Sublingual immunotherapy for peanut allergy: Long-term follow-up of a randomized multicenter trial

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Background: We previously reported the initial results of the first multicenter, randomized, double-blind, placebo-controlled clinical trial of peanut sublingual immunotherapy (SLIT), observing a favorable safety profile associated with modest clinical and immunologic effects in the first year.

Objective: We sought to provide long-term (3-year) clinical and immunologic outcomes for our peanut SLIT trial. Key end points were (1) percentage of responders at 2 years (ie, could consume 5 g of peanut powder or a 10-fold increase from baseline), (2) percentage reaching desensitization at 3 years, (3) percentage attaining sustained unresponsiveness after 3 years, (4) immunologic end points, and (5) assessment of safety parameters.

Methods: Response to treatment was evaluated in 40 subjects aged 12 to 40 years by performing a 10-g peanut powder oral food challenge after 2 and 3 years of daily peanut SLIT therapy. At 3 years, SLIT was discontinued for 8 weeks, followed by another 10-g oral food challenge and an open feeding of peanut butter to assess sustained unresponsiveness.

Results: Approximately 98% of the 18,165 doses were tolerated without adverse reactions beyond the oropharynx, with no severe symptoms or uses of epinephrine. A high rate (>50%) discontinued therapy. By study's end, 4 (10.8%) of 37 SLIT-treated participants were fully desensitized to 10 g of peanut powder, and all 4 achieved sustained unresponsiveness. Responders at 2 years showed a significant decrease in peanut-specific basophil activation and skin prick test titration compared with nonresponders.

Conclusions: Peanut SLIT induced a modest level of desensitization, decreased immunologic activity over 3 years in responders, and had an excellent long-term safety profile. However, most patients discontinued therapy by the end of year 3, and only 10.8% of subjects achieved sustained unresponsiveness. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Peanut allergy, sublingual immunotherapy, desensitization, food allergy, follow-up*

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Abbreviations used
OFC: Oral food challenge
OIT: Oral immunotherapy
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
SPT: Skin prick test

Peanut allergy is a leading cause of fatal food-induced anaphylaxis, affects approximately 1.4% of children and 0.6% of adults, and adversely affects quality of life.[1-3] Standard clinical care for peanut allergy involves strict dietary avoidance and ready access to emergency medications.[4] The onset of peanut allergy generally occurs in childhood, persists to adulthood in the vast majority of patients, and requires lifelong dietary avoidance to prevent severe allergic reactions.[3,5] Although the need is great, there are presently no treatments for peanut allergy ready for broad implementation in mainstream clinical care. The risk of potentially fatal reactions coupled with the need for lifelong and life-altering dietary and lifestyle modifications places significant burdens on affected patients and their families. The development of a safe and efficacious active therapy targeting peanut allergy is a critical unmet need to mitigate the adverse medical, psychosocial, and economic effects of this increasingly prevalent disorder.[3]

Traditional subcutaneous immunotherapy (SCIT) has proved unsafe for peanut allergy[6,7]; however, mucosally targeted immunotherapeutic approaches, such as oral immunotherapy (OIT) and sublingual immunotherapy (SLIT), have shown promise in phase I and early phase II trials.[8-13] Collectively, this work has established that mucosal immunotherapy can induce desensitization (reduced reactivity while on therapy) in subsets of subjects characterized by increases in the threshold dose required to elicit symptoms during peanut challenge and associated with changes in antigen-specific immune responses.

Although peanut OIT has shown potential as a treatment, it has been limited by heterogeneous clinical responses, high rates of adverse reactions, and potential for loss of protection with cessation of therapy.[14] Attempts to balance enhanced therapeutic efficacy with reduced allergic side effects have generated increased interest in the application of potentially safer and more convenient immunotherapeutic approaches. SLIT is an appealing alternative to OIT, with some studies reporting a better safety profile and demonstrated efficacy in treatment of food allergy to multiple foods, including kiwi, hazelnut, peach, milk, and peanut.[10,11,15-18] We previously reported initial results of the first multicenter, randomized, double-blind, placebo-controlled clinical trial of peanut SLIT,[11] observing that peanut SLIT had a favorable safety profile associated with modest clinical and immunologic effects in the first year of therapy. After 44 weeks of SLIT, 70% (14/20) of treated subjects were defined as responders (those who could consume either a cumulative dose of 5 g of peanut powder or a 10-fold increase in the amount of peanut powder compared with baseline oral food challenge [OFC]) compared with 15% (3/20) of placebo-treated subjects. After 68 weeks of SLIT, the median successfully consumed dose was significantly increased compared with week 44, suggesting the possibility that longer treatment duration conferred additional benefit to treated subjects.[11] However, longer-term safety and efficacy outcomes of peanut SLIT have not been reported, and these data are crucial for understanding the therapeutic potential of this approach.[19] The goal of the current report is to provide long-term (3-year) clinical and immunologic outcomes for subjects undergoing a peanut SLIT trial.

METHODS

Study design

The first phase of this randomized, double-blind, placebo-controlled peanut SLIT trial was reported previously.[11] In the first phase 40 subjects were randomized 1:1 to active versus placebo SLIT, with 20 subjects randomized to each group. The initial subjects in the active SLIT group were treated through week 44 with up to 1386 μg of peanut protein SLIT daily. At week 44, the peanut SLIT– and placebo-treated subjects completed a 5-g OFC and were unblinded, whereas placebo crossover subjects were escalated after unblinding at week 44 to higher-dose peanut SLIT up to 3696 μg/d (designated as the high-dose crossover group; the original peanut SLIT group maintained a maximum dose of 1386 μg/d peanut protein). The second open-label phase of this study is reported here; both groups were to receive up to a total of 164 weeks (3 years) of active peanut SLIT (Fig 1).

