

ORIGINAL ARTICLE

Allergen - Specific Immunotherapy and Biologics

Phase 2, randomized multi oral immunotherapy with omalizumab 'real life' study

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Abstract

Background: Oral immunotherapy (OIT) is frequently discontinued due to adverse events (AEs) and current data suggests that lowering OIT doses can minimize severity and frequency of AEs. However, the minimum daily dose that can enable desensitization and induce immune responses in multi-food OIT (mOIT) is unknown.

Methods: Participants aged 2–25 years with multi-food allergies were pretreated with fixed-dose omalizumab (150 mg, 3 doses, every 4 weeks), and randomized 1:1 to receive mOIT to a total maintenance dose of either 300 or 1200 mg total protein, (total dose includes at least two and up to a max of five allergens) and then transitioned to real-food protein equivalents after 18 weeks of treatment. The primary endpoint was the proportion of subjects with increases in IgG4/IgE ratio of at least 2 allergens by $\geq 25\%$ from baseline after 18 weeks of therapy. The primary efficacy and safety analyses were done in the intention-to-treat population.

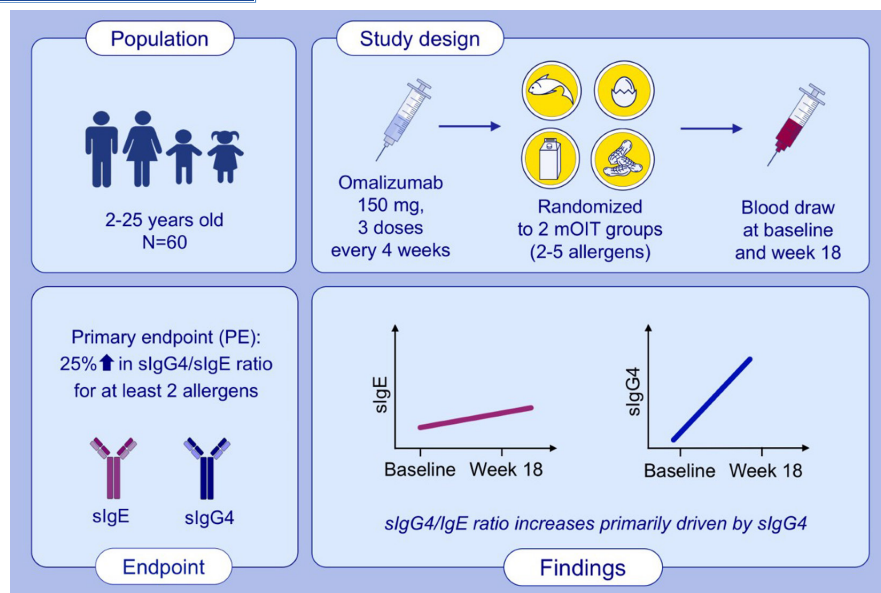
Results: Sixty participants were enrolled across two sites. Seventy percent of participants in both arms showed changes in sIgG4/sIgE ratio in at least 2 allergens with no difference between the treatment groups (OR [95% CI] = 1.00 [0.29, 3.49]). Overall, there were no differences in AEs between the 300 and 1200 mg groups (19% vs. 17%, $p = .69$), respectively.

Conclusions: Our data suggest that plasma marker changes are induced early, even at a total protein dose of 300 mg inclusive of multiple allergens when mOIT is combined with fixed-dose omalizumab. Identification of optimal mOIT dosing with adjunct omalizumab is needed for the long-term success of OIT.

Trial Registration: ClinicalTrials.gov (NCT03181009).

KEYWORDS

IgE, IgG4, maintenance dose, omalizumab, oral immunotherapy



GRAPHICAL ABSTRACT

We conducted a phase 2 mOIT pilot study to assess feasibility, safety, and immunological changes associated with low maintenance doses preceded by fixed dose omalizumab. Our findings show that the change in slgE/slG4 ratio is driven primarily by an increase in slgG4, with an increase in ratio by 25% in 70% of participants. Data suggests that plasma marker changes are induced earlier and at a lower dose of total protein than previously tested.

Abbreviations: mOIT, multi-food OIT; slgE, specific IgE; slgG4, specific IgG4

1 | INTRODUCTION

Food allergies have increased in prevalence over the last few decades and have become a significant health burden affecting about 8% of children¹ and 10.8% of adults² in the United States with up to 45% allergic to multiple foods.² In 2020, a peanut oral immunotherapy (OIT) flour was approved for children 4–17 years of age³; however, it does not address treatment for adults, or treatment for children with allergens other than peanut. For the majority of patients, the current standard of care remains avoidance, with treatment primarily directed to the management of acute allergic reactions with antihistamines and epinephrine auto-injectors. With attempted avoidance, quality of life (QoL) is significantly impacted secondary to constant anxiety, hypervigilance, and restricted diets.^{1,4,5}

Although numerous trials have demonstrated safety and efficacy of OIT,⁷ the underlying mechanisms of successful OIT have not yet been fully elucidated and key knowledge gaps remain. Adverse reactions during OIT are common and most notable during the build-up phase of immunotherapy. Low-dose OIT may mitigate these reactions and improve long-term adherence⁸; however, the long-term effects of low-dose OIT and data regarding compliance have not been well characterized, especially for multi-food OIT (mOIT). Several authors have reported using plasma markers to predict clinical outcomes,^{9,10} which can provide insight into patient response to OIT in lieu of OFCs. Numerous studies have indicated that an increased ratio of specific IgG4 (slgG4)/slgE may offer an alternate diagnostic method for determining desensitization and sustained unresponsiveness (SU).^{11–15} In previous mOIT studies conducted at our center, unpublished post hoc analyses indicate that over 91%¹⁶ and 97%¹⁷

of participants with a $\geq 25\%$ increase in slgG4/slGE ratio from baseline passed their exit OFCs, offering a potentially promising proxy for clinical response. However, the immune changes associated with varying maintenance doses in multi-allergen OIT (mOIT) have not been directly compared, neither has the minimal duration of OIT to affect such a change. A better understanding of these concepts can assist with clinical dosing and treatment strategies.

