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

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Abstract

Background—We previously reported initial results of the first multi-center 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—To provide long-term (3-year) clinical and immunologic outcomes for our peanut SLIT trial. Key endpoints: (1) percentage of responders at 2 years (could consume 5g 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 endpoints and (5) assessment of safety parameters.

Methods—Response to treatment was evaluated in 40 subjects aged 12-40 years by performing a 10g peanut powder oral food challenge (OFC) following 2 and 3 years of daily peanut SLIT therapy. At 3 years, SLIT was discontinued for 8 weeks followed by another 10g OFC, 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 end, 4/37 (10.8%) of SLIT treated participants were fully desensitized to 10g 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 to non-responders.

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.

Keywords

Peanut allergy; sublingual immunotherapy; desensitization; food allergy; follow-up

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 individuals, and requires life-long 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 life-long and life-altering

dietary and lifestyle modifications places significant burdens on affected individuals 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 proven 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 multi-center 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% of treated subjects (14/20) were defined as responders (those who could consume either a cumulative dose of 5 grams of peanut powder or a 10-fold increase in the amount of peanut powder compared with baseline oral food challenge), compared with 15% (3/20) of placebo treated subjects. After 68 weeks of SLIT, the median successfully consumed dose was significantly increased compared to 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 active SLIT subjects were treated through week 44 with up to 1386 μg of peanut protein SLIT daily. At week 44 the Peanut SLIT and Placebo subjects completed a 5g oral food challenge (OFC) and were unblinded, while placebo crossover subjects were escalated after unblinding at week 44 to higher dose peanut SLIT up to 3696 μg daily (designated as High Dose Crossover Group; the original Peanut SLIT group maintained a maximum dose of 1386 μg of peanut protein

daily). 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 (Figure 1).

Response to treatment was evaluated by performing a 10g peanut powder (~5g peanut protein; for reference, 1 peanut has 250-280 mg of peanut protein, thus 5 grams is equivalent to 16-18 peanuts). The intent was to escalate to a dose of 1386 mcg in all subjects, but some subjects tolerated only a much smaller dose. OFC at years 2 and 3 (week 116 and 164) while on peanut SLIT daily maintenance therapy. OFCs were performed per standard protocol as previously reported and included an initial OFC while on SLIT to assess clinical desensitization.[11] Subjects who passed the full 10g OFC at 3 years were discontinued from SLIT dosing for 8 weeks. The sustained unresponsiveness OFC after the 8 weeks was a combination of a 10g OFC followed by an open feeding of 2 tablespoons of peanut butter 1 hour later. Treatment responders were defined as the following: 1) Two-year Responder: subjects who either successfully consumed a cumulative dose of 5g of peanut powder (~2.5g peanut protein) while on peanut SLIT dosing or experienced at least a 10-fold increase in the amount of peanut powder compared to baseline OFC without dose-limiting symptoms; 2) Three-year Desensitization Responder: subjects who successfully consumed a cumulative dose of 10g of peanut powder (~5g peanut protein) without dose-limiting symptoms while on peanut SLIT dosing; and 3) Three-year Sustained Unresponsiveness Responder: subjects who successfully consumed a cumulative dose of 10g peanut powder (~5g 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 three-year evaluation whether on SLIT dosing or not, with those discontinuing from dosing followed for mechanistic studies only. Key endpoints 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 (could consume 5g of peanut powder or at least a 10-fold increase from baseline during an oral food challenge), (2) the percentage of subjects reaching desensitization at each time point, (3) the percentage of subjects attaining sustained unresponsiveness by year 3, (4) immunologic endpoints, including changes in peanut IgE, IgG4, endpoint titration skin prick test (SPT) 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, ages 12-40 years, from 5 US sites (New York, NY, Baltimore, MD, Little Rock, AR, Denver, CO, Durham, NC; the North Carolina subjects moved with the investigative team from Duke to the University of North 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 consents were obtained.

Study protocol

Subjects were instructed to remain on a peanut-free diet throughout the entire study and were required to carry an epinephrine auto-injector. Solicited dosing symptoms were recorded on a daily basis using a home diary. Other unsolicited adverse events were separately recorded. 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 Online Repository), 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 study. For placebo crossover subjects on active peanut SLIT, maintenance dosing continued at a minimum of 165 μg and a maximum maintenance dose of 3696 μg through the end of study.

