4	3	0	3
Median (range) (d)	1 (1-3)	1 (1-2)	2 (1-14)	—	1 (1-14)
Stomatitis, n	2	1	1	0	0
Median (range) (d)	1 (1-1)	1 (1-1)	1 (1-1)	—	—
Oral hypoesthesia, n	1	2	1	0	1
Median (range) (d)	2 (1-3)	1 (1-2)	1 (1-1)	—	21 (21-21)
Tongue edema, n	1	3	2	0	3
Median (range) (d)	7 (7-7)	1 (1-17)	12 (7-17)	—	16 (1-17)
Oral discomfort, n	0	0	0	0	1
Median (range) (d)	—	—	—	—	1 (1-1)

AM, Morning; *Amb a*, *Ambrosia artemisiifolia*; *BAU*, bioequivalent allergen unit; *PM*, Evening.
*Local AEs prespecified in the protocol. No subjects with available data reported laryngeal edema, oropharyngeal swelling, throat tightness, or dysphagia.
†An AE was counted in a period if it started in that period or if it started in previous periods but was still ongoing for that period.
‡Both tablets attributed as the cause of the AE, or the investigator was not sure which tablet attributed to the AE.

placebo comparison eliminated the ability to demonstrate that the higher event rate was indeed due to soliciting AEs. Another explanation is that the open-label trial design resulted in a reporting bias. Whatever the reason for the higher incidence of AEs, the overall rate of discontinuations due to AEs was 9%, which was similar to that observed in pivotal trials (range of 5%-10% for active treatments).[3,4,7,8] More importantly, it appears that sequential introduction of 2 SLIT tablets followed by simultaneous administration did not result in reduced tolerability or apparent increase in severe AEs. Furthermore, 88% of the subjects in period 3 reported that they would use the treatment if prescribed by their doctor. Together these data indicate that the AEs experienced did not dissuade subjects from dual SLIT-tablet treatment.

Mild events of mouth and tongue ulceration/sores, AEs specifically solicited on the WAO Side Effect Report Card, were reported in this study, which were not as frequently reported in pivotal trials. Investigators visually confirmed ulcers in only 1 subject, and it is uncertain whether the ulcer/sores were more a sensation than an objective finding. The brief recurrence of the ulcers suggests minimal mucosal lesions and suggests that subjects may have misinterpreted the question as "sore mouth/tongue." A published case report suggests that mucosal lesions could affect the safety of SLIT.[11] Therefore, the prescribing information for ragweed and timothy grass SLIT tablet recommends stopping treatment in the case of oral inflammation or wounds to allow complete healing of the oral cavity.[5,6]

Few other studies have investigated the tolerability of SLIT with multiple allergens. A postmarketing survey of 433 children investigated the tolerability of SLIT drops with a single extract versus a mixture of multiple extracts by soliciting AEs via diary cards.[12] During the follow-up period, there was no significant difference in the incidence of AEs between children receiving single or multiple extracts. Most of the AEs were mild and were

TABLE IV. Duration (min)* of prespecified local AEs† by treatment period

	Ragweed 12 *Amb a* 1-U and grass 2800 BAU SLIT tablet (N = 102)		
AE	**Period 1**	**Period 2**	**Period 3**
Throat irritation, n	19	24	11
Median (range) (min)	15 (2-1405)	25 (2-60)	20 (3-60)
Oral pruritus, n	10	12	11
Median (range) (min)	17.5 (5-176)	22.5 (2-60)	15 (5-60)
Ear pruritus, n	10	8	7
Median (range) (min)	15 (3-176)	20 (5-603)	15 (10-20)
Lip swelling, n	1	2	3
Median (range) (min)	25 (25-25)	22.5 (15-30)	20 (10-60)
Glossodynia, n	0	0	1
Median (range) (min)	—	—	120 (120-120)
Mouth edema, n	1	1	2
Median (range) (min)	30 (30-30)	480 (480-480)	21.5 (20-23)
Oral paresthesia, n	2	2	1
Median (range) (min)	27.5 (25-30)	17.5 (5-30)	60 (60-60)
Pharyngeal edema, n	1	2	0
Median (range) (min)	30 (30-30)	60 (60-60)	—
Swollen tongue, n	1	1	0
Median (range) (min)	176 (176-176)	15 (15-15)	—
Palatal edema, n	0	0	1
Median (range) (min)	—	—	20 (20-20)
Stomatitis, n	1	1	0
Median (range) (min)	10 (10-10)	10 (10-10)	—