We conducted a phase 2 mOIT pilot study with a pragmatic study design, at two sites to assess feasibility, safety, and immunological changes associated with low maintenance doses preceded by fixed-dose omalizumab (Xolair®; Genentech and Novartis Pharmaceuticals). Participants were treated with at least two and up to five of the following allergens: peanut, almond, cashew, hazelnut, walnut, pink fish, white fish, shellfish, egg, milk, sesame, soy, and wheat. Participants were pretreated with 3 fixed doses of 150 mg omalizumab before initiating mOIT. To increase safety and mimic a real-world outpatient setting where OFCs are done primarily to rule out food allergy and avoided when a patient is considered high-risk, screening and end-of-study OFCs were avoided but stricter eligibility criteria was used with higher cut-offs for skin prick test (SPT) and slgE results as well as a positive history of clinical allergic reaction (physician reported) to enroll food allergic individuals. At the end of the study, all participants were transitioned to a real-food protein equivalent to continue maintenance dosing under the care of a primary allergist. Changes in plasma markers were assessed in conjunction with conversion to real foods.

Our primary endpoint in this pilot study was to evaluate the percentage of participants who have an increase in the ratio of food allergen slgG4/slGE of at least 25% for at least 2 allergens from

screening to week 18. We chose this surrogate exploratory biomarker ratio since our laboratory and other groups had shown that a change in food allergen sIgG4/sIgE over time is associated with clinical outcomes.^{10,11,17–21}

2 | METHODS

We performed a randomized, double-blind controlled, phase 2, mOIT trial across two sites (Sean N. Parker Center for Allergy and Asthma Research at Stanford University and University of California at Los Angeles) from July 2017 to December 2018.

2.1 | Study design

Participants were randomized to two groups (maximum total protein dose of 300 or 1200 mg). The total protein volume amount was equal within each group; however, the individual allergen maintenance dose varied based on number of allergens included in the mix. The lowest allergen dose a participant would consume would be 60 mg if they had 5 allergens and were in the 300 mg total protein group and the highest allergen dose would be 600 mg per allergen if they had 2 allergens and were randomized into the 1200 mg group. Prior to initiating mOIT, all participants received three doses (150 mg) of omalizumab 4 weeks apart (Figure 1). After receiving the third omalizumab dose, a 5 mg total mOIT dose was introduced on the same day (week 0). Both groups underwent three dose-escalation visits every 4 weeks with blinded doses determined by treatment group. During these 3 dose-escalation visits, the group randomized to 300 mg maintenance received 5 mg, 60 mg, and 300 mg, whereas the group randomized to 1200 mg received 5 mg, 240 mg, and 1200 mg.

2.2 | Participants

Eligible participants included those 2–55 years of age with a physician-diagnosed food allergy, clinical history of allergic reaction and a positive SPT result ≥ 6 mm or a ImmunoCAP IgE (sIgE) >4 kU/L for each allergen considered for OIT, at screening. We chose these higher thresholds to decrease the likelihood of natural tolerance induction (ie, “losing an allergy”) over the course of the study as published in the European Academy of Allergy and Clinical Immunology (EAACI) guidelines.²² If clinical history was not elicited, then higher allergen-specific cut-off values for SPT and sIgE were used (Table S1). Exclusion criteria included diagnosis of eosinophilic disorders, oat allergy, uncontrolled asthma, cardiovascular disorders, and other chronic conditions considered unsafe for trial participation. This trial was registered on ClinicalTrials.gov, NCT03181009.

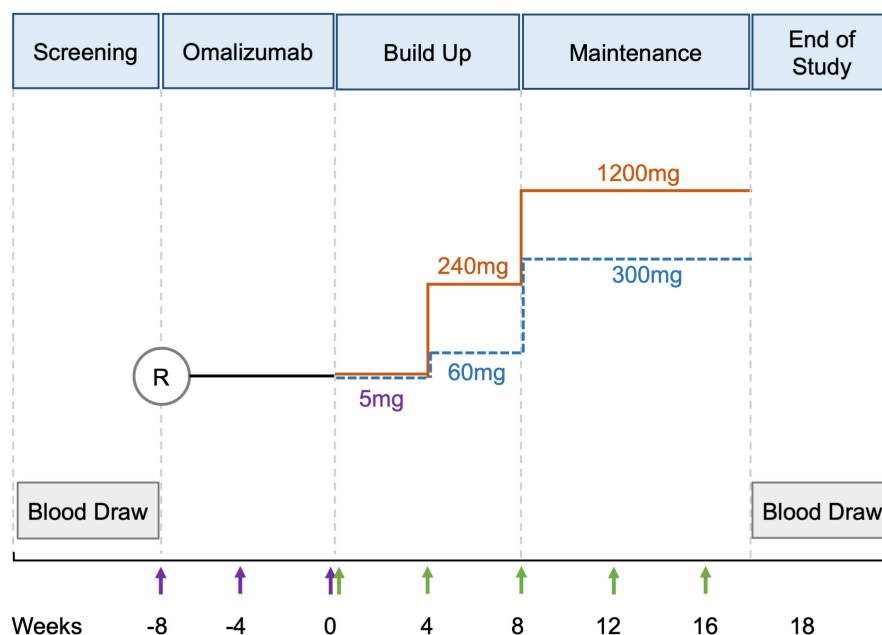
2.3 | Endpoints

The primary endpoint was the percentage of participants on a combination omalizumab and mOIT who have an increase in allergen sIgG4/sIgE ratio from baseline to week 18 by 25% for at least two allergens included in their maintenance. We also assessed whether age, gender, body mass index, omalizumab dose (mg per body weight and total IgE), years with disease and degree of polysensitization affect study outcomes.

The secondary endpoint was the percentage of participants on a combination omalizumab and mOIT who have an increase in allergen sIgG4/sIgE ratio from baseline to week 18 by 25% for at least three, four, and five allergens included in their maintenance from screening to week 18.

Safety was assessed by evaluation of AEs throughout the duration of the trial. To further characterize real-life experience, we

FIGURE 1 Study schema from screening to end of study. “R” denotes randomization. Purple and green arrows denote the omalizumab and OIT treatments, respectively. Black line denotes no OIT treatment, whereas red line denotes high-dose (1200 mg) group and blue dotted line denotes low-dose (300 mg) group. After 3 doses of fixed-dose omalizumab, the low-dose group received 5 mg, 60 mg, and 300 mg every 4 weeks, whereas the high-dose group received 5 mg, 240 mg, and 1200 mg every 4 weeks



collected survey data on long-term compliance, (Adverse events [AEs] and QoL) 2 years after completion of the trial.