Oral food challenge—A 10g OFC with peanut powder (~5g peanut protein) was conducted at years 2 and 3 of maintenance peanut SLIT dosing per protocol (see 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 10g OFC and an open feeding of 2 tablespoons peanut butter. Subjects who passed the final year 3 OFC assessing sustained unresponsiveness were instructed to add peanut to their diet, while those that failed either the year 3 OFC assessing desensitization or the year 3 OFC assessing sustained unresponsiveness were provided dietary guidance based on their OFC outcome, 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 using standard adverse event reporting criteria. Severity of adverse events was determined via site reporting with serious adverse events reviewed by a 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 e.g. a mild skin reaction could be 1-2 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 CoFAR case report forms and a Manual of Procedures.

Endpoint titration skin prick testing

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

Immunologic studies

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

Immunoglobulins—Total IgE was measured by immunoassay, and peanut-specific-IgE (PN-IgE) and peanut-specific IgG4 (PN-IgG4) were measured using the ImmunoCAP 100 (Thermo Fisher Scientific, Waltham, MA) at baseline and at weeks 29, 44, 68 and annually at the time of OFC, as previously reported.[11]

Statistical analysis

High Dose Crossover and Peanut SLIT groups as well as responder versus non-responder were compared using Fisher's Exact test for categorical variables and the Wilcoxon Rank Sum test for continuous variables. Repeated measures models were fit using unstructured covariance to evaluate basophil activation, immunoglobulin levels, and peanut endpoint titration area under the curve. As subjects who were non-responders 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).

RESULTS

As reported in the manuscript 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 a responder by week 44, compared to only 3 (15%) on the placebo arm ($P = 0.001$). From the placebo group, 17 subjects crossed over to the High Dose Crossover arm and 7/16 (44%) were categorized as responders at the week 44 crossover OFC (one subject declined the week 44 crossover OFC, and 4 discontinued dosing before the OFC and were counted as non-responders per the protocol). There were no statistical differences in baseline characteristics between treatment groups (Table 1).

Subject disposition over the course of the study is represented in Figure 1, including the reasons for subject withdrawals and the final subject status at the final OFC at year 3. In the High Dose Crossover group, 12/17 withdrew prior to the year 3 OFC, 2/5 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, 11/20 withdrew prior to the year 3 OFC, and 2/9 passed the year 3 OFC, both of whom passed the year 3 sustained unresponsiveness OFC. Using the definitions provided above, 4/17 (23.5%) in the High Dose Crossover group versus 11/20 (55%) in the Peanut SLIT group were categorized as responders at year 2 ($P = 0.09$), while 2/17 (11.8%) in the High Dose Crossover and 2/20 (10%) in the Peanut SLIT groups 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 Figure 2. This figure shows the median successfully consumed dose between these groups only to the year 2 OFC, because non-responders 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 impact 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 2 displays the details of the OFCs, divided by the 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 subjects and 825 days for the Peanut SLIT subjects. Of note, there are 3 fewer year 2 responders in both treatment groups compared to the 44 week OFC because these subjects withdrew prior to the year 2 OFC.

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

Dose-related adverse reactions after the OFC at 44 weeks on active therapy for High Dose Crossover subjects and after the week 44 OFC for Peanut SLIT subjects are summarized in Table 3. Overall, dose-related symptoms were reported in 18.3% of doses in the High Dose Crossover subjects following 44 weeks of active therapy and 18.1% doses received by Peanut SLIT subjects following 44 weeks of active therapy. The vast majority of reactions were isolated oropharyngeal symptoms; 1 Peanut SLIT subject 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 following 44 weeks of active therapy, there were 112 adverse events from 12 High Dose Crossover subjects reported; 6 were of moderate severity, none were severe, and all were unrelated to study product. During this same period, there were 83 adverse events from 13 Peanut SLIT subjects reported; 14 were of moderate severity, 1 was a life-threatening anaphylactic reaction to the year 3 OFC. The only adverse event definitely related to study product was a mild contact reaction to the study product.

Mechanistic Results

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

Immunoglobulins—Total IgE, PN-IgE levels, and PN-IgG_4 were not statistically different for those categorized as year 2 responders versus those who were not. However,

median PN-IgG_4 levels were observed to be slightly higher for year 2 responders (Online Repository, Figure E1).