Response to treatment was evaluated by using 10 g of peanut powder (approximately 5 g of peanut protein; for reference, 1 peanut has 250-280 mg of peanut protein, and thus 5 grams is equivalent to 16 to 18 peanuts). The intent was to escalate to a dose of 1386 μg in all subjects, but some subjects tolerated only a much smaller dose. OFCs at years 2 and 3 (weeks 116 and 164) occurred during peanut SLIT daily maintenance therapy. OFCs were performed per standard protocol as previously reported and included an initial OFC during SLIT to assess clinical desensitization.[11] Subjects who passed the full 10-g OFC at 3 years were discontinued from SLIT dosing for 8 weeks. The sustained unresponsiveness OFC after 8 weeks was a combination of a 10-g OFC followed by an open feeding of 2 tablespoons of peanut butter 1 hour later. Treatment responders were defined as the following: (1) *2-year responders* were subjects who either successfully consumed a cumulative dose of 5 g of peanut powder (approximately 2.5 g of peanut protein) during peanut SLIT dosing or experienced an at least 10-fold increase in the amount of peanut powder compared with the baseline OFC without dose-limiting symptoms; (2) *3-year desensitization responders* were subjects who successfully consumed a cumulative dose of 10 g of peanut powder (approximately 5 g of peanut protein) without dose-limiting symptoms during peanut SLIT dosing; and (3) *3-year sustained unresponsiveness responders* were subjects who successfully consumed a cumulative dose of 10 g of peanut powder (approximately 5 g of peanut protein) plus an open feeding of peanut protein without dose-limiting symptoms (8 weeks after discontinuation of peanut SLIT dosing). If a desensitization response was not attained by year 2, as defined above, dosing was discontinued. Subjects were scheduled for a 3-year evaluation irrespective of whether they were receiving SLIT dosing, with those discontinuing from dosing followed for mechanistic studies only. Key end points for SLIT treatment and for comparison between standard SLIT and higher-dose SLIT included the following: (1) the percentage of subjects who were responders at year 2 (ie, could consume 5 g of peanut powder or at least a 10-fold increase from baseline during an OFC); (2) the percentage of subjects reaching desensitization at each time point; (3) the percentage of subjects attaining sustained unresponsiveness by year 3; (4) immunologic end points, including changes in peanut IgE and IgG levels, end point titration skin prick test (SPT) responses, and basophil activation; and (5) assessment of safety parameters, including adverse events, serious adverse events in response to peanut SLIT, and long-term tolerability.

Study population

Subject recruitment, including inclusion and exclusion criteria, was previously described and included 40 subjects aged 12 to 40 years from 5 US sites (New York, New York; Baltimore, Maryland; Little Rock, Arkansas; Denver, Colorado; and Durham, North Carolina; the North Carolina subjects moved with the investigative team from Duke to the University of North

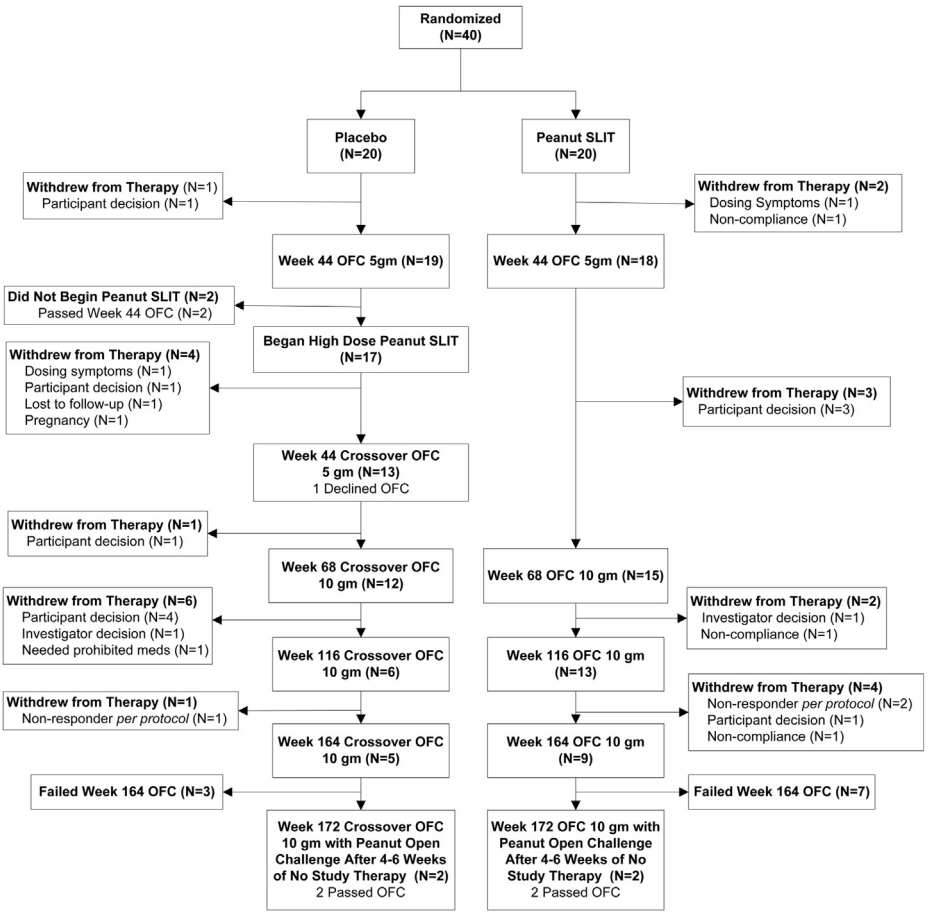

FIG 1. Subject disposition.