2.4 | Randomization and masking

Eligible participants were enrolled and randomized simultaneously 1:1 to receive either a maximum total protein dose of 300 mg or 1200 mg. A statistician generated the master randomization lists using randomized block design and stratified by site. The site-specific Master Randomization Assignment Lists were maintained by the Stanford Investigational Pharmacist and the participant information was provided to site unblinded personnel, which included the Stanford GMP facility and the UCLA investigational pharmacist. Upon completion of each participant's end-of-study visit including data entry, study staff and participants were unblinded by the Stanford Investigational Pharmacist.

2.5 | Procedures

SPTs were performed on the back or the volar section of the arm according to standard procedures at screening and Week 18 for participants who were off antihistamines for five half-lives. The average wheal diameter above that of the negative control was used to determine eligibility.

Blood samples for determination of food allergen sIgEs and sIgG4s, and total IgE (ImmunoCap, Phadia), were collected at screening and at the end of the study at Week 18. All dose escalations were performed in the clinical research center after a physical examination and lung function tests. Participants were provided with flours mixed at our GMP facility and mixed with vehicle of choice per participant. Participants were monitored for 2 h after dose ingestion. At the completion of the study, participants were transitioned to real-world foods at the final visit and provided with further instructions for home dosing.

During long-term follow-up in a convenience sample from a single site (Stanford), trial participants were asked to complete a survey regarding dosing and reactions. Food allergy QoL (FAQOL) questionnaires were provided to participants and their families for pre-OIT and post-OIT experience. Children (or parents of the children) between 0–12 years old were asked to fill the children's form, and their parents were asked to fill the parental burden form. Burden of treatment (BOT) questionnaires were sent to the participants at the end of the study. Participants were asked to rate the mOIT treatment on a 7-point scale ranging from 1 (=extremely positive) through 4 (=neutral) to 7 (=extremely negative). Higher scores in both QoL and BOT indicates poorer treatment outcome.

2.6 | Statistics

Baseline characteristics were summarized overall and by treatment group using medians and ranges as well as counts and percentages.

Categorical and continuous variables were tested across treatment arms using Fisher's exact test and the Wilcoxon rank sum test, respectively. The overall proportion of participants who met the primary and secondary endpoints was reported along with the 95% confidence interval (CI). Fisher's exact test was used to determine whether the probability of success differed by treatment group. The odds ratio (OR) of the 300 mg vs. 1200 mg group and 95% CI were reported. As part of our exploratory objectives, additional analysis was conducted in a similar fashion by whether or not maintenance was reached within each treatment arm and, by standard omalizumab dosing group. Each participant's standard omalizumab dose was calculated by dividing their 150 mg dose by their weight and total IgE and categorized into 2 groups (<0.016 mg/kg/[IU/ml] and ≥ 0.016 mg/kg/[IU/ml]). Additionally, the omalizumab dose per weight was calculated by dividing their 150 mg dose by participant's weight. Logistic regression was performed to test the associations between each of participants' characteristics and the primary endpoint. OR and *p*-value were summarized using forest plot. *Q*-value was used to denote the *p*-value after being adjusted for multiple testing using the Benjamini-Hochberg methods that controlled the false discovery rate. We further explored the association between change in sIgG4/sIgE ratio and maximum per-allergen dose within each allergen using Spearman's rank correlation test as the sensitivity analysis. The percentage of doses in which AEs occurred were summarized by treatment arm and study phase. The mixed effect negative binomial regression models were fit to determine whether AE rates were different by treatment group. Kaplan-Meier survival methods were used to describe the time from start of OIT to reach maintenance by treatment group and omalizumab dose group. Hazard ratios, 95% CIs, and the *p*-value for significant pairwise differences were reported from a Cox proportional hazards model.

Tests were two-sided and conducted at the 0.05 level of significance. No corrections were made for multiple comparisons. All analyses were conducted using R software v3.5.2.

2.7 | Study approval

The research protocol was approved by the site-specific institutional review boards or ethic committees. Written informed consent was received from participants prior to inclusion in the study.

3 | RESULTS

Sixty-five participants were initially screened for eligibility with 60 ultimately randomized 1:1 to the 300 mg and 1200 mg arms at two sites, among them, 2 participants withdrew early (Figure 2). All participants who reached 18 weeks were converted to dose-specific real-food protein equivalents, including those that did not reach the planned maintenance dose.

The median age was 10 years (range 4–20) and the majority of participants were non-Hispanic (93%), white (40%), males

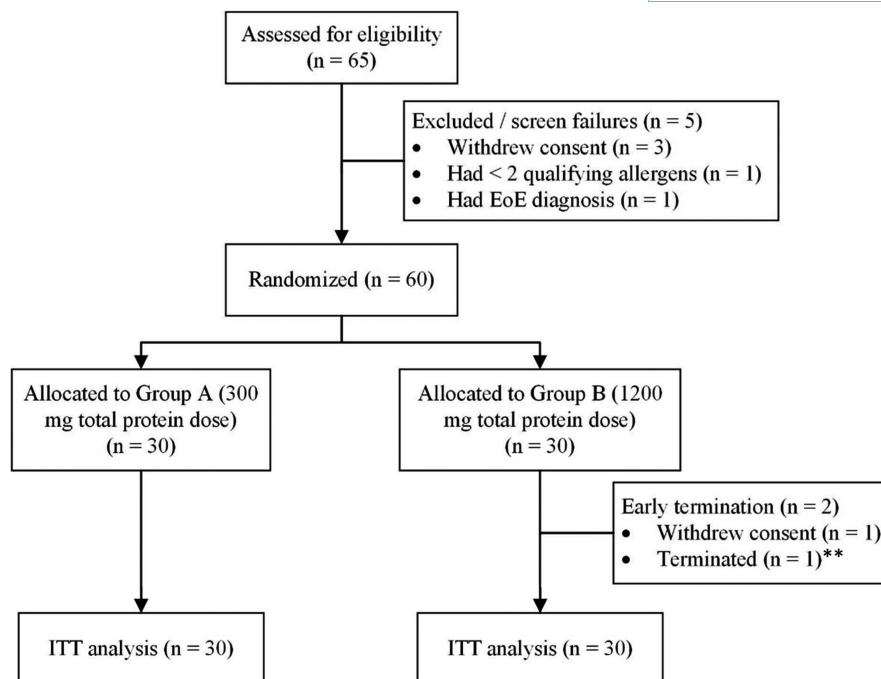


FIGURE 2 Flow chart for participant selection. *Patient withdrew consent to continue OIT at private allergist's office. **Patient was terminated due to persistent adverse events at 5 mg dosing. EoE, eosinophilic esophagitis

(68%) (Table 1). More than two-thirds of participants had atopic conditions such as allergic dermatitis (80%), asthma (65%), and allergic rhinitis (70%). There were no significant differences in baseline characteristics by treatment arm or study site (Table 1 and Table S2). Allergen-specific median sIgE and SPT is detailed in Table S3.