Basophil activation—Based on results from the repeated measures analyses of percent CD63 positivity (CD63+) basophils for the 4 different peanut stimulant levels, the 2 year responders had significantly lower percent CD63+ basophils than non-responders for the 0.1 μg ($P = 0.02$), 0.01 μg ($P = 0.002$), and 0.001 μg ($P = 0.03$) peanut stimulant levels. There was a significant interaction between study visit and 2 year responder status at the 0.01 μg ($P = 0.009$), and 0.001 μg ($P = 0.03$) peanut stimulant levels, indicating that the magnitude of the effect is not constant over time. The change from baseline of percent CD63+ was observed to be lower for the 2 year responders at all peanut stimulant levels at almost every visit (Figure 3). Note in Figure 3 that the median percent CD63+ basophil is predominantly below zero for the 2 year responders but not for the non-responders.

Peanut Skin Prick Test Endpoint Titration—Peanut SPT endpoint titration was performed at baseline and at around 1, 2 and 3 years of therapy. In a repeated measures analysis of the peanut endpoint titration area under the curve through year 2, there was a significantly greater decrease over time in area under the curve in 2 year responders versus non-responders ($P = 0.003$; Online Repository, Figure E2).

DISCUSSION

This study presents unique data on long term open-label follow-up from the first multi-center, 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 to placebo. The results presented here extend these observations beyond our previous report of week 68 data from the lower dose (1386 μg peanut protein/day) Peanut SLIT treated arm of the randomized study and week 44 results from the High Dose Crossover (3696 μg peanut protein/day) participants. The current study includes up to 3 years of therapy with a daily maintenance dose of 1386 μg peanut protein in persons originally randomized to active treatment and a dose of 3696 μg 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 10g peanut powder (~5g peanut protein). By study end, 4 participants were fully desensitized to 10g of peanut powder, one of whom was not considered a responder at year 2 and all 4 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 drop-out 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, two 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 where 95.2% were symptom free-excluding oropharyngeal symptoms. During the initial 44 weeks of therapy, one participant had experienced a dose-related serious adverse event. This follow-up after 44 weeks of therapy included 18,165 additional doses with > 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, and during long-term follow-up none did. 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 non-adherence (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 (i.e., subjects still reacting at follow-up OFCs may have been discouraged by the absence of more significant protection). Additionally, the participants were adolescents and adults where lifestyle issues may be a concern, in contrast to longer-term studies of food immunotherapy with young children where parental oversight may 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 subcutaneous immunotherapy (SCIT) for environmental allergens in the Netherlands, only 18% of users reached the minimally required duration of treatment of 3 years (SCIT, 23%; SLIT, 7%); for those on SLIT, 62% discontinued by 1 year and 93% 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, beyond 68 weeks, resulted in improved desensitization due to participant drop out 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, comparing responders to non-responders for mechanistic studies. Among the antibody tests, only median peanut-specific IgG4 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 OIT compared to 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 where basophil activation was suppressed in treated compared to untreated participants.[11] The change from baseline for the area under the SPT end point titration curve was improved in responders compared to non-responders 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 1-4 μg peanut protein compared to the gram quantities used in OIT, is associated with median increases in desensitization of >1 gm 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] While OIT may induce far greater degrees of desensitization, it still may 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, requiring approximately 1386 μg, and with a favorable safety profile, could result in useful rates of desensitization, and, for a few individuals, large improvements with sustained unresponsiveness. In addition, SLIT may also represent a safe means to progress toward OIT in highly sensitive patients, and/or may 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 over represented relative success, exclusion of patients with a past history of life-threatening peanut allergic reactions who may 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 endpoint assessments due to 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 may be a high likelihood of patient discontinuation. Future studies may focus on understanding patient motivation, addressing patient expectations of this therapy, and investigating alternative schedules to improve adherence, using SLIT as a gateway toward transitioning to additional therapies such as OIT,[25] or attempting to augment responses by the use of adjuvants.[26]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

%CD63	Percentage of CD63 positivity
DBPCFC	Double-blind, placebo-controlled food challenge
OFC	Oral food challenge
OIT	Oral immunotherapy
PN-IgE	Peanut-specific IgE
PN-IgG4	Peanut-specific IgG4

SCD	Successfully consumed dose
SLIT	Sublingual immunotherapy
SPT	Skin prick test

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Key Messages

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

Capsule Summary

Long-term follow-up (3-year) of the first multi-center randomized, double blind, placebo controlled clinical trial of peanut sublingual immunotherapy (SLIT) demonstrated a favorable safety profile associated with modest clinical and immunologic effects.

