

Omalizumab facilitates rapid oral desensitization for peanut allergy



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Background: Peanut oral immunotherapy is a promising approach to peanut allergy, but reactions are frequent, and some patients cannot be desensitized. The anti-IgE medication omalizumab (Xolair; Genentech, South San Francisco, Calif) might allow more rapid peanut up dosing and decrease reactions. **Objective:** We sought to evaluate whether omalizumab facilitated rapid peanut desensitization in highly allergic patients. **Methods:** Thirty-seven subjects were randomized to omalizumab (n = 29) or placebo (n = 8). After 12 weeks of treatment, subjects underwent a rapid 1-day desensitization of up to 250 mg of peanut protein, followed by weekly increases up to 2000 mg. Omalizumab was then discontinued, and subjects continued on 2000 mg of peanut protein. Subjects underwent an open challenge to 4000 mg of peanut protein 12 weeks after stopping study drug. If tolerated, subjects continued on 4000 mg of peanut protein daily. **Results:** The median peanut dose tolerated on the initial desensitization day was 250 mg for omalizumab-treated subjects versus 22.5 mg for placebo-treated subject. Subsequently, 23

(79%) of 29 subjects randomized to omalizumab tolerated 2000 mg of peanut protein 6 weeks after stopping omalizumab versus 1 (12%) of 8 receiving placebo ($P < .01$). Twenty-three subjects receiving omalizumab versus 1 subject receiving placebo passed the 4000-mg food challenge. Overall reaction rates were not significantly lower in omalizumab-treated versus placebo-treated subjects (odds ratio, 0.57; $P = .15$), although omalizumab-treated subjects were exposed to much higher peanut doses.

Conclusion: Omalizumab allows subjects with peanut allergy to be rapidly desensitized over as little as 8 weeks of peanut oral immunotherapy. In the majority of subjects, this desensitization is sustained after omalizumab is discontinued. Additional studies will help clarify which patients would benefit most from this approach. (*J Allergy Clin Immunol* 2017;139:873-81.)

Key words: Peanut allergy, food allergy, desensitization, omalizumab

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Abbreviations used

DBPCFC: Double-blind, placebo-controlled food challenge
 EoE: Eosinophilic esophagitis
 ITT: Intention to treat
 OIT: Oral immunotherapy
 SPT: Skin prick test

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Food allergy remains the leading cause of anaphylaxis among children, and its prevalence has increased over time.¹⁻⁴ In addition, food allergy is costly, increases anxiety, decreases patient and family quality of life, and might affect nutrition.⁵ Currently, the standard of care for food allergy is allergen avoidance and availability of self-injectable epinephrine. Peanut allergy is responsible for a large proportion of severe reactions to foods and, unlike milk and egg allergy, is typically lifelong.^{6,7} Although recent work suggests that early introduction of peanut can protect against peanut allergy, almost 10% of high-risk infants evaluated in the first year of life showed sensitization to peanut, rendering them ineligible for early peanut exposure.⁸ Therefore therapies for patients with established food allergies are clearly needed.

There has been substantial interest in oral immunotherapy (OIT) as a treatment for peanut and other food allergies. Successful desensitization has been demonstrated for a number of foods, including peanut, milk, and egg.⁹⁻¹⁷ Gradual exposure to increasing amounts of allergen can lead to the majority of subjects tolerating doses of food sufficient to prevent reaction on accidental exposure. Unfortunately, most subjects undergoing OIT experience allergic reactions during desensitization, with approximately 20% having severe reactions requiring injection of epinephrine and another 10% to 20% of patients being refractory to oral desensitization.¹⁸⁻²⁰ Furthermore, desensitization is less likely to be successful in patients with higher baseline food-specific IgE levels,^{10,21} resulting in an increased risk of anaphylaxis with desensitization relative to continued avoidance.²⁰ Although OIT allows some desensitized patients to have sustained unresponsiveness, which is defined as persistence of protection after discontinuation of OIT, this occurs in a small fraction of desensitized patients, generally those with lower baseline food-specific IgE levels.^{21,22} Lastly, current food allergy OIT clinical studies are hampered by dropout rates of up to 25% because of reactions and noncompliance over long periods of desensitization (2-4 years).²³

Recently, omalizumab (Xolair; Genentech, South San Francisco, Calif), an anti-IgE mAb, has been used to decrease reactions during oral desensitization. This medicine, which was initially approved for the treatment of asthma in adults and adolescents, binds free IgE and prevents allergic reactions.²⁴ We and others have reported in 3 open-label studies that omalizumab facilitates oral desensitization, in particular allowing more rapid and successful escalation of allergen dosing in subjects with high-risk food allergy.²⁵⁻²⁷ Furthermore, preliminary data suggest that interrupting IgE signaling during OIT/antigen exposure might reverse established allergy through induction of both T_H1 and regulatory T cells, which inhibit the allergic response.²⁸⁻³¹

Here we report the results of the Peanut Reactivity Reduced by Oral Tolerance in an anti-IgE Clinical Trial (PRROTECT), the first

randomized, double-blind, placebo-controlled, multicenter study of the efficacy of omalizumab in conjunction with peanut OIT.

METHODS

Study subject selection

This phase II study was conducted at 4 institutions with approval from their respective institutional review boards and from the US Food and Drug Administration through an investigational new drug application. Full inclusion and exclusion criteria are summarized in the **Methods** section in this article's Online Repository at www.jacionline.org. All patients had positive responses to peanut on both skin prick tests (SPTs) and specific IgE measurements and a significant reaction (see the **Methods** section in this article's Online Repository) to a peanut protein dose of 50 mg or less (cumulative dose of 88 mg of peanut protein) in a double-blind, placebo-controlled food challenge. No patients were undergoing immunotherapy to environmental allergens, and none had received omalizumab in the past. Written informed consent was obtained from parents or guardians of all subjects along with assent from children of appropriate age.

Randomization and treatment

From June 2013 through September 2014, a total of 37 eligible participants were enrolled and randomized in a 3.5:1 ratio to receive omalizumab (n = 29) or placebo (n = 8) in conjunction with peanut OIT. The selected randomization ratio was based on the power analysis and the strong therapeutic effect of omalizumab observed in previous open-label studies. The study design called for 28 subjects in the omalizumab arm, but 1 participant randomized to omalizumab withdrew before receiving the first injection and was replaced per protocol. Dosing for omalizumab (and placebo) was in accordance with the Xolair Global Dosing Schedule with slight modification.

Rapid oral desensitization and up dosing schedule

Twelve weeks after the first dose of study drug, subjects began OIT with an initial rapid oral desensitization day consisting of up to 10 doses (0.5, 1, 2, 4, 8, 15, 30, 60, 120, and 250 mg) of peanut protein (1 peanut contains 200-250 mg of peanut protein). The doses were spaced 30 minutes apart until either the 250-mg dose (cumulative 490.5 mg) was tolerated or a significant reaction occurred (see the **Methods** section in this article's Online Repository). The next day, the highest tolerated dose from the previous day was administered under medical supervision; subjects were then discharged to take this dose once daily at home for the next week. All patients continued after the rapid desensitization day, regardless of the highest peanut dose achieved, and returned the following week for weekly up dosing. Subjects who tolerated the 250-mg dose on the first day returned for weekly doses of 375, 500, 625, 750, 1000, 1250, 1625, and 2000 mg of peanut protein. Subjects who tolerated less than 250 mg of peanut protein on the first day underwent up dosing in smaller increments up to twice a week (see the **Methods** section in this article's Online Repository).