Carolina–Chapel Hill in March 2012).[11] The study was conducted with investigational new drug approval from the US Food and Drug Administration. The National Institute of Allergy and Infectious Diseases Allergy and Asthma Data and Safety Monitoring Board and local institutional review boards approved study procedures, and written informed consent was obtained.

Study protocol

Subjects were instructed to remain on a peanut-free diet throughout the entire study and required to carry an epinephrine autoinjector. Solicited dosing symptoms were recorded on a daily basis by using a home diary. Other unsolicited adverse events were recorded separately. The study drug was administered sublingually, held for 2 minutes, and then swallowed.

Maintenance SLIT dosing. A standard peanut SLIT solution was manufactured and administered to all subjects (see the Methods section in this article's Online Repository at www.jacionline.org), as previously described.[11] For subjects initially treated with active peanut SLIT, maintenance dosing continued at a minimum dose of 165 μg and a maximum maintenance dose of 1386 μg of peanut protein through the end of the study. For placebo crossover subjects receiving active peanut SLIT, maintenance dosing continued at a minimum dose of 165 μg and a maximum maintenance dose of 3696 μg through the end of the study.

OFC. A 10-g OFC with peanut powder (approximately 5 g of peanut protein) was conducted at years 2 and 3 of maintenance peanut SLIT dosing per protocol (see the Methods section in this article's Online Repository for full OFC methods). Subjects who passed the year 3 OFC assessing desensitization discontinued peanut SLIT therapy for 8 weeks and completed a sustained responsiveness OFC with a combination of a 10-g OFC and an open feeding of 2 tablespoons of peanut butter. Subjects who passed the final year 3 OFC assessing sustained unresponsiveness were instructed to add peanut to their diet, whereas those who failed either the year 3 OFC assessing desensitization or the year 3 OFC assessing sustained unresponsiveness were provided dietary guidance based on their OFC outcomes, with most participants resuming strict avoidance but others introducing peanut to the diet in amounts specified by the site investigator.

Adverse events. Mild, moderate, and severe adverse events were defined by using standard adverse event reporting criteria. Severity of adverse events was determined through site reporting, with serious adverse events reviewed by a Statistical and Clinical Coordinating Center (SACCC) medical monitor. For dosing and OFC symptoms, the site reported a severity associated with the symptoms. Severity was determined based on type of reaction; for example, a mild skin reaction could be 1 to 2 hives, a moderate reaction could be a few hives, and a severe reaction could be extensive hives and swelling. Sites were provided with guidance on how to assess severity based on standard Consortium of Food Allergy Research case report forms and a manual of procedures.

End point titration SPTs

End point titration SPTs were performed with serial 10-fold dilutions of peanut extract at baseline and annually, as previously reported.[11]

Immunologic studies

Basophil activation. Basophil activation, as measured by using CD63 upregulation, was evaluated by means of flow cytometry at baseline, week 29, week 44, and annually at the time of the OFC, as previously described.[11]

TABLE I. Baseline characteristics

	Treatment	
	High-dose crossover group, n = 17 (%)	Peanut SLIT group, n = 20 (%)
Male sex	64.7	65.0
Additional food allergy	64.7	85.0
Physician's diagnosis of asthma	58.8	55.0
Allergic rhinitis	70.6	70.0
Age (y), median (Q1-Q3)	16.0 (14.0-18.0)	14.0 (13.0-18.0)
Baseline SPT peanut score (mm), median (Q1-Q3)	12.0 (10.0-14.8)	13.3 (9.5-17.5)
Baseline peanut IgE (kU_A/L), median (Q1-Q3)	30.4 (7.1-91.1)	31.3 (3.2-42.4)
Baseline OFC dose at first symptom (mg), median (Q1-Q3)	6.0 (1.0-71.0)	6.0 (1.0-46.0)
Baseline successfully consumed OFC dose (mg), median (Q1-Q3)	71.0 (6.0-146.0)	21.0 (1.0-146.0)

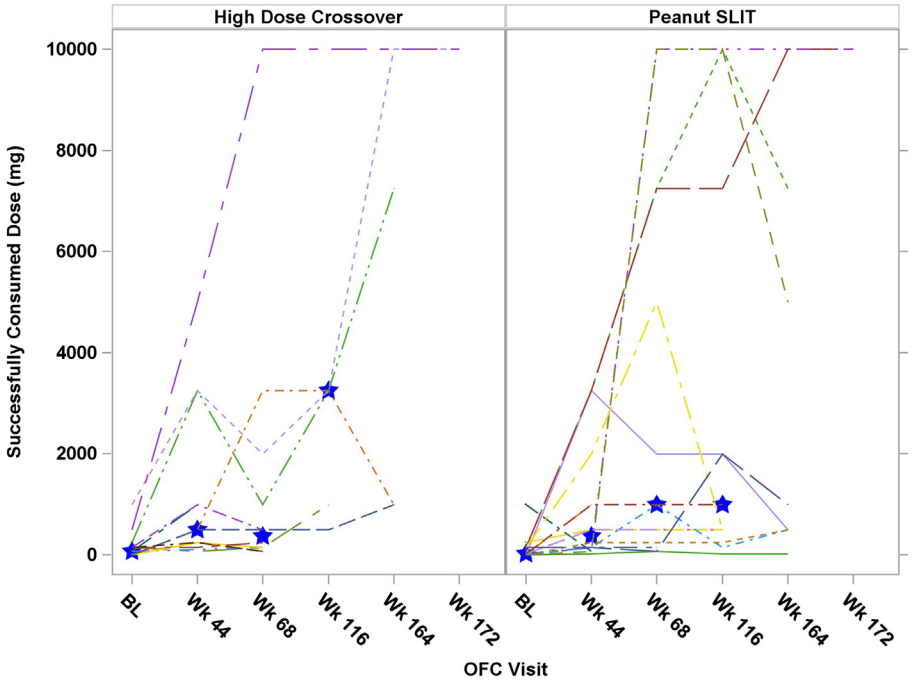

FIG 2. OFC results. Subjects were discontinued from treatment per protocol if they did not meet specific criteria at the year 2 OFC (OFC threshold ≥5000 mg or 10× baseline), and therefore the median values at year 3 are not presented. *Blue stars* indicate the group median at each time point. There was no statistically significant difference in medians between treatment groups. *BL*, Baseline.