3.1 | Primary endpoint

Forty-two of the 60 participants (70%) reached the primary endpoint of increase in allergen sIgG4/sIgE ratio of at least 25% from screening for at least 2 allergens after 18 weeks of treatment (Table 2). There were no differences in primary endpoint success, focused on the intention-to-treat (ITT) population, by mOIT treatment group (odds ratio [OR]: 1.00, 95% confidence interval [CI]: 0.29–3.49, $p = 1.00$) (Table 2) or by ability to reach maintenance dose (OR: 0.96, 95% CI: 0.22–4.97, $p = 1.00$) (Table 3).

There were no associations with baseline characteristics such as age, gender, race, and atopic history and achieving the primary endpoint (Figure 3). However, a higher total serum IgE (OR: 5.14, 95% CI: 1.27–25.60, $Q = 0.07$) was significantly associated with higher odds of primary endpoint success. When a fixed dose of 150 mg omalizumab was recalculated based on body weight and IgE (mg/kg [kU/L]*1000), a standardized omalizumab dose (OR: 0.94, 95% CI: 0.89–0.98, $Q = 0.008$) was significantly associated with lower odds of primary endpoint success. Similarly, a higher ratio of baseline cashew sIgG4/sIgE (OR: 0.98, 95% CI: 0.97–0.99, $Q = 0.003$) and baseline sesame sIgG4/sIgE (OR: 0.97, 95% CI: 0.90–1.00, $Q = 0.05$) were significantly associated with lower odds of primary endpoint success.

3.2 | Secondary endpoints

Twenty-four of 46 participants (52%), 8 of 23 participants (35%), and 2 of 7 participants (29%) reached the endpoint of increase in allergen sIgG4/sIgE ratio of at least 25% from screening for at least 3, 4, and 5 allergens, respectively, after 18 weeks of treatment. There were no differences in primary endpoint success, focused on the intention-to-treat (ITT) population, by mOIT treatment group for the 3-allergen group (odds ratio [OR]: 1.39, 95% confidence interval [CI]: 0.38–5.24, $p = .77$), the 4-allergen group (odds ratio [OR]: 1.39, 95% confidence interval [CI]: 0.02–2.51, $p = .38$), or the 5-allergen group (odds ratio [OR]: ∞ , 95% confidence interval [CI]: 0.14– ∞ , $p = .43$) (Table 2).

3.3 | Safety

There were no significant differences in AEs by the number of allergens in OIT ($p = .21$). The most common AE was gastrointestinal, with 15% of doses associated with gastrointestinal AEs (Table S4). Those in the 1200 mg group had a significantly higher percentage of doses associated with moderate AEs compared with the 300 mg group (4% vs. 3%, $p = .01$). Three AEs required the use of epinephrine (two were from 300 mg group, one was from 1200 mg group); one (from 1200 mg group) was due to accidental ingestion while the remaining two occurred in clinic during a dose build-up visit.

3.4 | Exploratory objectives

Figure S1 shows the sensitivity analysis of correlation between the change in sIgG4/sIgE ratio and the maximum per-allergen

TABLE 1 Baseline characteristics by mOIT treatment arm^a

Characteristic	Total (n = 60)	Treatment	
		300 mg (n = 30)	1200 mg (n = 30)
Age in years	10 [4, 20]	10 [4, 20]	10 [4, 17]
Male	41 (68%)	21 (70%)	20 (67%)
Ethnicity			
Hispanic or Latino	1 (2%)	0	1 (3%)
Non-Hispanic or Latino	56 (93%)	28 (93%)	28 (93%)
Prefer not to report	3 (5%)	2 (7%)	1 (3%)
Race			
White	24 (40%)	15 (50%)	9 (30%)
Asian	22 (37%)	8 (27%)	14 (47%)
Black or African American	1 (2%)	0	1 (3%)
Multiracial	10 (17%)	5 (17%)	5 (17%)
Prefer not to report	3 (5%)	2 (7%)	1 (3%)
Atopic history			
Allergic dermatitis	48 (80%)	24 (80%)	24 (80%)
Asthma	39 (65%)	21 (70%)	18 (60%)
Allergic rhinitis	42 (70%)	20 (67%)	22 (73%)
Number of food allergies	7 [2, 14]	7 [3, 13]	7 [2, 14]
Omalizumab dose ≥0.016 mg/kg/(IU/ml) group (standard dose) ^b	18 (30%)	9 (30%)	9 (30%)
Weight (kg)	30.1 [17.4, 72.3]	29.4 [17.4, 72.1]	30.5 [17.7, 72.3]

Note: Categorical and continuous variables are reported as count (percent) and median (range), respectively.

^aThere were no significant differences between the treatment groups.

^bEach participant's omalizumab dose was calculated by dividing their 150 mg dose by their weight and total IgE and categorized into 2 groups (<0.016 mg/kg/[IU/ml] and ≥0.016 mg/kg/[IU/ml]).

OIT dose by food. The association between change in sIgG4/sIgE ratio and maximum per-allergen dose was not statistically significant among any of the allergens. Figure S2 shows that the change in the ratio was driven primarily by a change in sIgG4 compared with a change in sIgE in major food allergens, peanut, cashew, and walnut.

The most common allergens used for OIT included peanut ($n = 39$), cashew ($n = 39$), and walnut ($n = 29$) (Figure S3). The allergens included in the OIT combinations are depicted in Figure S4. Co-occurrence of food allergy based on foods in OIT was noted between cashew and walnut with a similarity index of 0.58 ($p = .001$) followed by egg and milk with a similarity index of 0.55 ($p = .001$) (Figure S5).