Discontinuation of study drug and OIT maintenance

At week 19, the last dose of blinded study drug was given to subjects who were tolerating the 1625-mg dose, and they progressed to 2000 mg at week 20. Subjects who did not reach 1625 mg received additional doses of study drug while continuing to up dose for a maximum of 6 additional weeks. The primary outcome of the study was the ability to tolerate 2000 mg of peanut protein 6 weeks after withdrawal of study drug, which was defined as at least 1 day during the preceding week when this dose was consumed with no reaction. If the 2000-mg dose of peanut protein was not reached after the 6-week extension, the study drug was stopped, but weekly up dosing continued as tolerated. Those who could not tolerate 250 mg of peanut protein by week 19 were considered treatment failures and had the option to receive open-label omalizumab with peanut OIT, but initial therapy remained blinded (ie, patients and investigators were not aware which treatment these subjects had initially received). Subjects who transitioned to open-label omalizumab continued on

the highest dose of peanut protein tolerated while receiving omalizumab for 12 weeks and then followed the same updosing protocol as in the blinded portion of the study.

Challenge to 4000 mg of peanut protein

Study subjects tolerating a daily oral dose of 2000 mg of peanut protein underwent an oral food challenge with peanut 12 weeks after their last dose of study drug (week 31 for subjects who tolerated 2000 mg of peanut protein at week 20). Three doses of peanut protein were given 30 minutes apart (1250, 1250, and 1500 mg), for a cumulative dose of 4000 mg. Subjects who reacted during the challenge maintained a 2000-mg daily dose of peanut protein for the remainder of the study. Subjects who did not react continued on 4000 mg of peanut protein daily.

Assessments

Total peanut-specific IgE levels and SPT responses to peanut extract were assessed at baseline, 12 weeks after the last dose of study drug, and at the end of the study. Adverse events, as defined by US Food and Drug Administration regulation, were documented for the duration of the study and recorded and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03.³² Events not included in the National Cancer Institute's Common Terminology Criteria for Adverse Events listing were graded as grade 1 to 5 (mild, moderate, severe, life-threatening, and death), according to the General Grade Definitions. Allergic reactions to peanut OIT were graded according to the Bock criteria (see the [Methods](#) section in this article's Online Repository).³³

Study registration

The study was registered as NCT01781637 at www.clinicaltrials.gov.

Statistical analysis

Full details of the statistical analysis are shown in the [Methods](#) section in this article's Online Repository. Briefly, primary and secondary end points were compared between the study arms by using the Fisher exact test. Prespecified analyses were conducted with intention-to-treat (ITT) analysis. Reactions per dose were compared between study arms by using generalized estimating equations with logit link. *P* values of .05 or less were considered significant.

Role of the funding source

The sponsors of the study had no role in study design or data collection. After the study started, Dr Umetsu changed employment from Boston Children's Hospital to Genentech, one of the sponsors. He subsequently was involved in data analysis, data interpretation, and writing the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Baseline characteristics and initial food challenge

Sixty-nine subjects underwent baseline food challenge to peanut. Thirty-seven of these subjects were randomized: 29 to omalizumab and 8 to placebo ([Fig 1](#)). Baseline characteristics, including dose of peanut protein eliciting a reaction, of the 37 subjects enrolled in the study are presented in [Table I](#) and were similar between groups. The median age of the subjects was 10 years, and the median peanut-specific IgE levels were 91 and 88 kU_A/L in the omalizumab and placebo groups, respectively. The median cumulative peanut dose eliciting a reaction during the baseline double-blind, placebo-controlled food challenge (DBPCFC) was 38 mg (range, 0.5-88 mg) for subjects randomized to omalizumab and 88 mg for those randomized to placebo (range, 13-88 mg). Seventeen subjects required treatment with epinephrine during the baseline food challenge.

Initiation of study drug and oral desensitization

Of the 29 subjects randomized to omalizumab (ITT population), 1 withdrew before receiving the first dose of omalizumab and was replaced per protocol; another withdrew before commencing OIT because of a hospitalization for an eating disorder judged to be unrelated to the study drug. Twenty-three of the 27 subjects remaining in the omalizumab group completed the 250-mg desensitization versus 1 of the 8 subjects treated with placebo (*P* = .0003, [Fig 2](#)). The median tolerated dose after this first day of the desensitization process for subjects receiving omalizumab was 250 mg (490.5 mg cumulative) versus 22.5 mg for those receiving placebo.

The 24 subjects who successfully tolerated the rapid first day of the desensitization process (23 were omalizumab treated and 1 was placebo treated) had their peanut dose increased weekly up to 2000 mg of peanut protein (equivalent to 8-10 peanuts) over 8 weeks. Twenty-one of 29 omalizumab-treated and 1 of 8 placebo-treated subjects reached 2000 mg of peanut protein by study week 20 (*P* < .01, ITT population).

Primary end point: Ability to tolerate a 2000-mg peanut dose 6 weeks after withdrawal of study drug

The primary end point of this study was the ability to tolerate a 2000-mg dose of peanut protein 6 weeks after stopping omalizumab or placebo injection. This was achieved in 23 of 29 of subjects randomized to omalizumab (79% of the ITT population) and 23 (85%) of 27 who actually received peanut immunotherapy compared with 1 (12.5%) of 8 receiving placebo (*P* < .01 for the ITT population, [Table II](#)).

Treatment failures

Six (75%) subjects in the placebo group and 2 (7.4%) in the omalizumab group were unable to tolerate 250 mg of peanut protein after 8 weeks of desensitization. These subjects were considered treatment failures and received open-label omalizumab and peanut OIT per protocol. All 8 were able to tolerate 2000 mg of peanut protein while receiving open-label omalizumab. In total, 31 (89%) of the 35 subjects (31/33 [94%] who received omalizumab and peanut OIT) were able to tolerate 2000 mg of peanut 6 weeks after stopping omalizumab. The 2 subjects (1 initially randomized to omalizumab and 1 to placebo) who did not reach this end point both had symptoms suggestive of eosinophilic esophagitis (EoE), 1 documented by esophageal biopsy (discussed below).

Oral challenge with 4000 mg of peanut protein

Subjects able to tolerate 2000 mg of peanut protein continued on this dose and underwent an open peanut challenge with a cumulative dose of 4000 mg of peanut protein 12 weeks after discontinuation of study drug (a secondary end point). Twenty-two of 29 subjects randomized to omalizumab (22/27 who actually received peanut immunotherapy) and 1 of 8 randomized to placebo passed this challenge (*P* = .002, ITT population; [Table III](#)). They continued to consume 4000 mg of peanut protein daily in a form of their choosing. One subject who failed this challenge resumed taking peanut at 2000 mg/d. Sixteen of the 22 omalizumab-treated subjects and the single placebo-treated