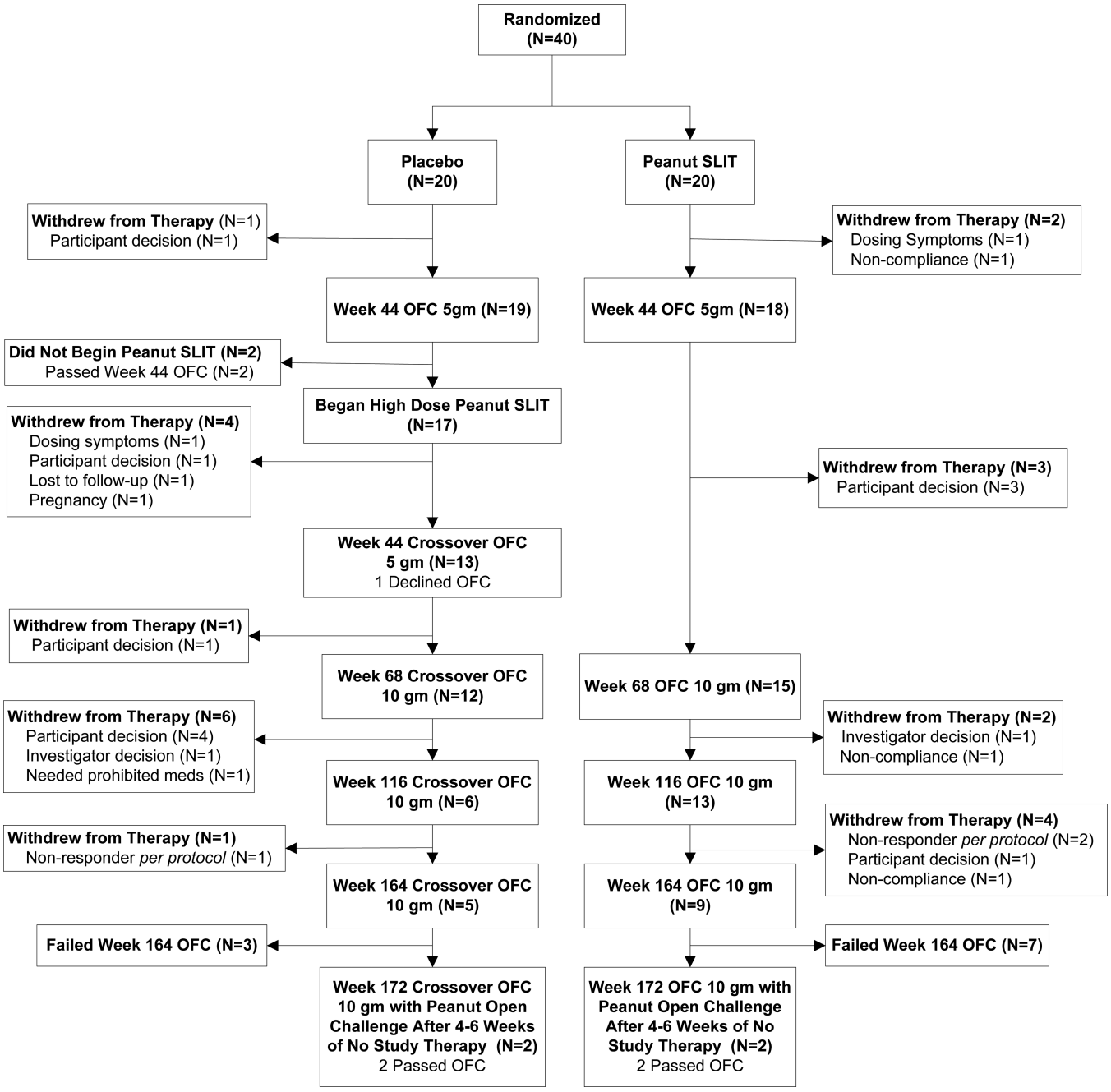

Figure 1.
Subject Disposition

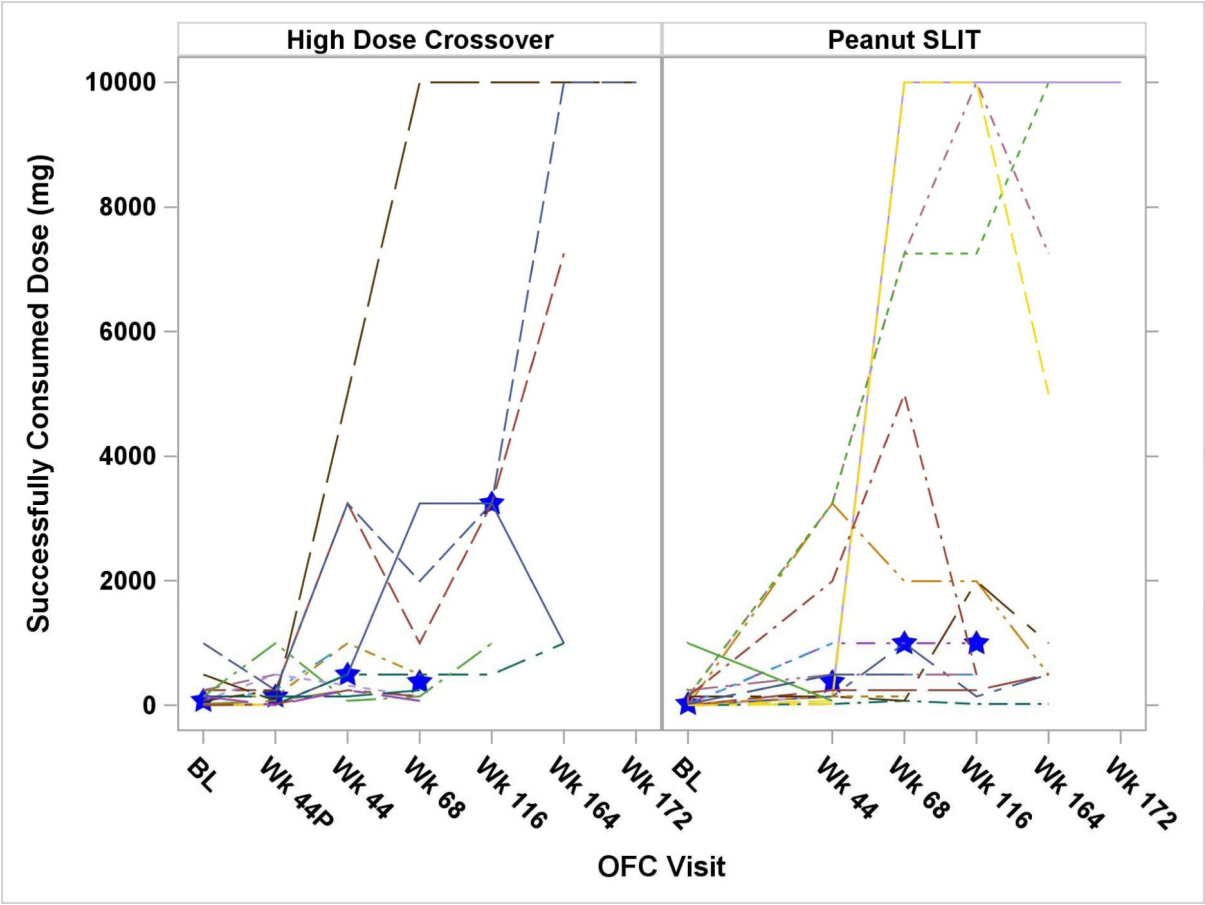

Figure 2.

Oral Food Challenge Results

Note: Subjects were discontinued from treatment per protocol if they did not meet specific criteria at the year 2 OFC (OFC threshold at least 5000 mg or 10 times baseline). 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 the medians between the treatment groups.