Time-to-maintenance (TTM) was not different between treatment arms (hazard ratio: 0.7; 95% CI: 0.4–1.3; $p = .23$, Figure S6) or by number of allergens in OIT mix ($p = .92$, Figure 4). Each participant's fixed omalizumab dose (150 mg) was divided by their weight

and total IgE and was categorized into 2 groups (<0.016 mg/kg/[IU/ml] and ≥0.016 mg/kg/[IU/ml]). When TTM was stratified by omalizumab dose group, significant differences in time-to-maintenance were found ($p = .018$, Figure 5), specifically among participants in the 1200 mg group, those on the higher omalizumab dose (≥0.016 mg/kg/[IU/ml]) were 4.2 times as likely to reach maintenance compared with those in the low dose (hazard ratio: 4.2; 95% CI: 1.7–10.7; $p = .0026$). The omalizumab dose was further calculated as dose/weight and there was no association between omalizumab per weight and achieving the primary endpoint (Figure 3). Primary endpoints and safety were stratified by omalizumab dose group and there were no significant differences.

3.5 | Long-term follow-up

At completion of the study, 88% (53/60) of participants who reached at least 60 mg of each allergen in their OIT mix (even if they did not reach maintenance while in the study) were transitioned to real-food protein equivalents and continued daily dosing at home with foods readily available at supermarkets and measurements done with household tools. For instance, 60 mg of peanut would be ¼ of a whole peanut, and 60 mg milk could be obtained with 1/3 teaspoon or 9 ml of fluid milk (8 gm protein/8oz). Higher maintenance dosing options were also provided.

Based on a convenience sample, at one site (Stanford), long-term follow-up questionnaires were obtained 2 years after completion of the study under an IRB-approved long-term follow-up protocol. Twenty-one participants completed the detailed questionnaire. Among them 16 (76.2%) continued at least one of their OIT allergens; 9 (56%) increased the daily maintenance dose per food in at least one of their OIT allergens, 7 (44%) remained on the same dose per food in at least one of their OIT allergens; 3 (19%) decreased the daily dose of all allergens. Since participants had multiple allergens in their dosing regimen, a few participants reported decrease in some allergens with increases in another. Allergen-specific details for the outcome of each food is provided in Table S5. Five participants discontinued OIT, 3 due to AEs and 2 did not report their reasons. We assessed BOT among 21 responders (out of 30 who were contacted); 12 participants (0–12 years) or their parents completed FAQLQ child forms, and 13 caregivers filled FAQLQ parental burden form. Majority of participants who participated in the questionnaires (77%) reported “extremely positive” or “positive” to the OIT treatment of this study (Table S6). The QoL score of FAQLQ-PB significantly decreased after completion of study ($p = .05$), which indicates an improvement of QoL and relief of parental burden after mOIT treatment (Figure S7).

4 | DISCUSSION

This is the first randomized, phase 2, pilot study with a pragmatic study design, conducted at two sites evaluating two low doses of

TABLE 2 Primary and secondary endpoints

	300 mg (n = 30)	1200 mg (n = 30)	Estimate ^a (95% CI)	p-value ^a
Primary endpoint: IgG4/IgE ratio increase from baseline ≥25% for at least 2 allergens				
Overall	42/60 (70%)		0.70 (0.59, 1.00)	—
By treatment	21/30 (70%)	21/30 (70%)	1.00 (0.29, 3.49)	1.00
Secondary endpoints: IgG4/IgE ratio increase from baseline ≥25% for at least...				
3 allergens	24/46 (52%)		0.52 (0.39, 1.00)	—
	14/25 (56%)	10/21 (48%)	1.39 (0.38, 5.24)	.77
4 allergens	8/23 (35%)		0.35 (0.19, 1.00)	—
	2/10 (20%)	6/13 (46%)	0.31 (0.02, 2.51)	.38
5 allergens	2/7 (29%)		0.29 (0.05, 1.00)	—
	2/4 (50%)	0/3 (0%)	∞ (0.14, ∞)	.43

^aThe probability of success and 95% CI was reported. To determine whether the probability of success differed by treatment arm, Fisher's exact test was used to calculate the odds ratio and 95% CI. The odds ratio (OR) of the 300 mg vs. 1200 mg group and 95% CI were reported.

TABLE 3 Primary endpoint by whether or not maintenance was reached

	Did not reach maintenance (n = 13)	Reached maintenance (n = 47)	Odds ratio (95% CI)	p-value
Primary endpoint: IgG4/IgE ratio increase from baseline ≥25% for at least 2 allergens				
Overall	9/13 (69%)	33/47 (70%)	0.96 (0.22, 4.97)	1.00
Treatment group				
300 mg	4/4 (100%)	17/26 (65%)	∞ (0.28, ∞)	.29
1200 mg	5/9 (56%)	16/21 (76%)	0.40 (0.06, 2.87)	.39
Omalizumab dose group				
<0.016 mg/kg/(IU/ml)	8/12 (67%)	26/30 (87%)	0.32 (0.05, 2.12)	.20
≥0.016 mg/kg/(IU/ml)	1/1 (100%)	7/17 (41%)	∞ (0.03, ∞)	.44

Note: To determine whether the probability of success differed by whether or not maintenance was reached, Fisher's exact test was used to calculate the odds ratio and 95% CI.

mOIT maintenance doses in conjunction with a low fixed dose of omalizumab and displays both safety and feasibility in desensitizing participants with up to 5 food allergens simultaneously over a short period of time. Our study showed that low-dose OIT for multiple foods triggered an immune response (increase in sIgG4/sIgE ratio) even over a short period of time (18 weeks). Multiple trials have adequately demonstrated the safety and efficacy of multi-OIT; however, the ability to transition to real-foods and its long-term effects have not been well characterized.^{8,23} Additionally, with concerns over OIT-induced eosinophilic esophagitis and eosinophilic esophagitis-like OIT-related syndrome,²⁴ it is of crucial importance to explore the benefits of lower maintenance doses. This is the first study that explores low-dose multi-OIT with long-term follow-up survey data 2 years after completion of study.