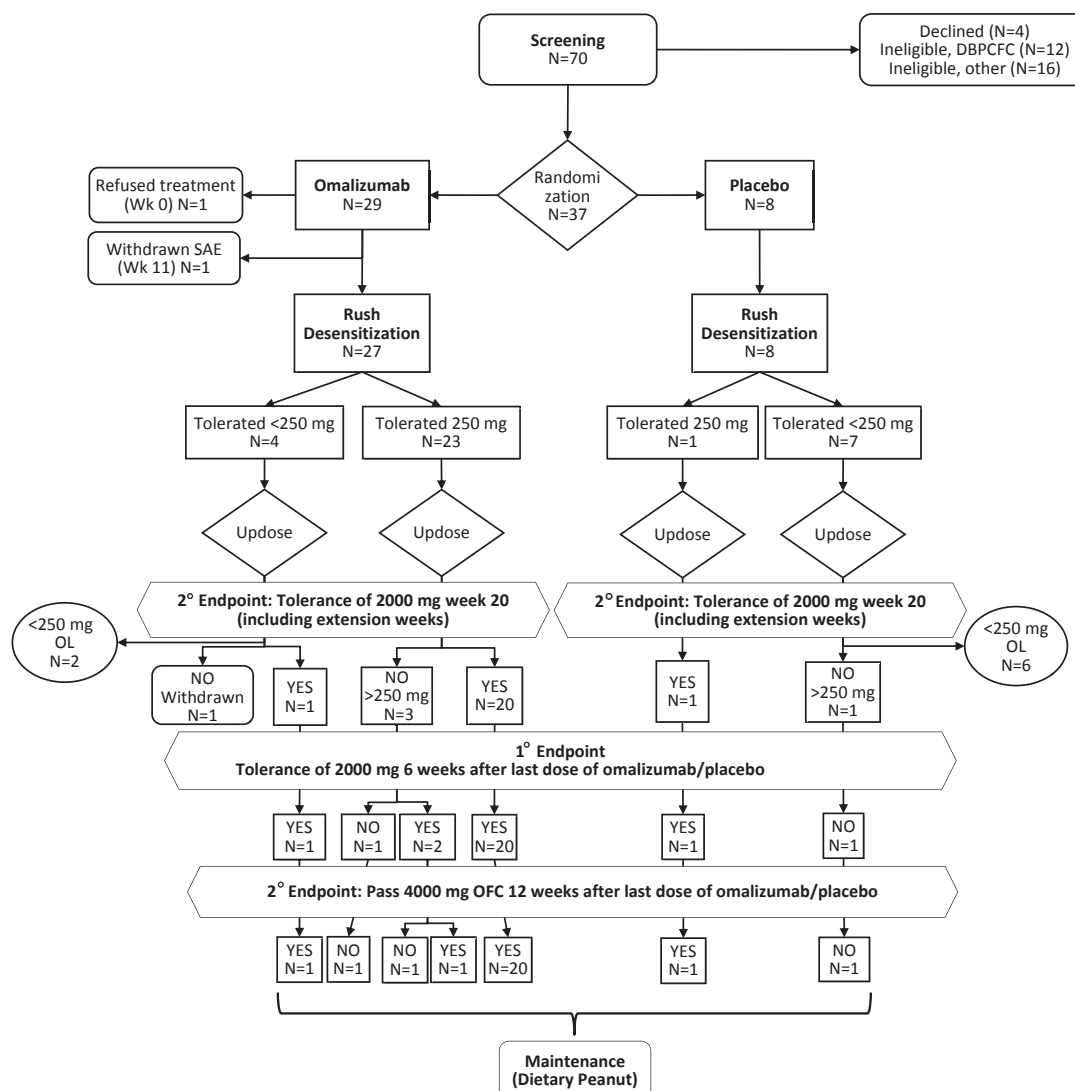


FIG 1. Study enrollment, randomization, procedures, and outcomes. OL, Open label. OL also indicates subjects who were considered to have failed peanut OIT and went on to receive open-label omalizumab.

subject who passed the 4000-mg challenge maintained this dose for an additional 21 weeks (the end of the study). Six of the omalizumab-treated subjects who passed the 4000-mg challenge subsequently had allergic reactions on the 4000-mg maintenance dose, including 4 requiring epinephrine. All of these subjects were successfully converted to a 2000-mg peanut maintenance dose.

Safety data and reactions

Safety data were characterized by body system and Bock grade.³³ Focusing on the initial rapid desensitization (because most placebo-treated subjects never tolerated 250 mg of peanut protein), 4 of 28 omalizumab-treated subjects versus 6 of 8 placebo-treated subjects had significant (Bock grade 2) reactions. Grade 1 reactions were seen in 16 of 28 omalizumab-treated subjects versus 5 of 8 placebo-treated subjects. Overall, reactions occurred after 7.8% of OIT doses administered in the omalizumab arm versus 16.8% in the placebo arm, despite omalizumab-treated

subjects receiving higher doses of peanut. This difference was not statistically significant (odds ratio, 0.57; $P = .15$). Most reactions were mild (Bock grade 1) and localized to the gastrointestinal tract. The majority of reactions occurred during the initial desensitization day and subsequent dose-escalation visits. No significant reactions were attributed to omalizumab or placebo administration.

There were 7 grade 3 reactions judged to be study related: 3 in subjects receiving blinded omalizumab, 1 in a subject receiving placebo, and 3 in subjects receiving open-label omalizumab (see Tables E4-E7 in this article's Online Repository at www.jacionline.org). All reactions were reversible and thought to be due to peanut exposure. A total of 14 reactions requiring epinephrine treatment occurred in 8 subjects receiving OIT. Seven reactions occurred in subjects receiving blinded therapy: 3 reactions in 2 patients in the placebo arm and 4 reactions in 3 patients in the omalizumab arm. The remaining 7 reactions occurred in subjects receiving open-label omalizumab. All subjects who received epinephrine recovered with no clinical sequelae and

TABLE I. Baseline characteristics

Baseline characteristics	No.	Omalizumab	Placebo	Odds ratio (95% CI)	P value
Age at baseline (y), median (range)	37	10 (7-19)	10 (6-17)		.56
Female sex, no. (% of study group)	15	11 (37.9)	4 (50)	0.61 (0.13-2.95)	.69
Male sex, no. (%)	22	18 (62.1)	4 (50)	Reference	—
Total IgE level (IU/L), median (range)	37	430 (65-1172)	391 (125-1511)		.78
Peanut-specific IgE level (kU _A /L), median (range)	37	91 (10-535)	88 (26-483)		.57
IgE ratio, median (range)	37	0.28 (0.03-0.58)	0.29 (0.06-0.73)		.73
Peanut skin test wheal size (mm), median (range)	37	11 (5-18)	10 (7-13)		.49
Peanut skin test erythema size (mm), median (range)	37	33 (0-58)	31 (24-46)		.80
DBPCFC cumulative failure dose (peanut protein [mg]), median (range)	37	38 (1-88)	88 (13-88)		.08

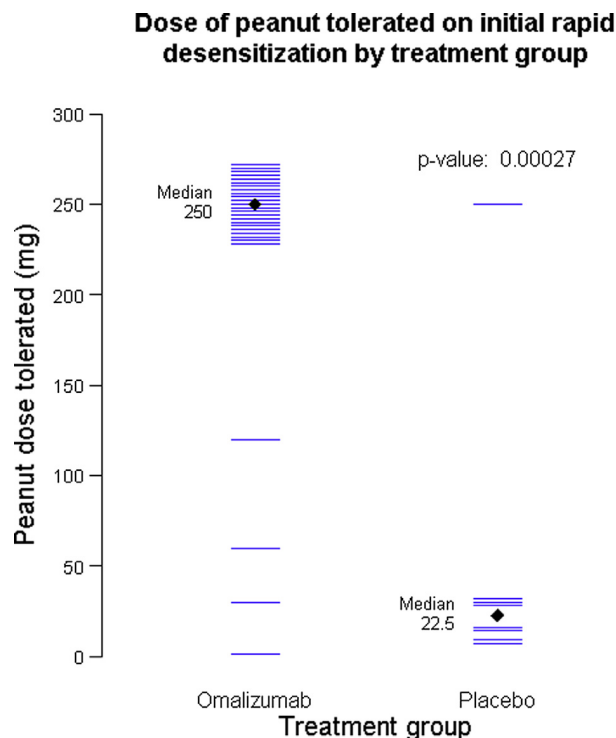


FIG 2. Highest dose of peanut protein tolerated during initial rapid desensitization.

continued in the study. Nonsteroidal anti-inflammatory drug (ibuprofen) ingestion, viral infections, and exercise were noted to be possible cofactors. One reaction requiring epinephrine occurred in a college student in the maintenance phase who did not take the peanut doses for 6 days and then, without contacting the site, took 4000 mg of peanut protein.