Immunoglobulins. Total IgE levels were measured by means of immunoassay, and peanut-specific IgE and IgG_4 levels were measured with the ImmunoCAP 100 (Thermo Fisher Scientific, Waltham, Mass) at baseline; at weeks 29, 44, and 68; and annually at the time of the OFC, as previously reported.[11]

Statistical analysis

The high-dose crossover and peanut SLIT groups, as well as the responder versus nonresponder groups, were compared by using the Fisher exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. Repeated-measures models were fit by using unstructured covariance to evaluate basophil activation, immunoglobulin levels, and the peanut end point titration area under the curve. Because subjects who were nonresponders were intentionally discontinued from dosing at year 2 per protocol, models were limited to data through year 2. Covariates included study visit, baseline values, and year 2 response. Interactions were evaluated and included if statistically significant. All analyses were performed with the use of SAS software, version 9.2 (SAS Institute, Cary, NC).

RESULTS

As reported in the article by Fleischer et al,[11] a total of 40 subjects were initially randomized, with 20 receiving low-dose peanut SLIT and 20 receiving placebo. Among the 20 subjects who received peanut SLIT, 14 (70%) were defined as responders by week 44 compared with only 3 (15%) from the placebo arm ($P = .001$). From the placebo group, 17 subjects crossed over to the high-dose crossover arm, and 7 (44%) of 16 were categorized as responders at the week 44 crossover OFC (1 subject declined the week 44 crossover OFC, and 4 discontinued dosing before the OFC and were counted as nonresponders per the protocol). There were no statistical differences in baseline characteristics between treatment groups (Table I).

Subject disposition over the course of the study is represented in Fig 1, including the reasons for subject withdrawal and the final subject status at the final OFC at year 3. In the high-dose crossover group 12 of 17 withdrew before the year 3

TABLE II. Successfully consumed dose by year 2 response and treatment group

		Treatment group												
		Placebo/high-dose crossover group							Peanut SLIT group					
		No.	Mean	Minimum	Q1	Median	Q3	Maximum	No.	Mean	Minimum	Q1	Median	Q3	Maximum
OFC type	2-y Responder														
Baseline (2 g)	Yes	4	186	1.0	1.0	123.5	371.0	496	11	44.1	0.0	1.0	1.0	146	146
	No	13	159.1	1.0	21.0	71.0	146.0	996	9	297.6	0.0	21.0	146	246	996
	All	17	165.4	1.0	6.0	71.0	146.0	996	20	158.2	0.0	1.0	21.0	146	996
Initial week 44 (5 g)	2-y Responder														
	Yes	4	82.3	6.0	6.0	38.5	158.5	246	11	1,091.5	21.0	146	246	3,246	3,246
	No	13	240.2	1.0	21.0	146	246	996	7	603.1	21.0	71	496	996	1,996
	All	17	203.1	1.0	6.0	146	246	996	18	901.6	21.0	146	371	996	3,246
Crossover week 44 (5 g)	2-y Responder														
	Yes	4	2,308.5	496	496	1,871	4,121	4,996	—	—	—	—	—	—	—
	No	8	774.1	71	196	246	996	3,246	—	—	—	—	—	—	—
	All	12	1,285.6	71	246	496	2,121	4,996	—	—	—	—	—	—	—
Crossover week 68/week 68 (10 g)	2-y Responder														
	Yes	4	3,683.5	496	746	2,121.0	6,621	10,000	11	3,578.5	71	246	996	7,246	10,000
	No	8	414.8	71	108.5	146.0	371	1,996	4	1,533.5	146	321	496	2,746	4,996
	All	12	1,504.3	71	146	371.0	1,496	10,000	15	3,033.2	71	246	996	7,246	10,000
Crossover year 2/year 2 (10 g)	2-y Responder														
	Yes	4	4,246	496	1,871	3,246	6,621	10,000	11	3,922.1	21.0	246	1,996	10,000	10,000
	No	2	2,121	996	996	2,121	3,246	3,246	2	496	496	496	496	496	496
	All	6	3,537.7	496	996	3,246	3,246	10,000	13	3,395	21.0	496	996	7,246	10,000
Crossover year 3/year 3 (10 g)	2-y Responder														
	Yes	4	4,808.5	996	996	4,121	8,621	10,000	9	3,860.3	21.0	496	996	7,246	10,000
	No	1	10,000	10,000	10,000	10,000	10,000	10,000	—	—	—	—	—	—	—
	All	5	5,846.8	996	996	7,246	10,000	10,000	9	3,860.3	21.0	496	996	7,246	10,000
Crossover year 3/year 3 (10 g)	2-y Responder														
	Yes	1	10,000	10,000	10,000	10,000	10,000	10,000	2	10,000	10,000	10,000	10,000	10,000	10,000
	No	1	10,000	10,000	10,000	10,000	10,000	10,000	—	—	—	—	—	—	—
	All	2	10,000	10,000	10,000	10,000	10,000	10,000	2	10,000	10,000	10,000	10,000	10,000	10,000

OFC, 2 of 5 passed the year 3 OFC, and both of those subjects passed the year 3 sustained unresponsiveness OFC after being off treatment for 8 weeks. In the initial active peanut SLIT group, 11 of 20 withdrew before the year 3 OFC, and 2 of 9 passed the year 3 OFC, both of whom passed the year 3 sustained unresponsiveness OFC. By using the definitions provided above, 4 (23.5%) of 17 in the high-dose crossover group versus 11 (55%) of 20 in the peanut SLIT group were categorized as responders at year 2 ($P = .09$), whereas 2 (11.8%) of 17 in the high-dose crossover group and 2 (10%) of 20 in the peanut SLIT group were categorized both as desensitized at year 3 and having sustained unresponsiveness at year 3.