The primary endpoint was to assess whether low-dose maintenance mOIT would induce immunological changes (a 25% increase in sIgG4/sIgE ratio in at least 2 allergens) over a short period of time. In our study, an increase in sIgG4/sIgE ratio by 25% in at least 2 allergens was achieved in 70% of ITT population. Both treatment arms (300 mg and 1200 mg) showed immunological changes and there were no differences detected. Our findings suggest that immune changes develop earlier and at a lower maintenance dose than previously thought. In previous mOIT studies with adjunct omalizumab performed by our group, unpublished post hoc analyses showed that over 91%¹⁶ and 97%¹⁷ of participants with a >25% increase in sIgG4/sIgE ratio passed their exit OFCs. It is likely that some of the changes in sIgE are driven by omalizumab as previously shown in the literature regarding total IgE^{25,26}; however, our current data show

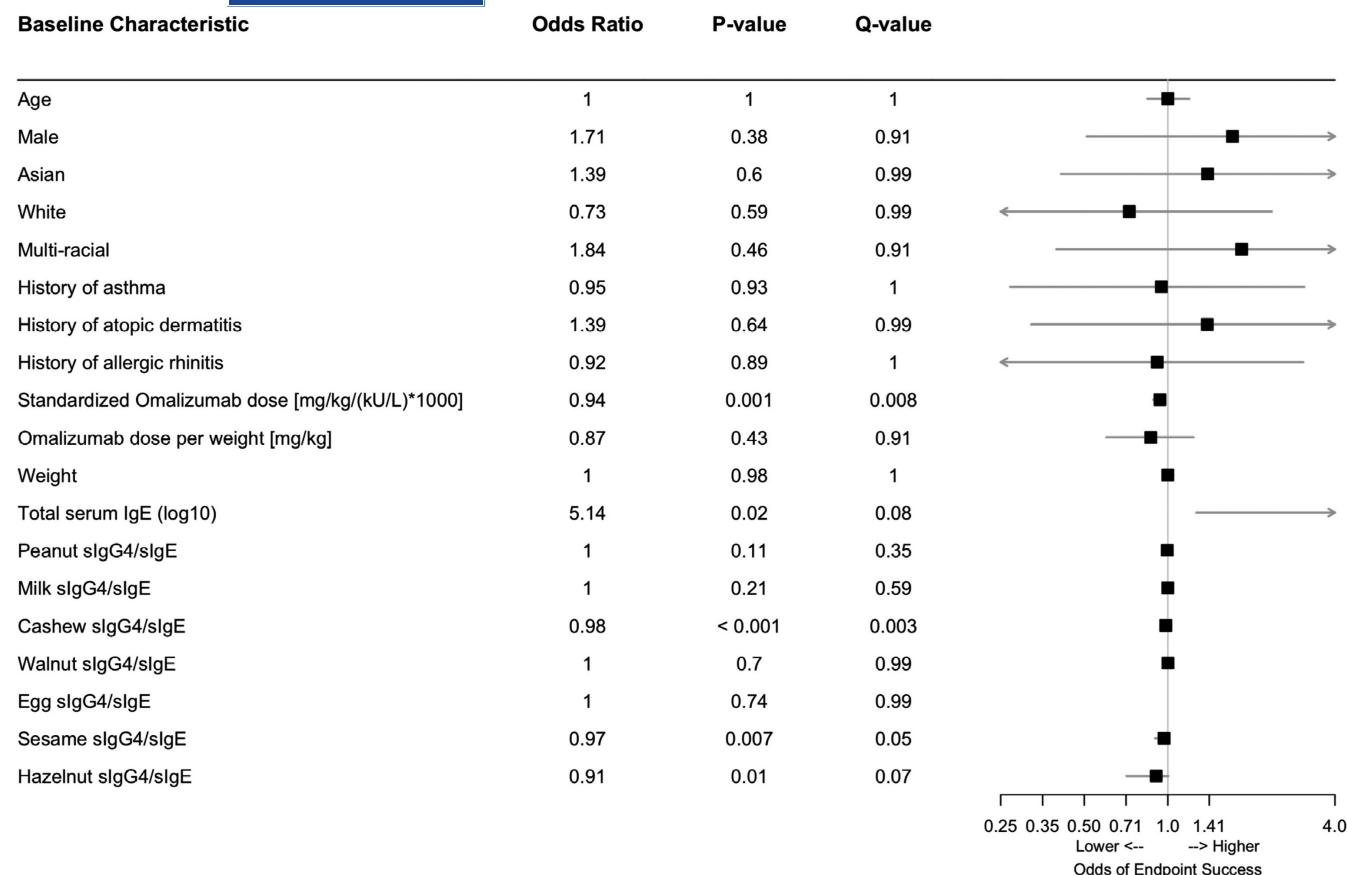


FIGURE 3 Forest plot characterizing the association between baseline features and whether or not a participant had at least a 25% increase in their IgG4/IgE ratio from baseline for at least two allergens (primary endpoint). Each row corresponds to a logistic regression model fitting the primary endpoint as a function of each baseline characteristic, adjusting for treatment group and maximum per-allergen maintenance dose. Almond, cod, salmon, shrimp, and soy plasma markers not shown due to small sample size

that the increase in slgG4/slGE ratio is primarily driven by slgG4 changes rather than changes in slGE, consistent with prior data from our center.¹⁶