Three subjects had persistent gastrointestinal symptoms consistent with EoE and stopped peanut dosing. At study week 14, an omalizumab-treated subject had gastrointestinal symptoms consistent with EoE and was withdrawn from the study at week 17 because of persistent symptoms; endoscopy was not performed. A second omalizumab-treated subject withdrew at extension week 2 because of persistent gastrointestinal symptoms, and an esophageal biopsy specimen taken 11 days after stopping peanut while receiving proton pump inhibitor therapy showed 21 eosinophils/high-power field, which is consistent with a diagnosis of EoE. A placebo-treated subject had persistent gastrointestinal

symptoms requiring reduction of peanut dose. Endoscopy done at week 23 while receiving high-dose proton pump inhibitor therapy demonstrated EoE (peak, 29 eosinophils/high-power field) and eosinophilic gastritis; peanut OIT was stopped. In all 3 subjects symptoms resolved with discontinuation of peanut intake; follow-up endoscopies were not performed.

Changes in immunologic parameters

Subjects treated with omalizumab showed decreased wheal size on skin testing but increased peanut-specific IgE values at week 31 compared with baseline values ($P < .0001$ for both), which is consistent with data from other desensitization studies (Fig 3).^{9,31,34-36} Although week 31 (11-12 weeks after stopping omalizumab) occurred at about 3 half-lives after the last omalizumab dose (the half-life of omalizumab in the circulation is about 26 days),³⁷ the small amounts of omalizumab remaining in circulation at that time are thought to only minimally affect skin test reactivity.³⁸ Increased peanut-specific IgE levels and decreased SPT wheal sizes were also seen in subjects who received open-label omalizumab. The single placebo-treated subject who tolerated the 4000-mg food challenge showed increases in both peanut-specific IgE levels and SPT responses.

DISCUSSION

This randomized, double-blind, placebo-controlled study demonstrates that a short treatment course of omalizumab improves the safety and tolerability of peanut up dosing during peanut OIT, allowing a large majority of subjects to achieve a 2000-mg maintenance dose of peanut protein at a median of 8 weeks. As the first placebo-controlled trial of omalizumab with peanut OIT, this study extends our previous work²⁵ and that of others³⁹ and provides rigorous scientific confirmation that omalizumab can facilitate rapid OIT of high-risk subjects with peanut allergy that is maintained even after omalizumab treatment is discontinued. Thus omalizumab pretreatment allowed 23 of 29 subjects to tolerate 250 mg of peanut protein (cumulative dose, 490 mg), roughly the amount found in 2 peanuts, during the first day of desensitization compared with 1 of 8 placebo-treated subjects (median dose, 22.5 mg). Furthermore, 23 of 29 (76% of the ITT population) omalizumab-treated subjects were able to quickly achieve a 2000-mg maintenance dose of peanut protein and maintain nonreactivity for 6 weeks after discontinuing omalizumab versus 1 of 8 placebo-treated subjects. Although subjects likely retained some protection from omalizumab at this time point

TABLE II. Tolerance of 2000 mg of peanut protein after discontinuation of study drug

Outcome	No. (% of treatment group)		Odds ratio (95% CI)	P value
	Omalizumab	Placebo		
Tolerated 2000 mg of peanut protein	23 (73.9)	1 (12.5)	26.8 (2.7-262.3)	<.01
Did not tolerate 2000 mg of peanut protein	6 (20.7)	7 (87.5)		
Withdrew from study	3 (50.0)	0 (0.0)		
Updosed to <250 mg, started open-label omalizumab	2 (33.3)	6 (85.7)		
Updosed to x, where 250 mg ≤ x <2000 mg	1 (16.7)	1 (14.3)		

TABLE III. Oral food challenge 12 weeks after last dose of study drug

Outcome	No. (% of treatment group)		Odds ratio (95% CI)	P value
	Omalizumab	Placebo		
Passed 4000 mg of peanut protein OFC	22 (75.9)	1 (12.5)	22.0 (2.3-211.1)	<.01
Did not pass 4000 mg of peanut protein OFC	7 (24.1)	7 (87.5)		
Experienced allergic reaction during OFC	1 (14.3)	0 (0.0)		
Tolerating <2000 mg and did not receive OFC	1 (14.3)	1 (14.3)		
Withdrew from study before time point	3 (37.5)	0 (0.0)		
Switched to open-label before time point	2 (28.6)	6 (85.7)		

OFC, Oral food challenge.

(the half-life of omalizumab is 26 days), successful achievement of this end point indicated that omalizumab could indeed facilitate rapid dose escalation to a 2000-mg dose of peanut. Moreover, 16 omalizumab-treated subjects tolerated 4000 mg of peanut protein, and an additional 7 tolerated 2000 mg 33 weeks after discontinuing therapy (>9 half-lives after the last omalizumab dose), demonstrating that the presence of omalizumab was not required to maintain the peanut-desensitized state.

The rapid desensitization in subjects treated with omalizumab in our study contrasts with the results of investigations using oral peanut desensitization alone. For example, in a previous study of conventional OIT (without omalizumab), only 10 of 39 subjects achieved the highest initial dose of 50 mg of peanut protein on the initial desensitization day.⁹ In another study Blumchen et al²³ reported that only 5 of 22 subjects were able to tolerate 125 mg of peanut protein after a 7-day rush desensitization. The final dose tolerated after this 7-day desensitization was not significantly higher than the dose to which subjects reacted at baseline.

Moreover, in our study the final target dose of peanut (2000 mg) was achieved in the majority of omalizumab-treated subjects (21/29 subjects randomized to omalizumab, of whom 27 received both omalizumab and OIT) after only 8 weeks of desensitization. In contrast, other recent studies not using omalizumab reported much slower increases in peanut dosing, ranging from 41⁴⁰ to 44¹¹ weeks to reach a final dose of 800 to 4000 mg of peanut protein. For example, Anagnostou et al¹⁰ demonstrated that peanut dosing could be increased to 800 mg of peanut protein over approximately 16 weeks, but only 24 of 49 subjects were able to tolerate 1400 mg of peanut protein after 26 weeks of therapy. Thus use of omalizumab allowed rapid desensitization to a high dose of peanut.

Wood et al⁴¹ recently reported that omalizumab can facilitate milk OIT and that rates of allergic reactions were significantly lower in omalizumab-treated subjects using a long desensitization period (>2 years of treatment with omalizumab) and a posttreatment oral food challenge. In this study 71.4% of placebo-treated subjects (and 89% of omalizumab-treated subjects) passed the

final 10,000 mg oral food challenge, which is consistent with previous studies showing that slow persistent OIT up dosing without omalizumab can be successful. Successful treatment at month 32 in this study was associated with lower milk-specific IgE levels (median, 24 kU_A/L), as has been previously suggested.¹⁰ Our study included patients with high peanut-specific IgE levels (median, 91 kU_A/L) who might be at increased risk of having difficulty with conventional immunotherapy.^{21,23,34,42-45}

The use of omalizumab allowed rapid desensitization to 2000 mg of peanut protein, with low rates of peanut reactions and adverse effects. Although the reaction rates were not statistically lower with omalizumab (7.8% of doses) compared with placebo (16.8%), omalizumab-treated subjects were exposed to much higher doses of peanut protein. For example, during the initial rapid desensitization day, grade 2 reactions were observed in 4 of 27 omalizumab-treated subjects versus 6 of 8 placebo-treated subjects, but omalizumab-treated subjects reached a median dose of 250 mg of peanut protein compared with 22.5 mg for placebo. Therefore the safety of omalizumab in facilitating OIT might be underestimated because of the study design. However, it is important to note that rates of reaction are likely to be increased in subjects with peanut allergy undergoing OIT compared with continued avoidance.