Amb a, *Ambrosia artemisiifolia*; *BAU*, bioequivalent allergen unit.
*Duration after observed doses during clinic visits.
†Local AEs prespecified in the protocol. No subjects with available data reported laryngeal edema, oropharyngeal swelling, throat tightness, dysphagia, oral hypoesthesia, lip edema, tongue edema, or oral discomfort during the clinic visits.

TABLE V. Onset day of prespecified local AEs* by treatment period†

	Ragweed 12 *Amb a* 1-U and grass 2800 BAU SLIT tablet (N = 102)		
AE	**Period 1**	**Period 2**	**Period 3**
Throat irritation, n	54	47	29
Median (range) (d)	2 (1-15)	2 (1-37)	2 (1-14)
Oral pruritus, n	51	48	35
Median (range) (d)	2 (1-14)	2 (1-41)	1 (1-15)
Ear pruritus, n	34	34	21
Median (range) (d)	2 (1-13)	2 (1-15)	2 (1-15)
Lip swelling, n	12	14	10
Median (range) (d)	3 (1-9)	4 (1-17)	2 (1-8)
Glossodynia, n	8	9	7
Median (range) (d)	7 (1-12)	7 (1-13)	6 (1-12)
Mouth edema, n	4	6	9
Median (range) (d)	1 (1-8)	8 (1-15)	1 (1-16)
Oral paresthesia, n	6	3	1
Median (range) (d)	1 (1-2)	1 (1-2)	1.5 (1-2)
Pharyngeal edema, n	5	9	3
Median (range) (d)	9 (1-10)	5.5 (1-13)	8 (1-16)
Swollen tongue, n	5	10	3
Median (range) (d)	4 (1-10)	3.5 (1-8)	3 (2-8)
Lip edema, n	3	3	1
Median (range) (d)	9 (1-14)	12 (1-35)	6.5 (2-11)
Palatal edema, n	3	7	3
Median (range) (d)	3.5 (1-8)	8.5 (1-13)	3.5 (1-14)
Stomatitis, n	2	2	0
Median (range) (d)	1 (1-1)	6 (1-11)	—
Oral hypoaesthesia, n	1	2	1
Median (range) (d)	1.5 (1-2)	1 (1-5)	16 (16-16)
Tongue edema, n	1	4	3
Median (range) (d)	11 (11-11)	7 (1-14)	1 (1-12)
Oral discomfort, n	0	0	1
Median (range) (d)	—	—	1 (1-1)

Amb a, *Ambrosia artemisiifolia*; *BAU*, bioequivalent allergen unit.
*Local AEs prespecified in the protocol. No subjects with available data reported laryngeal edema, oropharyngeal swelling, throat tightness, or dysphagia.
†Onset days are calculated on the basis of AE start date and the period start date.

equally distributed between the 2 groups. Three children discontinued because of persistent oral pruritus; 2 of the children who discontinued were receiving multiple extracts. A double-blind, randomized, placebo-controlled trial of 58 subjects was primarily focused on the efficacy of single versus a mixture of multiple allergen SLIT drops, but found no significant difference in the number of AEs between these groups.[13]