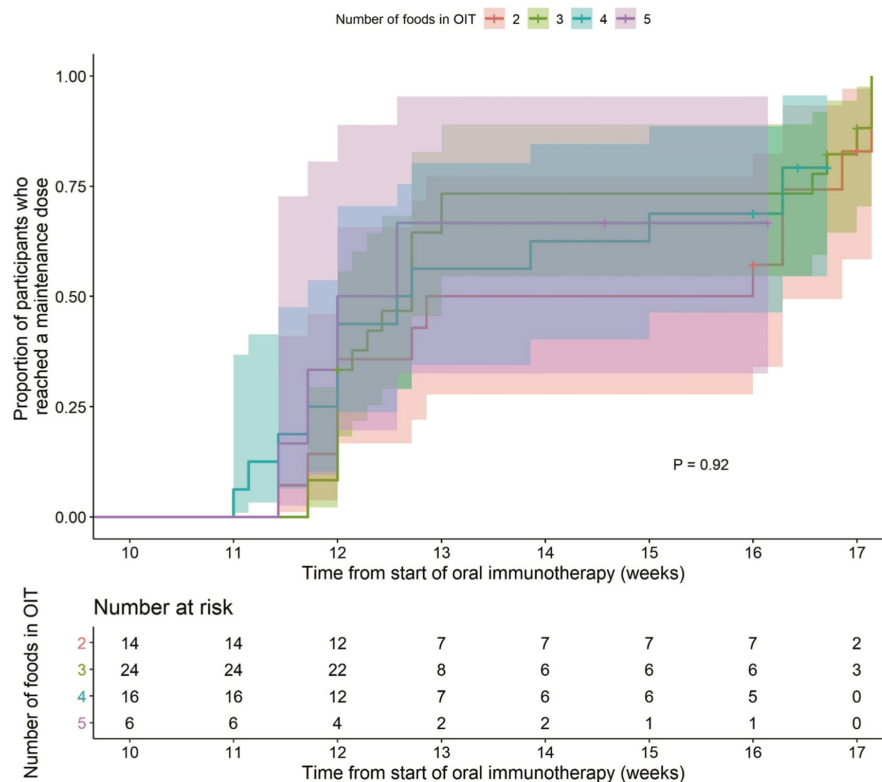
Several publications have recently explored a range of lower maintenance dosing with peanut, egg, and milk. The studies showed evidence of immunological changes and SU; however, all in the setting of single foods.^{11,20,27-30} Our findings are consistent with those of Nagakura et al,²⁰ who found that slGE and slG4 were significantly increased even after a short period of treatment, within a month of low-dose peanut immunotherapy and those of Kulis et al,¹¹ where participants undergoing high and low-dose maintenance of peanut OIT (300 mg vs. 3000 mg) displayed similar changes in peanut slG4 and peanut slGE though not statistically significant. Our findings are promising in that even in participants with 5 allergens in their mix and in the lowest, 300 mg dose where each allergen maintenance dose was 60 mg, the low dose was enough to induce immunological changes by 18 weeks.

A higher baseline total serum IgE was associated with higher odds of primary endpoint success whereas a standardized omalizumab dose (adjusted for weight and total IgE) was associated with lower odds of primary endpoint success. Although these findings were surprising, previous data in the literature suggest that the

efficacy of omalizumab may be dependent on multiple competing mechanisms, some of which being associated with baseline basophil sensitivity and total IgE.³¹⁻³³ Larger phase 2 studies are needed to better understand and identify the exact mechanisms driving such observations. Inclusion of cashew and sesame was associated with lower odds of reaching our primary endpoint. From our prior analyses, it has been found that cashew may have a higher failure rate than other foods. In the mOIT trial by Andorf et al., cashew had a higher rate of discontinuation and failure of OFC, even after OIT.¹⁶ There are no reported studies in the literature suggesting difficulty achieving desensitization with sesame. However, sesame is an emerging allergen that is difficult to outgrow³⁴ and not commonly studied for desensitization.

Although oral food challenges (OFCs) are the gold standard for the diagnosis of food allergy, in recent years, there have been an increase in clinical trials and publications that forego OFCs.^{6,35-37} Our trial purposefully did not include standardized controlled OFCs at screening or exit of the study since our goal was to perform a pragmatic “real life” exploratory pilot study. We chose to forego OFCs for this clinical trial in accordance with patient preferences and to mimic real-life outpatient settings. Additionally, OFCs were not necessary to assess our primary endpoint and answer our research

FIGURE 4 Kaplan-Meier curves of time-to-maintenance and corresponding 95% confidence bands by number of allergens in oral immunotherapy mix. X-axis begins at week 10 since no one reaches maintenance prior to week 11. Two participants in the 1200 mg arm are not included in the plot (1 dropped out prior to starting OIT and 1 was an early termination). Participants who did not reach maintenance are censored at the last visit in which they received a dose (represented by the "+"). *p*-value extracted from the log-rank test across all groups. Time-to-maintenance was also not different by number in OIT mix within the 300 mg ($p = .36$) or 1200 mg ($p = .40$) treatment groups



questions. Many parents have a desire for protection against severe reactions from accidental ingestions^{38,39} and not necessarily to routinely consume the food ad lib. In our experience, many families have turned down clinical trials at the prospect of OFCs. Although it has been standard practice to utilize end-of-study OFCs as a marker for treatment success, there is poor correlation between the outcomes of a graded food challenge and outcomes of accidental ingestion in the community.^{40,41} Greater availability of OIT and advancing its use into clinical practice will require not only just rigorous-placebo-controlled studies but also more flexible trials that mimic real-world settings. If low-dose maintenance dosing is found to be efficacious, it will allow clinicians greater flexibility in shared-decision making with families as maintenance dosing is discussed.

This is the first study exploring an alternate dose of omalizumab for OIT for food allergy. There is currently no definitive or approved omalizumab dose in the setting of OIT. Previous OIT studies utilizing omalizumab have mirrored the dose used in asthma, 0.016 mg/kg/IgE (IU/ml)/month is used based on weight and pretreatment serum IgE.⁴² Brandstrom et al stratified dosing based on omalizumab responders and non-responders as assessed by basophil allergen threshold sensitivity (CD-sens) and adjusted the dose of omalizumab if needed.⁴³ In this study, we explored a fixed dose of 150 mg omalizumab, as used for the treatment of chronic urticaria.^{44,45} Based on our findings, standard, total IgE and weight-based dosing of omalizumab seems to be a significant factor when aiming for higher maintenance mOIT dosing. However, in lower mOIT maintenance dosing, a lower dose of omalizumab can be used successfully. However, the findings are based on post hoc analyses and additional clinical trials are needed.

There were several limitations to our study. The majority of participants were non-Hispanic (93% of ITT). There was no comparison to an mOIT alone arm (ie, without omalizumab-facilitation) or omalizumab only group; further studies are needed to test this comparison. The sample size was relatively small but similar in size to other OIT studies.⁴⁶⁻⁴⁸ Ideally, with omalizumab therapy free IgE should have been measured instead of total IgE which may be artificially elevated for up to 1 year after administration (could be about 2-3 fold higher than baseline); however, measuring free IgE was difficult to accomplish at the time of this study. Our previous experience with mOIT and omalizumab has shown increases in the sIgG4/sIgE ratio is primarily driven by sIgG4 rather than changes in sIgE.¹⁶ OFCs were not used during screening or at end-of-study; therefore, clinical efficacy associated with changes in plasma markers could not be assessed. To overcome the risk of false-positive results, stricter inclusion criteria were used with requirements for a physician-diagnosed food allergy and higher allergen-sIgE and SPT values. We chose to forego OFCs to reflect real-world scenarios where they can be an additional burden for clinical practices and to accommodate patient/family concerns. The questionnaires on the burden of treatment and QOL were collected from a subset of the patients and the results may be biased. Therefore, conclusions should not be made from these results.