Three subjects (2 treated with omalizumab) had persistent gastrointestinal symptoms consistent with EoE. Peanut consumption was stopped in these subjects, leading to complete resolution of symptoms. EoE has been observed in other trials of OIT at rates comparable with those seen in this study,⁴⁶ which is consistent with the idea that omalizumab is not effective for treatment of EoE,⁴⁷ although this study was not powered to evaluate rates of EoE. It is possible the rapid up dosing used in this study increases the risk of EoE. Of note, of 27 patients randomized to omalizumab who received peanut OIT, 23 tolerated 2000 mg of peanut protein during the double-blind phase of the trial, 2 more tolerated this dose after open-label omalizumab, and 2 did not achieve this end point because of EoE-like symptoms. The inability to tolerate high doses of antigen caused by persistent gastrointestinal

Immunologic characteristics of patients undergoing OIT

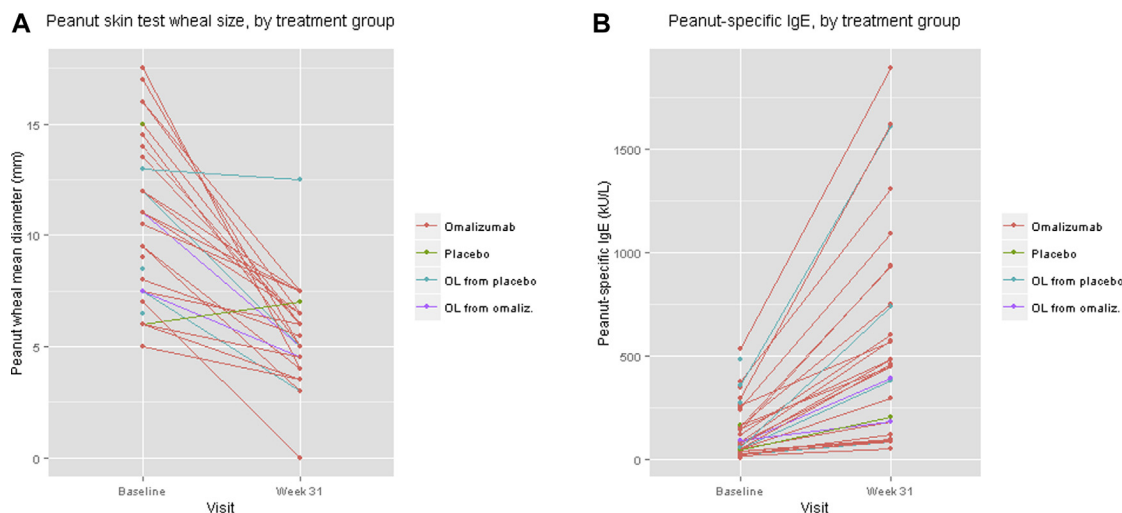


FIG 3. Changes in immunologic characteristics. Wheal size for peanut SPTs (A) and peanut-specific IgE measurements (B) are shown at baseline and week 31 of the study after 12 weeks off study drug. OL, Open-label.

symptoms consistent with EoE remains a significant obstacle to successful use of OIT,⁴⁸ and omalizumab does not seem to significantly decrease this risk.

Interestingly, a single placebo-treated subject was able to meet all study end points, and 2 subjects in whom blinded omalizumab treatment failed were able to meet all study end points when they received open-label omalizumab. Baseline characteristics of these subjects were unremarkable. The latter 2 subjects suggest that some subjects might benefit from a prolonged course of omalizumab before OIT; alternatively, the likelihood of having allergic symptoms during OIT might be lower in the setting of open-label omalizumab administration.

A potential concern with use of omalizumab is that subjects might be at risk for allergic reactions once omalizumab treatment is stopped (week 19 of this study, just before subjects received their first 2000-mg dose of peanut). Six of 22 omalizumab-treated subjects who passed the 4000-mg food challenge at week 31 had to reduce their peanut dose at some point over the following 21 weeks because of allergic reactions. However, all were able to then safely tolerate a daily maintenance dose of 2000 mg of peanut protein, suggesting the 2000-mg dose might be easier to tolerate. Missed doses of peanut, use of nonsteroidal anti-inflammatory drugs, exercise, and concurrent infections might all increase the risk of reactions. Whether using omalizumab beyond 20 weeks used in our study would reduce the frequency of these reactions is not clear.

In our current study we did not examine sustained unresponsiveness, although we plan to evaluate for this following additional time on maintenance therapy and after peanut-specific IgE levels decrease to less than 10 kU/L (median peanut-specific IgE at week 52 was 70 kU/L). Unfortunately, sustained unresponsiveness after OIT appears to be difficult to achieve, even with prolonged intake of high daily doses of peanut, except in patients who begin OIT with low food-specific IgE levels.^{21,22,41} Whether high (eg, 2000 mg) or low (eg, 250 or 300 mg) doses of peanut protein are optimal for induction of sustained unresponsiveness remains unknown. Further study of the

most appropriate maintenance dose and the length of omalizumab and maintenance therapy would help to optimize this treatment. Given that peanut OIT does not consistently lead to sustained unresponsiveness, the benefits of protection against accidental exposure versus the risks of allergic reactions occurring during OIT must be balanced before considering the use of omalizumab-facilitated OIT.

There are several weaknesses of our study. First, the sample size was relatively small and included only 8 placebo-treated subjects. We chose this low number of placebo-treated subjects because the power analysis, based on our previous open-label study, indicated that 8 placebo-treated subjects was more than sufficient and because we hoped to limit the number of subjects exposed to the rapid up dosing of peanut on the first day of desensitization (250-mg maximum dose, cumulative 490 mg), which was expected to induce allergic reactions in placebo-treated subjects. Although only 37 subjects were randomized, this is one of the largest trials of peanut desensitization to date and was sufficient to demonstrate a highly significant difference between the placebo- and omalizumab-treated groups in achieving the 2000-mg maintenance peanut dose.

Second, given the small number of placebo-treated patients and the potent therapeutic effect of omalizumab in this situation, subjects might have deduced which therapy they were receiving. The ability to tolerate 250 mg on the initial up dosing day would not be expected in placebo-treated subjects and might have been a clue that subjects were receiving active therapy. In addition, omalizumab might have improved control of concomitant asthma or allergic rhinitis. However, the 250-mg dose was achieved in 1 placebo-treated subject, and 4 omalizumab-treated subjects did not achieve the 250-mg dose on the first up dosing day, suggesting that the blinding was effective.