The present trial was designed using an "add-on" dosing approach. The use of sequential introduction of the SLIT tablets ensured that tolerance to the first tablet was developed before the introduction of the second tablet and that tolerance to both tablets was established before simultaneous administration. The proportion of subjects experiencing a new onset of local swelling or local AEs was markedly lower in period 3 compared with that in period 2, indicating that tolerance was indeed achieved before simultaneous administration. During the trial, subjects who were still experiencing AEs from a previous period were allowed to continue into the next period. In real-world practice, physicians should use discretion when proceeding to dual administration by considering the characteristic and intensity of any recurring AE. During period 2, the administration of the 2 tablets was at different times of the day to allow subjects to determine which tablet was the cause of an AE, if an AE occurred. The use of medications to pretreat for AEs was prohibited to ensure adequate safety monitoring, and the trial was conducted outside the pollen seasons to reduce the incidence of AR/C symptomatic medication use, which could confound AE reporting. This trial was subject to the limitations inherent in open-label studies, including reporting bias as mentioned above. Furthermore, because of the overall low rate of systemic allergic reactions to SLIT, the sample size in this study was not adequate to rule out an increased risk of systemic allergic reactions with dual administration and the results must therefore be interpreted with caution. The safety of dual SLIT-tablet administration in patients with uncontrolled asthma was not assessed and is therefore unknown. In addition, the population of subjects with asthma in the present trial may have been overestimated because asthma status was determined by clinical history and was not confirmed by reversibility or challenge testing.

This trial demonstrated that a 4-week sequential SLIT-tablet dosing schedule without uptitration followed by simultaneous intake of ragweed and timothy grass tablets was well tolerated. This study found that patients who tolerate both grass and ragweed tablets when administration is separated by several hours

may be able to proceed to dual administration of 2 SLIT tablets within 5 minutes of each other under proper supervision. If well tolerated, this may be followed by daily home simultaneous administration of both tablets.

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Dr. Maloney is currently affiliated with Regeneron Pharmaceuticals, Inc., Tarrytown, NY.

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TABLE E1. Side effect report card

	Day ___ _____ Month/day/year		Day ___ _____ Month/day/year	
Record	**Yes**	**No**	**Yes**	**No**
Did you take the study tablet today?				
For each day you took your study tablet, mark whether or not you experienced any of the side effects listed below within 60 min after you took the study tablet. If the answer is Yes, please record the side effect start time in the box:				
Side effect	**Yes**	**No**	**Yes**	**No**
Taste alteration/food tastes different				
Mouth ulcer/sore in the mouth				
Swelling of the uvula/back of the mouth				
Itching in the mouth				
Itching in the ear				
Swelling of the lips				
Swelling of the tongue				
Tongue pain				
Tongue ulcer/sore on the tongue				
Throat irritation/tickle				
Throat swelling				
Stomach pain				
Nausea				
Diarrhea				
Vomiting				
If you took any medications to treat the side effect(s) you experienced, please answer the questions below.				
	Yes	**No**	**Yes**	**No**
Did you take a medication for any of the above side effects?				
If yes, please list them for each day				

TABLE E2. Treatment-related AEs experienced by ≥5% of the subjects overall and by treatment period

		Ragweed 12 *Amb a* 1-U and Grass 2800 BAU SLIT tablet (N = 102)				
		Period 1	Period 2			Period 3
% of subjects reporting	Overall*	Grass SLIT tablet	Ragweed SLIT-tablet AM	Grass SLIT-tablet PM	Both SLIT tablets†	Grass SLIT tablet and ragweed SLIT tablet
Throat irritation	70	53	34	27	1	28
Oral pruritus	66	50	31	32	2	34
Ear pruritus	50	33	20	20	3	21
Lip swelling	25	12	7	8	0	9
Glossodynia	18	8	3	6	1	7
Upper abdominal pain	17	7	7	8	0	6
Mouth ulceration	17	7	2	5	0	5
Pharyngeal edema	15	5	6	5	0	3
Swollen tongue	15	5	5	7	0	3
Mouth edema	12	4	4	4	0	8
Tongue ulceration	12	8	1	2	0	1
Palatal edema	12	3	4	3	0	3
Nausea	9	3	4	5	0	2
Oral paresthesia	9	6	3	0	0	1
Eye pruritus	7	3	1	0	1	3
Rhinorrhea	7	5	0	2	1	1
Dysgeusia	7	5	1	0	0	1
Tongue edema	5	1	3	2	0	3
Lip pruritus	5	2	1	0	0	2
Lip edema	5	3	2	2	0	1

AM, Morning; *Amb a*, *Ambrosia artemisiifolia*; *BAU*, bioequivalent allergen unit; *PM*, evening.
*Subjects reporting at least 1 event at any time during the trial.
†Both tablets attributed as the cause of the AE, or the investigator was not sure which tablet attributed to the AE.