A comparison of OFC results between the high-dose crossover and peanut SLIT groups is presented in Fig 2. This figure shows the median successfully consumed dose between these groups only to the year 2 OFC because nonresponders at year 2 were subsequently withdrawn from dosing per protocol. There were no significant differences in successfully consumed dose at any challenge time point between the 2 treatment groups. The effect of dosing beyond year 2 could not be determined because of subject withdrawal and per-protocol discontinuation of dosing for those not responding by year 2. Table II displays the details of the OFCs divided by treatment group, as well as the year 2 response. The median time on dosing through year 2 was 771 days for the high-dose crossover group and 825 days for the peanut SLIT group. Of note, there are 3 fewer year 2 responders in both treatment groups compared with the 44-week OFC because these subjects withdrew before the year 2 OFC.

As noted, there was a high rate of subject withdrawal from this protocol. One subject withdrew while receiving placebo, and of the 17 subjects who crossed over to the high-dose group, one withdrew because of dosing symptoms, 6 withdrew because of participant decision, 1 was withdrawn per protocol as a nonresponder; the remaining 4 withdrew for other miscellaneous reasons (ie, lost to follow-up, investigator decision, need for a prohibited medication, and pregnancy). From the original peanut SLIT group, 4 withdrew because of participant decision, 3 withdrew because of noncompliance, 2 were withdrawn as nonresponders, 1 withdrew because of dosing symptoms, and 1 was withdrawn because of investigator decision. With regard to the participants who chose to withdraw for reasons other than dosing symptoms or noncompliance, most believed that the daily dosing was too difficult to maintain.

Dose-related adverse reactions after the OFC at 44 weeks on active therapy for the high-dose crossover group and after the week 44 OFC for the peanut SLIT group are summarized in Table III. Overall, dose-related symptoms were reported in 18.3% of doses in the high-dose crossover group after 44 weeks of active therapy and 18.1% of doses received by subjects in the peanut SLIT group after 44 weeks of active therapy. The vast majority of reactions were isolated oropharyngeal symptoms; 1 subject receiving peanut SLIT had a moderate dosing symptom of throat tightness without hoarseness. No subjects had severe dosing-related symptoms, and no dosing-related reaction required treatment with epinephrine. Adverse events were reported separately from dosing reactions. In the period after 44 weeks of active therapy, there were 112 adverse events from

TABLE III. Post–week 44 crossover OFC/week 44 OFC dosing symptom summary by dose

Visit type	No. of doses	Any symptom		Any symptom excluding oral pharyngeal		Oral pharyngeal symptoms		Skin		Respiratory	
		No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent
High-dose crossover group											
All	7,385	1,352	18.3	301	4.1	1,326	18.0	17	0.2	262	3.5
Clinic	12	9	75.0	3	25.0	9	75.0	0	0.0	3	25.0
Home	7,373	1,343	18.2	298	4.0	1,317	17.9	17	0.2	259	3.5
Peanut SLIT group											
All	10,780	1,950	18.1	75	0.7	1,912	17.7	8	0.1	60	0.6
Escalation	5	5	100.0	4	80.0	4	80.0	0	0.0	4	80.0
Clinic	55	26	47.3	1	1.8	25	45.5	0	0.0	1	1.8
Home	10,720	1,919	17.9	70	0.7	1,883	17.6	8	0.1	55	0.5

12 high-dose crossover subjects reported; 6 were of moderate severity, none were severe, and all were unrelated to the study product. During this same period, there were 83 adverse events from 13 subjects receiving peanut SLIT reported; 14 were of moderate severity, and 1 was a life-threatening anaphylactic reaction to the year 3 OFC. The only adverse event definitely related to the study product was a mild contact reaction to the study product.

Mechanistic results

Immunologic changes. In the repeated-measures analysis described in the Methods section, there was no significant difference between treatment groups over time in immunoglobulin levels, basophil activation, or peanut-titrated SPT responses. We focused our analysis on differences between subjects who were responders and those who were nonresponders at 2 years. For the subjects who were treated with placebo during the first year and then given a high dose of peanut SLIT (the high-dose crossover group), immunoglobulin and basophil baseline values for the analyses were from the time point just before crossing over.

Immunoglobulins. Total IgE, peanut-specific IgE, and peanut-specific IgG_4 levels were not statistically different for those categorized as year 2 responders versus those who were not. However, median peanut-specific IgG_4 levels were observed to be slightly higher for year 2 responders (see Fig E1 in this article's Online Repository at www.jacionline.org).

Basophil activation. Based on results from the repeated-measures analyses of percentages of $CD63^+$ basophils for the 4 different peanut stimulant levels, the 2-year responders had significantly lower percentages of $CD63^+$ basophils than nonresponders for peanut stimulant levels of 0.1 μg ($P = .02$), 0.01 μg ($P = .002$), and 0.001 μg ($P = .03$). There was a significant interaction between study visit and 2-year responder status at peanut stimulant levels of 0.01 μg ($P = .009$) and 0.001 μg ($P = .03$), indicating that the magnitude of effect is not constant over time. The change from baseline in percentage of $CD63^+$ basophils was observed to be lower for the 2-year responders at all peanut stimulant levels at almost every visit (Fig 3). Note in Fig 3 that the median percentage of $CD63^+$ basophils is predominantly less than zero for the 2-year responders but not for the nonresponders. [F3-4/C]

Peanut SPT end point titration

Peanut SPT end point titration was performed at baseline and at around 1, 2, and 3 years of therapy. In a repeated-measures analysis of the peanut end point titration area under the curve through year 2, there was a significantly greater decrease over time in the area under the curve in 2-year responders versus nonresponders ($P = .003$, see Fig E2 in this article's Online Repository at www.jacionline.org).