Finally, 3 previous studies showed that treatment alone with an anti-IgE mAb led to increased tolerance to peanut with reactions at median doses of 1315 mg,³⁹ 500 mg,⁴⁹ or 6500 mg⁵⁰ of peanut, with wide variation within each study. It should be noted that subjects in the 3 studies had significantly lower median peanut-

specific IgE levels (14.3 and 25.9 kU_A/L and one not reported) than in our study (91 kU_A/L) and smaller SPT responses to peanut (only reported in 1 study: 7.8 vs 11 mm) and tolerated higher doses of peanut at baseline food challenge (eg, 80 mg in the study by Savage et al⁵⁰). Although some of our omalizumab-treated patients might have been able to tolerate 250 mg or even 2000 mg of peanut in 1 day after omalizumab treatment alone, our experience is that most of our patients, particularly those with high baseline peanut-specific IgE levels, require desensitization over several weeks to reach doses of 2000 mg. Most importantly, the goals of these 3 studies were significantly different from those of our omalizumab-facilitated OIT approach, in which omalizumab treatment is limited to 5 to 6 months, as opposed to indefinitely.

OIT remains a promising approach for patients with peanut and other food allergies, but it is still not recommended for general use, in part because reaction rates are high and many patients are sensitized to more than 1 food allergen. However, our study demonstrates that peanut OIT in combination with omalizumab allows for rapid effective desensitization in the majority of patients with peanut allergy, including those with high peanut-specific IgE levels. Although omalizumab is expensive, requires repeated injections, and is associated with a risk of hypersensitivity reactions, we suggest that the benefits of omalizumab-enabled OIT might outweigh these downsides; additional studies will be required to further evaluate this proposition.

We acknowledge the assistance of Heather Litman, Les Kalish, and Emily Blood in planning, coding, data management, and early statistical analysis.

Clinical implications: Omalizumab allows rapid and safe desensitization of patients with peanut allergy. Desensitization is maintained after omalizumab treatment is stopped.

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METHODS

Inclusion and exclusion criteria

Eligibility criteria for participation were as follows: age 7 to 25 years, baseline levels of peanut-specific IgE of 10 kU_A/L or greater, total IgE level of 50 IU/L or greater but 2000 IU/L or less, and a positive SPT response to peanut with a wheal diameter of 6 mm or greater compared with that elicited by the saline control. Exclusion criteria included a history of severe anaphylaxis requiring intensive care unit admission or intubation; chronic immunologic disease that might interfere with the study or pose additional risk to subjects; FEV₁ or peak flow of less than 80% of predicted value; ongoing use of systemic corticosteroids, tricyclic antidepressants, or β -blockers; previous exposure to experimental peanut immunotherapy; a positive pregnancy test result; or a reaction to placebo during the DBPCFC.

DBPCFC details

For the DBPCFC, subjects received 5 doses of peanut protein or placebo spaced 20 minutes apart (0.5, 2.5, 10, 25, and 50 mg) in separate series, with the order of peanut or placebo being random. Challenges were stopped based on the criteria in [Table E1](#).

Source of peanut flour and omalizumab

Peanut flour from a commercial source, Byrd Mill Peanut Flour Light (approximately 50% peanut protein), was used for OIT. Omalizumab and corresponding placebo (study drug) were supplied by Genentech.

Dosing regimen for omalizumab

Omalizumab dosing was based on weight and IgE level and slightly modified from that used for asthma to allow inclusion of patients with high total IgE levels ([Table E2](#)). Study drug was administered by means of subcutaneous injection every 2 or 4 weeks based on weight and baseline total IgE level.

Stopping criteria for rapid peanut desensitization

The rapid desensitization was stopped for severe reactions based on [Table E3](#). More mild symptoms were treated with antihistamines (diphenhydramine or cetirizine), and the desensitization resumed.

Full details of statistical analysis

Descriptive statistics were used to characterize the study population. Continuous demographic and clinical characteristics were presented by using medians and ranges and compared between study arms by using the Wilcoxon test. Categorical demographic and clinical characteristics were presented as counts and frequencies and compared between study arms by using the Fisher exact test. All analyses were performed with SAS 9.4 software (SAS Institute, Cary, NC) and the packages base, ggplot2, and gridExtra of R statistical software.^{E1-E3}

Updosing protocol for patients who did not reach 250 mg on the initial desensitization day

Subjects who did not tolerate 250 mg on initial desensitization were updosed starting with their highest tolerated dose according to the following up-dosing protocol: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 11, 15, 22, 30, 45, 60, 90, 120, 180, and 250 mg of peanut protein, with increases 1 to 2 times weekly. Once the 250 mg-dose was achieved, the updosing protocol from 375 mg to up to 2000 mg was followed.

Details of skin testing

Skin tests consisting of a histamine control (Hollister-Stier, Spokane, Wash), negative saline control (Hollister-Stier), and peanut extract (Greer Laboratories, Lenoir, NC) were performed at baseline, 12 weeks after the last dose of study drug, and at the end of the study.

Details of screening results

Sixty-nine subjects were screened, 37 of whom were randomized. Twelve subjects did not qualify for the study because they did not react to peanut (8 subjects), reacted to placebo (3 subjects), or reacted to both (1 subject). Four declined to participate, and 16 were excluded for other reasons.

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TABLE E1. Stopping criteria for double-blind, placebo-controlled oral food challenge

Category	Grade and symptom(s)
Skin	
Rash	Grade 0: Sign or symptom not observed
	Grade 1: Few areas of faint erythema
	Grade 2: Areas of erythema, macular and raised rash
	Grade 3: Generalized marked erythema (>50%); extensive raised lesion (>25%); vesiculation and/or piloerections
Pruritus	Grade 0: Sign or symptom not observed
	Grade 1: Occasional scratching
	Grade 2: Scratching continuously for >2 min at a time
Urticaria	Grade 3: Hard continuous scratching leading to excoriations
	Grade 0: Sign or symptom not observed
	Grade 1: Less than 3 hives
Angioedema	Grade 2: Three to <10 hives
	Grade 3: Generalized involvement
	Grade 0: Sign or symptom not observed
	Grade 1: One site of angioedema
	Grade 2: Two or more sites of angioedema
	Grade 3: Generalized involvement, including airway involvement
Nasal	
Sneezing	Grade 0: Sign or symptom not observed
	Grade 1: Rare bursts of sneezing
	Grade 2: Less than 10 bursts of sneezing
	Grade 3: Continuous rubbing of nose and/or eyes; periocular swelling and/or long bursts of sneezing
Nasal itching	Grade 0: Sign or symptom not observed
	Grade 1: Mild itching
	Grade 2: Intermittent rubbing of nose or eyes
Nasal congestion	Grade 3: Continuous rubbing of nose and/or eyes; periocular swelling and/or long bursts of sneezing
	Grade 0: Sign or symptom not observed
	Grade 1: Some hindrance to breathing
	Grade 2: Nostrils feel blocked, breathes through mouth most of the time
Rhinorrhea	Grade 3: Nostrils occluded
	Grade 0: Sign or symptom not observed
	Grade 1: Occasional sniffing
	Grade 2: Frequent sniffing, requires tissues
Airway obstruction	Grade 3: Nose runs freely despite sniffing and tissues
	Grade 0: Sign or symptom not observed
	Grade 1: Voice change mild
	Grade 2: Voice change moderate
	Grade 3: Voice change severe
Chest	
Wheezing	Grade 0: Sign or symptom not observed
	Grade 1: Expiratory wheezing to auscultation or 15% decrease from highest FEV₁ value observed on study or FEV₁ ≤65%
	Grade 2: Dyspnea, inspiratory, and expiratory wheezing
	Grade 3: Dyspnea, use of accessory muscles, audible wheezing
Abdomen	
Nausea	Grade 0: Sign or symptom not observed
	Grade 1: Mild complaint of nausea
	Grade 2: Frequent complaint of nausea
	Grade 3: Nausea causing notable distress
Abdominal pain	Grade 0: Sign or symptom not observed
	Grade 1: Complaint of abdominal pain
	Grade 2: Frequent complaints of abdominal pain, decreased activity
	Grade 3: In bed, crying, or notably distressed
Emesis	Grade 0: Sign or symptom not observed
	Grade 1: One episode of emesis
	Grade 2: Two to 3 episodes of emesis or 1 of emesis and 1 of diarrhea
	Grade 3: >3 Episodes of emesis or ≥2 of emesis and ≥2 of diarrhea
Diarrhea	Grade 0: Sign or symptom not observed
	Grade 1: One episode of diarrhea
	Grade 2: Two of 3 episodes of diarrhea or 1 of emesis and 1 of diarrhea
	Grade 3: More than 3 episodes of diarrhea or ≥2 of emesis and ≥2 of diarrhea

Grades in boldface indicate a severity level at which the oral food challenge should be stopped immediately. Challenges could also be stopped at investigator's discretion for multiple grade 1 reactions.