In conclusion, our study is the first mOIT trial exploring low maintenance doses for multiple food allergens. Our data suggest that changes in plasma markers are induced early and at a lower maintenance dose than previously known. These findings are important when considering improvements to compliance in long-term dosing of OIT, particularly for multiple foods. Our study also attempted to

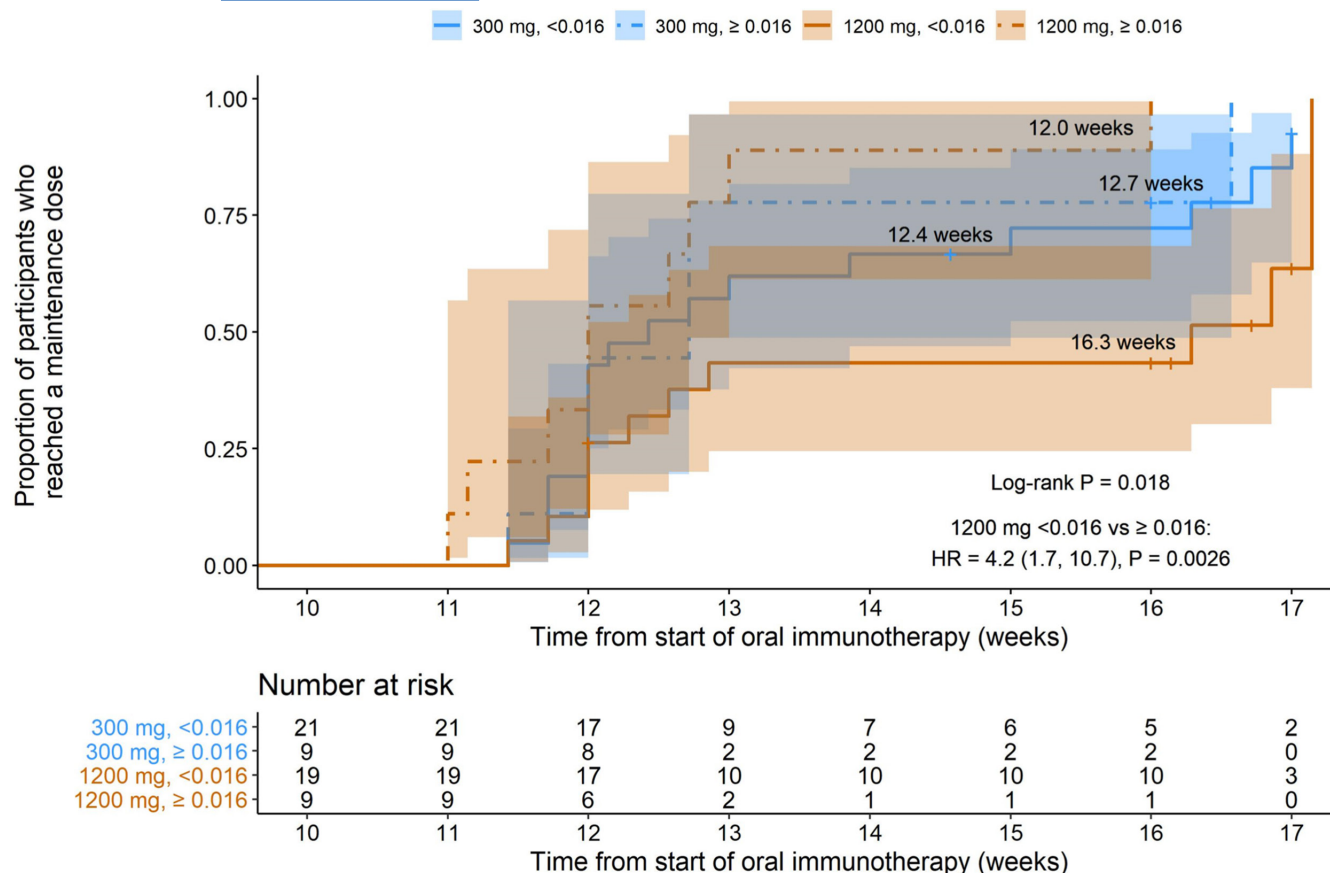


FIGURE 5 Kaplan-Meier curves of time-to-maintenance and corresponding 95% confidence bands by treatment group and omalizumab dose. Solid lines represent the low omalizumab dose arms while dashed lines represent the standard omalizumab dose arms. X-axis begins at week 10 since no one reaches maintenance prior to week 11. Two participants in the 1200 mg arm are not included in the plot (1 dropped out prior to starting OIT and 1 was an early termination). Participants who did not reach maintenance over several attempts are censored at their maximum attainable dose (represented by the "+"). Median time-to-maintenance is reported for each group. Hazard ratio (HR), 95% confidence interval, and *p*-value for the group comparison extracted from a Cox proportional hazards model. "<0.016" and ">0.016" denote the omalizumab dose in mg/kg/(IU/ml)

mimic real-world outpatient settings with elimination of OFCs and conversion to real-food protein equivalents at the end-of-study to continue maintenance dosing at home. This was a proof-of-concept study designed to test whether lower maintenance OIT doses with multiple foods can be safely provided to patients with high IgE levels for whom food challenges may be unsafe due to risk of severe allergic reactions. Larger phase 2 trials are needed to confirm these findings.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

SBS, DK, RSC involved in conceptualization and supervision; SBS, DK, NP, AL, RSC involved in methodology; DK, SBS, MAW involved in project administration; SBS, DK, NP, VS, RSC involved in writing and critical review of manuscript; NP and SC involved in formal analysis and visualization; AL and SC involved in investigation and data Curation; MG performed study, collected data and critically reviewed manuscript; AL reviewed and edited the manuscript; RSC involved in funding acquisition.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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