DISCUSSION

This study presents unique data on long-term open-label follow-up from the first multicenter, randomized, placebo-controlled trial of peanut SLIT.[11] Briefly, our previous study showed that peanut SLIT was generally safe and induced a modest level of desensitization in the majority of treated subjects compared with placebo. The results presented here extend these observations beyond our previous report of week 68 data from the lower-dose (1386 μg/d peanut protein) peanut SLIT–treated arm of the randomized study and week 44 results from the high-dose crossover (3696 μg/d peanut protein) participants. The current study includes up to 3 years of therapy with a daily maintenance dose of 1386 μg of peanut protein in persons originally randomized to active treatment and a dose of 3696 μg of peanut protein in the group crossing over to active treatment from the placebo group. This longer-term study includes assessment of sustained unresponsiveness (after 8 weeks off of peanut SLIT) at year 3 for participants showing desensitization to 10 g of peanut powder (approximately 5 g of peanut protein). By study's end, 4 participants were fully desensitized to 10 g of peanut powder, 1 of whom was not considered a responder at year 2, and all 4 of whom showed sustained unresponsiveness. Overall, we report here 4 important new findings in the novel context of long-term treatment with peanut SLIT: (1) differences in outcomes using 1386 or 3696 μg of daily peanut protein were not observed, but conclusions are limited due to the high dropout rate; (2) peanut SLIT induced a modest level of desensitization, but only a few achieved sustained unresponsiveness; (3) a high rate of participants discontinued therapy; and (4) peanut SLIT has a favorable long-term safety profile. Additionally, we observed immunologic responses to therapy correlating with clinical outcomes.

Of the above findings, 2 key observations were the low rate of significant adverse reactions to dosing and, despite this, a high rate of participant withdrawal. Regarding safety, the previously reported first 44 weeks of treatment included 10,855 doses in which 95.2% were symptom free, excluding oropharyngeal

TABLE III. *(Continued)*

Visit type	No. of doses	Gastrointestinal		Other		Treated		Treated with epinephrine		Mild		Moderate		Severe	
		No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent
High-dose crossover group															
All	7,385	16	0.2	13	0.2	26	0.4	0	0.0	301	4.1	0	0.0	0	0.0
Clinic	12	0	0.0	0	0.0	0	0.0	0	0.0	3	25.0	0	0.0	0	0.0
Home	7,373	16	0.2	13	0.2	26	0.4	0	0.0	298	4.0	0	0.0	0	0.0
Peanut SLIT group															
All	10,780	7	0.1	2	0.0	5	0.0	0	0.0	74	0.7	1	0.0	0	0.0
Escalation	5	0	0.0	0	0.0	0	0.0	0	0.0	4	80.0	0	0.0	0	0.0
Clinic	55	0	0.0	0	0.0	0	0.0	0	0.0	1	1.8	0	0.0	0	0.0
Home	10,720	7	0.1	2	0.0	5	0.0	0	0.0	69	0.6	1	0.0	0	0.0

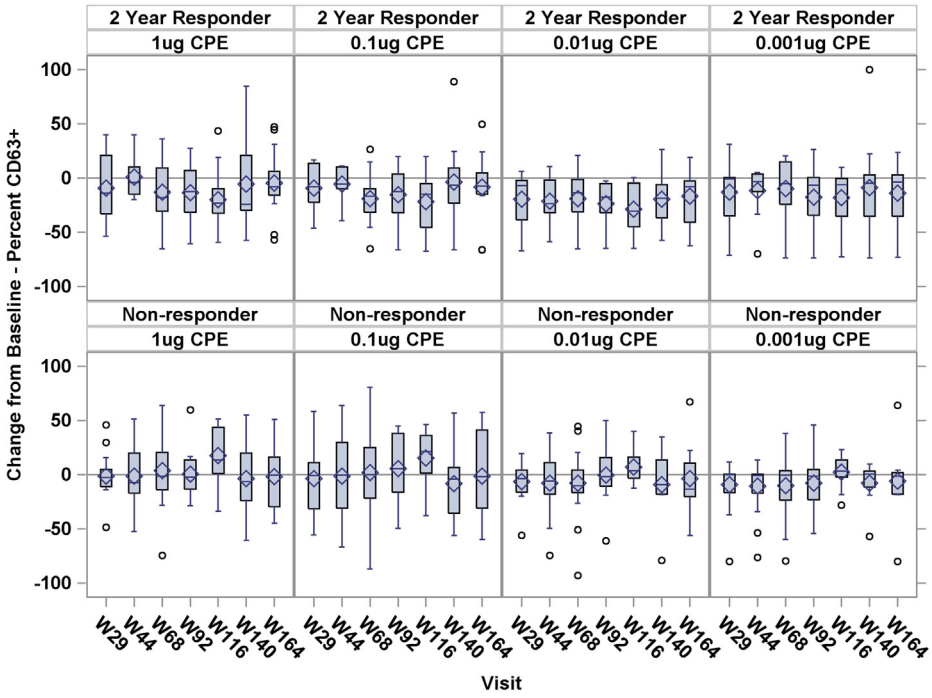

FIG 3. Change from baseline in percentage of $CD63^+$ basophils by 2-year response: all subjects. *CPE,* Crude peanut extract.