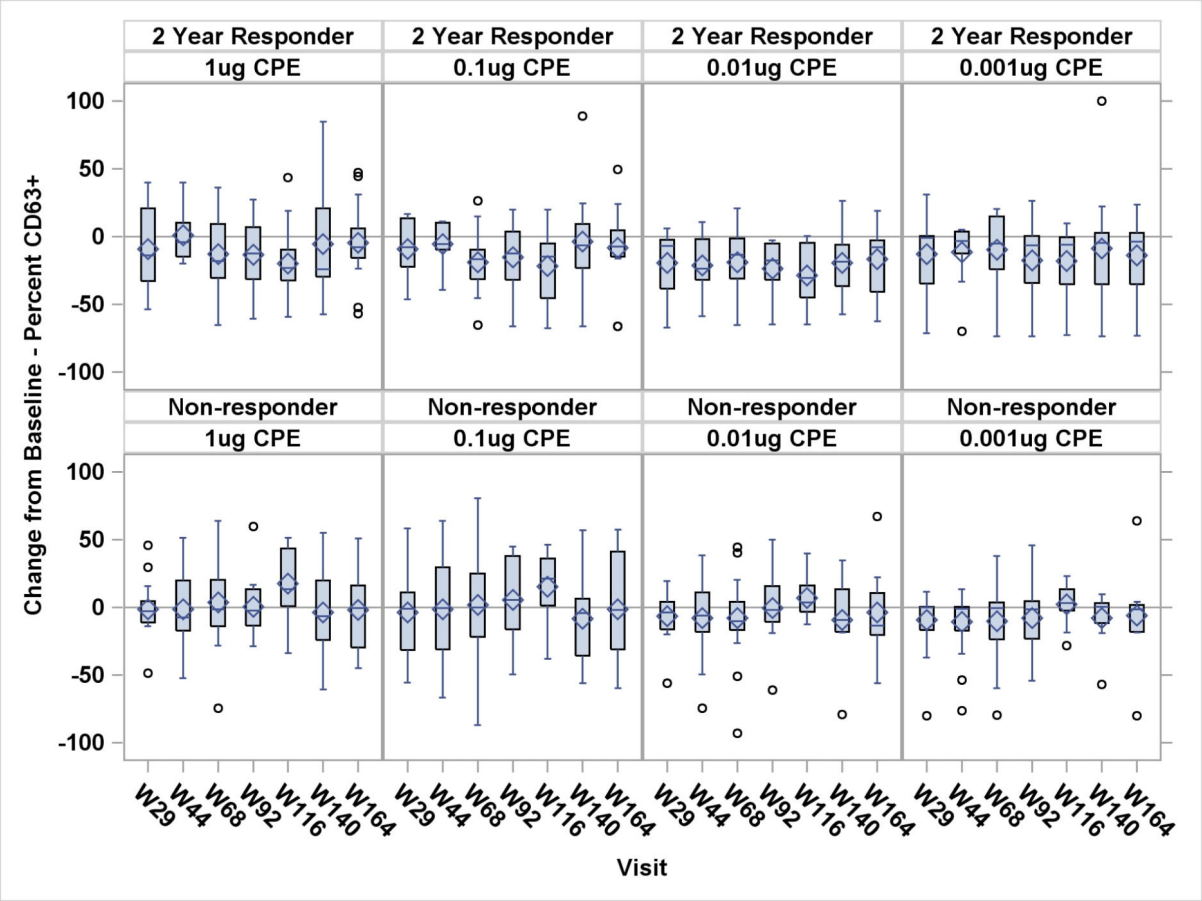

Figure 3.
Change from Baseline in Percent CD63+ Basophils by 2-Year Response – All Subjects

Table 1

Baseline Characteristics

	Treatment	
	High Dose Crossover (n = 17 [%])	**Peanut SLIT (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

	Median (Q1–Q3)	**Median (Q1–Q3)**
Age (y)	16.0 (14.0–18.0)	14.0 (13.0–18.0)
Baseline SPT peanut score (mm)	12.0 (10.0–14.8)	13.3 (9.5–17.5)
Baseline peanut IgE (kU_A/L)	30.4 (7.1–91.1)	31.3 (3.2–42.4)
Baseline OFC dose at first symptom (mg)	6.0 (1.0–71.0)	6.0 (1.0–46.0)
Baseline OFC successfully consumed dose (mg)	71.0 (6.0–146.0)	21.0 (1.0–146.0)