TABLE E2. Dosing of omalizumab based on body weight and baseline total IgE level (mg study drug)

Dosing interval	Screening IgE (IU/mL)	Body weight (kg)								
		15-20 kg	21-25 kg	26-30 kg	31-40 kg	41-50 kg	51-60 kg	61-70 kg	71-80 kg	81-90 kg
Every 4 wk	30-100	75 mg	75 mg	75 mg	75 mg	150 mg	150 mg	150 mg	150 mg	150 mg
	101-200	150 mg	150	150	150	300	300	300	300	300
	201-300	150 mg	150	150	225	300	300			
	301-400	225 mg	225	225	300					
	401-500	225 mg	225	300						
	501-600	300 mg	300	300						
	601-700	300 mg	300							
Every 2 wk	201-300							225 mg	225 mg	225 mg
	301-400					225 mg	225 mg	225	300	300
	401-500				225 mg	225	300	300	375	375
	501-600				225	300	300	375	450	525
	601-700			225 mg	225	300	375	450	525	600
	701-800	225 mg	225 mg	225	300	375	450	450	600	*
	801-900	225 mg	225	225	300	375	450	525	*	*
	901-1000	225 mg	225	300	375	450	525	600	*	*
	1001-1100	225 mg	225	300	375	450	600	*	*	*
	1101-1200	300 mg	300	300	450	525	600	*	*	*
	1201-3000	300 mg	300	375	450	525	*	*	*	*
	1301-1500	300 mg	300	375	525	600	*	*	*	*
	1500-2000	375 mg	450	600	600	600	*	*	*	*

Asterisks denote parameters in which no study subject will be dosed with drug.

TABLE E3. Scoring of clinical reactions during peanut desensitization

Category	Grade and symptom(s)
Skin	
Rash	Grade 0: Sign or symptom not observed <i>Grade 1: Few areas of faint erythema</i> Grade 2: Areas of erythema, macular and raised rash Grade 3: Generalized marked erythema (>50%); extensive raised lesion (>25%); vesiculation and/or piloerections
Pruritus	Grade 0: Sign or symptom not observed <i>Grade 1: Occasional scratching</i> Grade 2: Scratching continuously for >2 min at a time Grade 3: Hard continuous scratching leading to excoriations
Urticaria	Grade 0: Sign or symptom not observed <i>Grade 1: <3 Hives</i> <i>Grade 2: 3 to <10 Hives</i> Grade 3: Generalized involvement
Angioedema	Grade 0: Sign or symptom not observed <i>Grade 1: One site of angioedema</i> <i>Grade 2: Two or more sites of angioedema</i> Grade 3: Generalized involvement, including airway involvement
Nasal sneezing	Grade 0: Sign or symptom not observed <i>Grade 1: Rare bursts of sneezing</i> <i>Grade 2: Less than bursts of sneezing</i> Grade 3: Continuous rubbing of nose and/or eyes; periocular swelling &/or long bursts of sneezing
Nasal itching	Grade 0: Sign or symptom not observed <i>Grade 1: Mild itching</i> <i>Grade 2: Intermittent rubbing of nose or eyes</i> Grade 3: Continuous rubbing of nose and/or eyes; periocular swelling and/or long bursts of sneezing
Nasal congestion	Grade 0: Sign or symptom not observed <i>Grade 1: Some hindrance to breathing</i> <i>Grade 2: Nostrils feel blocked, breathes through mouth most of the time</i> Grade 3: Nostrils occluded
Rhinorrhea	Grade 0: Sign or symptom not observed <i>Grade 1: Occasional sniffing</i> <i>Grade 2: Frequent sniffing, requires tissues</i> Grade 3: Nose runs freely despite sniffing and tissues
Airway obstruction	Grade 0: Sign or symptom not observed <i>Grade 1: Voice change mild</i> Grade 2: Voice change moderate Grade 3: Voice change severe
Chest wheezing	Grade 0: Sign or symptom not observed Grade 1: Expiratory wheezing to auscultation or 15% decrease from highest FEV₁ value observed on study or FEV₁ ≤65% Grade 2: Dyspnea, inspiratory, and expiratory wheezing Grade 3: Dyspnea, use of accessory muscles, audible wheezing
Abdomen	
Nausea	Grade 0: Sign or symptom not observed <i>Grade 1: Mild complaint of nausea</i> Grade 2: Frequent complaint of nausea Grade 3: Nausea causing notable distress
Abdominal pain	Grade 0: Sign or symptom not observed <i>Grade 1: Complaint of abdominal pain</i> Grade 2: Frequent complaints of abdominal pain, decreased activity Grade 3: In bed, crying, or notably distressed
Emesis	Grade 0: Sign or symptom not observed Grade 1: One episode of emesis Grade 2: Two or 3 episodes of emesis or 1 of emesis and 1 of diarrhea Grade 3: More than 3 episodes of emesis or ≥2 of emesis and ≥2 of diarrhea
Diarrhea	Grade 0: Sign or symptom not observed <i>Grade 1: One episode of diarrhea</i> Grade 2: Two or 3 episodes of diarrhea or 1 of emesis and 1 of diarrhea Grade 3: More than 3 episodes of diarrhea or ≥2 of emesis and ≥2 of diarrhea

Grades in boldface indicate a severity level at which the oral desensitization was stopped. Grades in italics indicate severity level at which patients were treated with antihistamines either cetirizine (Zyrtec) or diphenhydramine (Benadryl).