symptoms. During the initial 44 weeks of therapy, 1 participant had experienced a dose-related serious adverse event. This follow-up after 44 weeks of therapy included 18,165 additional doses, with greater than 97.9% of doses without reactions beyond the oropharynx and no severe symptoms or use of epinephrine. Despite this safety profile,[20,21] participant withdrawal was high and evenly distributed between the 2 phases of the study. In the first phase of the study through 44 weeks of active therapy, 2 participants withdrew because of dosing symptoms, although none did so during long-term follow-up. Therefore dosing side effects after a year of therapy do not appear to be a cause for withdrawal. However, withdrawal was common for "participant decision" (n = 11) or nonadherence (n = 3). Although motivation for discontinuation was not formally assessed, the difficulty of maintaining daily therapies, mild oral discomfort (17.8% of doses), and a lack of robust responses as measured during OFCs are likely causes (ie, subjects still reacting at follow-up OFCs might have been discouraged by the absence of more significant protection). Additionally, the participants were adolescents and adults in whom lifestyle issues might be a concern, which is in contrast to longer-term studies of food immunotherapy with young children in which parental oversight might maintain adherence.[22] The high rate of discontinuation in this study was still not as high as that seen in clinical treatment for environmental allergies. In a review of 6486 patients starting SLIT or SCIT for environmental allergens in The Netherlands, only 18% of users reached the minimally required treatment duration of 3 years (SCIT, 23%; SLIT, 7%); for those receiving SLIT, 62% discontinued by 1 year and 93% discontinued by 3 years.[23] Clearly, more studies will be needed to evaluate the practical application of SLIT and other proposed daily immunotherapies to address safety and adherence.

We previously noted improved desensitization with longer duration of therapy from 44 to 68 weeks of treatment with peanut SLIT.[11] Unfortunately, in this follow-up study it is not possible to conclude whether longer treatment (ie, beyond 68 weeks) resulted in improved desensitization because of participant dropout and elimination from dosing per protocol when participants did not meet the definition of a responder at year 2. However, there were sufficient participant data to address 2-year outcomes when comparing responders with nonresponders for mechanistic studies. Among the antibody tests, only median peanut-specific IgG_4 levels were observed to be slightly higher among the year 2 responders, but the repeated-measures analysis did not find a statistically significant difference. This marker of successful desensitization has been noted in prior immunotherapy studies,[9,22,24] with a more robust response observed in those receiving OIT compared with those receiving SLIT.[12] Similarly, our year 2 responders showed a stronger reduction in basophil activation than nonresponders, an effect that is an extension of our initial observation in which basophil activation was suppressed in treated compared with untreated participants.[11] The change from baseline for the area under the SPT end point titration curve was improved in responders compared with nonresponders to year 2, an extension of our prior observation on this difference from week 44. These markers confirm the immune activity associated with clinical outcomes for long-term SLIT.

It is notable that treatment with very low doses of antigen, on the order of 1 to 4 μg of peanut protein compared with the gram quantities used in OIT, is associated with median increases in desensitization of greater than 1 g at year 2, and with evidence of immune changes. The magnitude of desensitization in this study is similar to that reported in a similar study in younger children.[10] Although OIT can induce far greater degrees of desensitization, it still might be reasonable to pursue interventions with low rates of risk that provide some measure of protection from accidental exposure. Thus the results here underscore the notion that low-dose peanut SLIT, which requires approximately 1386 μg and has a favorable safety profile, could result in useful rates of desensitization and, for a few subjects, large improvements with sustained unresponsiveness. In addition, SLIT might also represent a safe means to progress toward OIT in highly sensitive patients and/or might be a particularly advantageous approach to combining a type of oral mucosal immunotherapy with adjuvants.

The limitations of the current study include the definition of a responder, which might have overrepresented relative success; exclusion of patients with a past history of life-threatening peanut-induced allergic reactions who might benefit from such therapies and respond differently to them; the high rate of dropouts in the study; and the lack of a placebo control for final end point assessments caused by the crossover design.

Overall, these results suggest that SLIT is safe and can result in modest desensitization at low doses. However, the response is overall less robust than with OIT, and there might be a high likelihood of patient discontinuation. Future studies might focus on understanding the patient's motivation, addressing the patient's expectations for this therapy, and investigating alternative schedules to improve adherence with SLIT as a gateway toward transitioning to additional therapies, such as OIT,[25] or attempting to augment responses through use of adjuvants.[26]

Key messages

- **In our multicenter trial peanut SLIT had an excellent long-term safety profile.**
- **Peanut SLIT induced a modest level of desensitization, with less than 15% achieving sustained unresponsiveness. Responders at 2 years showed a significant decrease in peanut-specific basophil activation and SPT titration compared with nonresponders.**
- **A high rate of participants discontinued therapy, a finding similar to other SLIT trials. Many had difficulty maintaining daily dosing as the primary reason.**

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METHODS

Peanut and placebo sublingual drops

Greer Laboratories (Lenoir, NC) provided the peanut and placebo sublingual drops. They prepared the allergenic extract from the edible portion of whole nonroasted peanut with 0.5% sodium chloride and 0.54% sodium bicarbonate at a pH of 6.8 to 8.4 as aqueous extracts in 50% glycerin. Placebo extract was prepared from a glycerinated saline solution plus phenol with caramel coloring. The standard concentration (1:20 wt/vol) was 3300 μg/mL, and dilutions were made by Greer and shipped in prepacked vials with 50- or 140-μL actuators.

Double-blind, placebo-controlled food challenges

Medically supervised OFCs with established intravenous access were conducted over a 1- to 2-day period depending on whether a subject reacted to the first part of the double-blind, placebo-controlled food challenge, with at least 2 hours separating the first and second halves of the challenge. Subjects discontinued antihistamines for an appropriate length of time (5 half-lives of the antihistamine). A centrally distributed peanut powder from the same bulk lot of peanuts was used to produce the active doses, and commercially purchased oat flour was used for the placebo portion. All sites used the same standard operating procedure to locally prepare the OFC food material and maintain records documenting the procedure.