Table 2

Successfully Consumed Dose by Year 2 Response and Treatment Group

		Treatment Group												
		Placebo/High Dose Crossover							Peanut SLIT					
		n	Mean	Min	Q1	Median	Q3	Max	n	Mean	Min	Q1	Median	Q3	Max
OFC Type	**2 Year Responder**														
Baseline (2g)	**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 (5g)	**2 Year Responder**														
	Yes	4	82.3	6.0	6.0	38.5	158.5	246	11	1091.5	21.0	146	246	3246	3246
	No	13	240.2	1.0	21.0	146	246	996	7	603.1	21.0	71	496	996	1996
	All	17	203.1	1.0	6.0	146	246	996	18	901.6	21.0	146	371	996	3246
Crossover Week 44 (5g)	**2 Year Responder**														
	Yes	4	2308.5	496	496	1871	4121	4996	.	.	.	.	.	.	.
	No	8	774.1	71	196	246	996	3246	.	.	.	.	.	.	.
	All	12	1285.6	71	246	496	2121	4996	.	.	.	.	.	.	.
Crossover Week 68/Week 68 (10g)	**2 Year Responder**														
	Yes	4	3683.5	496	746	2121.0	6621	10000	11	3578.5	71	246	996	7246	10000
	No	8	414.8	71	108.5	146.0	371	1996	4	1533.5	146	321	496	2746	4996
	All	12	1504.3	71	146	371.0	1496	10000	15	3033.2	71	246	996	7246	10000
Crossover Year 2/Year 2 (10g)	**2 Year Responder**														
	Yes	4	4246	496	1871	3246	6621	10000	11	3922.1	21.0	246	1996	10000	10000
	No	2	2121	996	996	2121	3246	3246	2	496	496	496	496	496	496
	All	6	3537.7	496	996	3246	3246	10000	13	3395	21.0	496	996	7246	10000
Crossover Year 3/Year 3 (10g)	**2 Year Responder**														
	Yes	4	4808.5	996	996	4121	8621	10000	9	3860.3	21.0	496	996	7246	10000
	No	1	10000	10000	10000	10000	10000	10000	.	.	.	.	.	.	.
	All	5	5846.8	996	996	7246	10000	10000	9	3860.3	21.0	496	996	7246	10000
Crossover Year 3/Year 3 (10g)	**2 Year Responder**	1	10000	10000	10000	10000	10000	10000	2	10000	10000	10000	10000	10000	10000

		Treatment Group												
		Placebo/High Dose Crossover							Peanut SLIT					
		n	Mean	Min	Q1	Median	Q3	Max	n	Mean	Min	Q1	Median	Q3	Max
Yes															
No		1	10000.	10000	10000	10000	10000	10000	.	.	.	.	.	.	.
All		2	10000	10000	10000	10000	10000	10000	2	10000	10000	10000	10000	10000	10000

Table 3

Post-Week 44 Crossover OFC/Week 44 OFC Dosing Symptom Summary by Dose

High Dose Crossover Subjects																							
		Any Symptom		Any Symptom Excluding Oral Phary		Oral Phary Symptoms		Skin		Resp.		GI		Other		Treated		Treated with Epi.		Mild		Moderate		Severe	
Visit Type	# Doses	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
All	7385	1352	18.3	301	4.1	1326	18.0	17	0.2	262	3.5	16	0.2	13	0.2	26	0.4	0	0.0	301	4.1	0	0.0	0	0.0
Clinic	12	9	75.0	3	25.0	9	75.0	0	0.0	3	25.0	0	0.0	0	0.0	0	0.0	0	0.0	3	25.0	0	0.0	0	0.0
Home	7373	1343	18.2	298	4.0	1317	17.9	17	0.2	259	3.5	16	0.2	13	0.2	26	0.4	0	0.0	298	4.0	0	0.0	0	0.0

Peanut SLIT Subjects																							
		Any Symptom		Any Symptom Excluding Oral Phary		Oral Phary Symptoms		Skin		Resp.		GI		Other		Treated		Treated with Epi.		Mild		Moderate		Severe	
Visit Type	# Doses	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
All	10780	1950	18.1	75	0.7	1912	17.7	8	0.1	60	0.6	7	0.1	2	0.0	5	0.0	0	0.0	74	0.7	1	0.0	0	0.0
Escalation	5	5	100.0	4	80.0	4	80.0	0	0.0	4	80.0	0	0.0	0	0.0	0	0.0	0	0.0	4	80.0	0	0.0	0	0.0
Clinic	55	26	47.3	1	1.8	25	45.5	0	0.0	1	1.8	0	0.0	0	0.0	0	0.0	0	0.0	1	1.8	0	0.0	0	0.0
Home	10720	1919	17.9	70	0.7	1883	17.6	8	0.1	55	0.5	7	0.1	2	0.0	5	0.0	0	0.0	69	0.6	1	0.0	0	0.0

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