TABLE E4. Reactions by Bock grade, phase, dose, and study drug received: Patients receiving blinded study drug

	Omalizumab			Placebo		
Total peanut doses	7245			726		
Peanut doses per child, mean (range)	251.0 (2-358)			93.6 (16-322)		
	No. of reactions	No. of patients with reactions	Mean (range) for patients with reactions	No. of reactions	No. of patients with reactions	Mean (range) for patients with reactions
Total reactions	563	25	22.5 (1-71)	122	8	15.3 (4-30)
Bock grade 1						
Initial desensitization day	28	15	1.9 (1-5)	9	5	1.8 (1-3)
Dose escalation	251	19	13.2 (1-28)	94	7	13.4 (4-25)
<2-g Maintenance peanut dose	37	13	2.8 (1-8)	2	1	2 (2-2)
2-g Maintenance peanut dose	136	14	9.7 (1-37)	0	0	0 (0-0)
4-g Maintenance peanut dose	72	14	5.1 (1-14)	0	0	0 (0-0)
Bock grade 2						
Initial desensitization day	6	4	1.5 (1-3)	8	6	1.3 (1-3)
Dose escalation	1	1	1 (1-1)	6	3	2 (1-3)
<2-g Maintenance peanut dose	7	3	2.3 (1-4)	0	0	0 (0-0)
2-g Maintenance peanut dose	4	3	1.3 (1-2)	0	0	0 (0-0)
4-g Maintenance peanut dose	18	5	3.6 (1-14)	2	1	2 (2-2)
Bock grade 3						
Initial desensitization day	0	0	0 (0-0)	0	0	0 (0-0)
Dose escalation	1	1	1 (1-1)	1	1	1 (1-1)
<2-g Maintenance peanut dose	1	1	1 (1-1)	0	0	0 (0-0)
2-g Maintenance peanut dose	0	0	0 (0-0)	0	0	0 (0-0)
4-g Maintenance peanut dose	1	1	1 (1-1)	0	0	0 (0-0)

TABLE E5. Reactions by Bock grade, phase, dose, and study drug received: Week 31 and before

	Omalizumab			Placebo			Open-label omalizumab		
Total peanut doses	3868			593			1056		
Peanut doses per child, mean (range)	133.4 (2-204)			74.1 (16-169)			132.0 (59-153)		
	No. of reactions	No. of patients with reactions	Mean (range) for patients with reactions	No. of reactions	No. of patients with reactions	Mean (range) for patients with reactions	No. of reactions	No. of patients with reactions	Mean (range) for patients with reactions
Total reactions	372	23	13.9 (1-41)	120	8	15 (4-30)	97	7	16.2 (1-39)
Bock grade 1									
Initial desensitization day	28	15	1.9 (1-5)	9	5	1.8 (1-3)	0	0	0 (0-0)
Dose escalation	251	19	13.2 (1-28)	94	7	13.4 (4-25)	56	4	14 (2-23)
<2-g Maintenance peanut dose	20	10	2 (1-5)	2	1	2 (2-2)	15	4	3.8 (1-7)
2-g Maintenance peanut dose	64	11	5.8 (1-13)	0	0	0 (0-0)	22	5	4.4 (1-12)
Bock grade 2									
Initial desensitization day	6	4	1.5 (1-3)	8	6	1.3 (1-3)	0	0	0 (0-0)
Dose escalation	1	1	1 (1-1)	6	3	2 (1-3)	0	0	0 (0-0)
<2-g Maintenance peanut dose	0	0	0 (0-0)	0	0	0 (0-0)	1	1	1 (1-1)
2-g Maintenance peanut dose	1	1	1 (1-1)	0	0	0 (0-0)	2	2	1 (1-1)
Bock grade 3									
Initial desensitization day	0	0	0 (0-0)	0	0	0 (0-0)	0	0	0 (0-0)
Dose escalation	1	1	1 (1-1)	1	1	1 (1-1)	0	0	0 (0-0)
<2-g Maintenance peanut dose	0	0	0 (0-0)	0	0	0 (0-0)	0	0	0 (0-0)
2-g Maintenance peanut dose	0	0	0 (0-0)	0	0	0 (0-0)	1	1	1 (1-1)

TABLE E6. Reactions by Bock grade, phase, dose, and study drug received: Weeks 31 to 52

	Omalizumab			Placebo			Open-label omalizumab		
Total peanut doses	3908			152			760		
Peanut doses per child, mean (range)	146.5 (119-163)			152 (152-152)			126.7 (24-156)		
	No. of reactions	No. of patients with reactions	Mean (range) for patients with reactions	No. of reactions	No. of patients with reactions	Mean (range) for patients with reactions	No. of reactions	No. of patients with reactions	Mean (range) for patients with reactions
Total reactions	185	18	10.3 (1-35)	2	1	2 (2-2)	97	4	4.8 (2-8)
Bock grade 1									
<2-g Maintenance peanut dose	12	3	4 (3-6)	0	0	1.8 (1-3)	7	2	3.5 (2-5)
2-g Maintenance peanut dose	72	8	9 (1-24)	0	0	2 (2-2)	4	2	2 (1-3)
4-g Maintenance peanut dose	72	14	5.1 (1-14)	0	0	0 (0-0)	2	1	2 (2-2)
Bock grade 2									
<2-g Maintenance peanut dose	7	3	2.3 (1-4)	0	0	1.3 (1-3)	0	0	0
2-g Maintenance peanut dose	3	2	1.5 (1-2)	0	0	0 (0-0)	4	3	1.3 (1-2)
4-g Maintenance peanut dose	18	5	3.6 (1-14)	2	1	2 (2-2)	1	1	1 (1-1)
Bock grade 3									
<2-g Maintenance peanut dose	0	0	0 (0-0)	0	0	0 (0-0)	0	0	0 (0-0)
2-g Maintenance peanut dose	0	0	0 (0-0)	0	0	0 (0-0)	1	1	1 (1-1)
4-g Maintenance peanut dose	1	1	1 (1-1)	0	0	0 (0-0)	0	0	0 (0-0)

TABLE E7. Reactions by Bock grade, phase, dose, and study drug received: Entire study

	Omalizumab			Placebo			Open-label omalizumab		
Total peanut doses	7245			726			2203		
Peanut doses per child, mean (range)	251.0 (2-358)			93.6 (16-322)			278.5 (131-394)		
	No. of reactions	No. of patients with reactions	Mean (range) for patients with reactions	No. of reactions	No. of patients with reactions	Mean (range) for patients with reactions	No. of reactions	No. of patients with reactions	Mean (range) for patients with reactions
Total reactions	563	25	22.5 (1-71)	122	8	15.3 (4-30)	137	8	17.1 (1-42)
Bock grade 1									
Initial desensitization day	28	15	1.9 (1-5)	9	5	1.8 (1-3)	0	0	0 (0-0)
Dose escalation	251	19	13.2 (1-28)	94	7	13.4 (4-25)	69	5	17.1 (1-42)
<2-g Maintenance peanut dose	37	13	2.8 (1-8)	2	1	2 (2-2)	22	5	4.4 (2-7)
2-g Maintenance peanut dose	136	14	9.7 (1-37)	0	0	0 (0-0)	26	6	4.3 (1-12)
4-g Maintenance peanut dose	72	14	5.1 (1-14)	0	0	0 (0-0)	3	2	1.5 (1-2)
Bock grade 2									
Initial desensitization day	6	4	1.5 (1-3)	8	6	1.3 (1-3)	0	0	0 (0-0)
Dose escalation	1	1	1 (1-1)	6	3	2 (1-3)	4	2	2 (1-3)
<2-g Maintenance peanut dose	7	3	2.3 (1-4)	0	0	0 (0-0)	3	3	1 (1-1)
2-g Maintenance peanut dose	4	3	1.3 (1-2)	0	0	0 (0-0)	6	4	1.5 (1-3)
4-g Maintenance peanut dose	18	5	3.6 (1-14)	2	1	2 (2-2)	1	1	1 (1-1)
Bock grade 3									
Initial desensitization day	0	0	0 (0-0)	0	0	0 (0-0)	0	0	0 (0-0)
Dose escalation	1	1	1 (1-1)	1	1	1 (1-1)	1	1	1 (1-1)
<2-g Maintenance peanut dose	1	1	1 (1-1)	0	0	0 (0-0)	0	0	0 (0-0)
2-g Maintenance peanut dose	0	0	0 (0-0)	0	0	0 (0-0)	2	2	1 (1-1)
4-g Maintenance peanut dose	1	1	1 (1-1)	0	0	0 (0-0)	0	0	0 (0-0)