The double-blind, placebo-controlled food challenges consisted of administering peanut powder (or placebo) in gradually increasing doses at 15- to 30-minute intervals until the total amount was reached, and repeat doses were permitted. Two grams was administered at baseline, 5 g at week 44, and 10 g at weeks 68, 116, 164, and 172. When a total of 10 g was administered, the following doses were delivered: 1, 5, 15, 50, 75, 100, 250, 500, 1000, 1250, 1750, 2250, and 2750 mg. The OFC was stopped when objective signs indicated a positive reaction. The successfully consumed dose was the total consumed dose if no limiting symptoms occurred or the cumulative dose before the dose that caused dose-limiting symptoms.

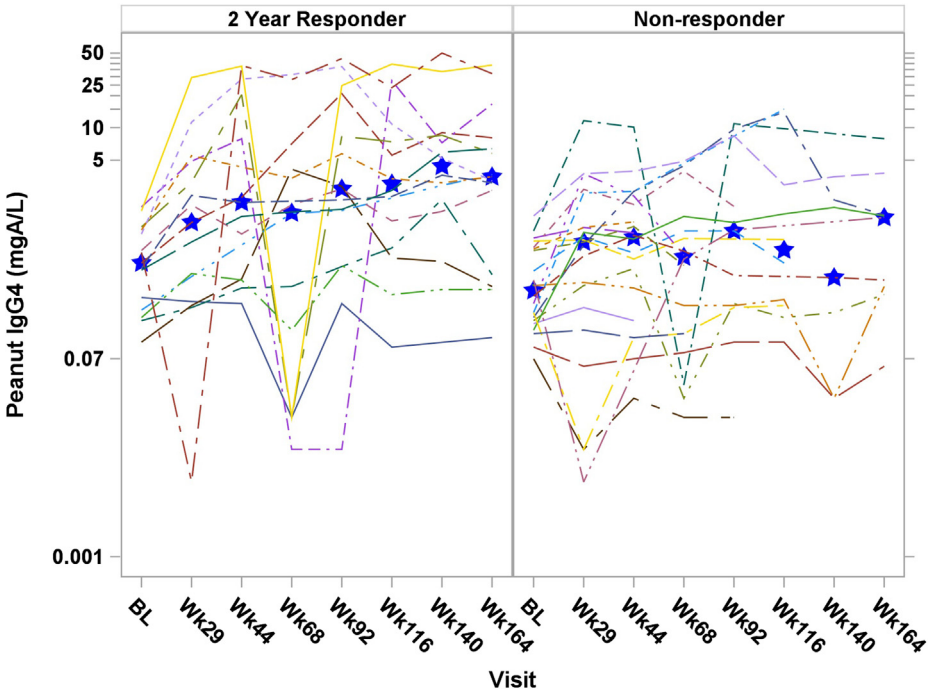

FIG E1. Peanut IgG_4 levels by 2-year response for all subjects. *Subject-specific plots are shown, and *blue stars* indicate the group median at each time point. Repeated-measures analysis across all time points yielded a *P* value of .11, indicating that there was no statistically significant difference between 2-year responders compared with nonresponders. *BL*, Baseline.

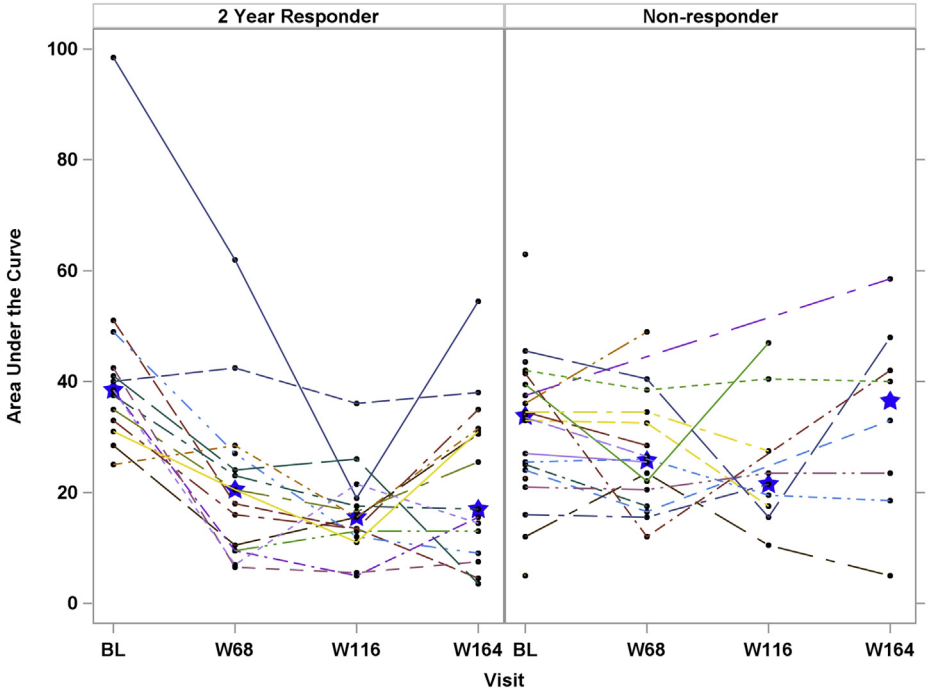

FIG E2. Peanut end point titration area under the curve by 2-year response for all subjects. *Subject-specific plots are shown, and *blue stars* indicate the group median at each time point. Repeated-measures analysis across time points through year 2 yielded a *P* value of .003, indicating there was a statistically significant decrease over time in 2-year responders compared with nonresponders. *BL*, Baseline.