

Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective

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Background: Oral immunotherapy (OIT) is an effective experimental food allergy treatment that is limited by treatment withdrawal and the frequent reversibility of desensitization if interrupted. Newly diagnosed preschool children may have clinical and immunological characteristics more amenable to treatment.

Objective: We sought to test the safety, effectiveness, and feasibility of early OIT (E-OIT) in the treatment of peanut allergy.

Methods: We enrolled 40 children aged 9 to 36 months with suspected or known peanut allergy. Qualifying subjects reacted to peanut during an entry food challenge and were block-randomized 1:1 to receive E-OIT at goal maintenance doses of 300 or 3000 mg/d in a double-blinded fashion. The primary end point, sustained unresponsiveness at 4 weeks after stopping early intervention oral immunotherapy (4-SU), was assessed by double-blinded, placebo-controlled food challenge either upon achieving 4 prespecified criteria, or after 3 maintenance years. Peanut-specific immune responses were serially analyzed. Outcomes were compared with 154 matched standard-care controls.

Results: Of 40 consented subjects, 3 (7.5%) did not qualify. Overall, 29 of 37 (78%) in the intent-to-treat analysis achieved 4-SU (300-mg arm, 17 of 20 [85%]; 3000 mg, 12 of 17 [71%], $P = .43$) over a median of 29 months. Per-protocol, the overall proportion achieving 4-SU was 29 of 32 (91%). Peanut-specific IgE levels significantly declined in E-OIT-treated children, who were 19 times more likely to successfully consume dietary peanut than matched standard-care controls, in whom peanut-specific IgE levels significantly increased (relative risk, 19.42;

95% CI, 8.7-43.7; $P < .001$). Allergic side effects during E-OIT were common but all were mild to moderate.

Conclusions: At both doses tested, E-OIT had an acceptable safety profile and was highly successful in rapidly suppressing allergic immune responses and achieving safe dietary reintroduction. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: Oral immunotherapy, desensitization, sustained unresponsiveness, early intervention, peanut allergy, randomized clinical trial

Over the last 20 years, peanut allergy has become a global public health problem affecting now 1.5% to 3% of children.^{1,2} The lack of therapeutic options is a substantial unmet need. In previous randomized studies of children grade-school age and older, oral immunotherapy (OIT) has shown promise as an immunomodulatory treatment that can provide a margin of safety protecting against a potentially life-threatening accidental exposure.³⁻⁶ Yet because little evidence for cure exists, even OIT successes must continue vigilance with strict dietary restrictions and self-injectable epinephrine. Furthermore, up to 20% cannot tolerate the treatment and there is substantial potential for relapse if treatment is interrupted.⁷ However, we previously showed that long-term treatment response was significantly associated with lower peanut-specific IgE (pIgE) levels at study entry. These subjects achieved “sustained unresponsiveness (SU)” to peanut after 5 years of treatment with goal maintenance doses of 4 g/d, permitting them to stop OIT and safely introduce peanut-containing

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Abbreviations used

AE:	Adverse event
DBPCFC:	Double-blinded, placebo-controlled food challenge
E-OIT:	Early intervention oral immunotherapy
4-SU:	Sustained unresponsiveness at 4 weeks after stopping early intervention oral immunotherapy
IQR:	Interquartile range
ITT:	Intent-to-treat
LEAP:	Learning Early About Peanut Allergy
OFC:	Oral food challenge
OIT:	Oral immunotherapy
psIgE:	Peanut-specific IgE
psIgG ₄ :	Peanut-specific IgG ₄
SPT:	Skin prick test
SU:	Sustained unresponsiveness

foods into the diet.⁸ This result suggests that the strength of allergic sensitization at baseline may largely influence durable OIT treatment success.

Although it is now known that the production of food-specific IgE frequently begins in infancy,⁹⁻¹¹ T-cell receptor affinity is weak¹² and GATA-3 expression unstable.⁹ IgE production is further driven by progressive intensification of T_H2 cytokine expression over the first 2 years of life, and is strongly correlated with the clinical expression of allergic disease.¹³⁻¹⁵ In the approximately 80% of affected patients for whom peanut allergy persists as a lifelong disease, psIgE production has been shown to increase over the first 5 years of life.^{15,16} Taken together, these data suggest that the allergic program requires time to fully differentiate, and in the food allergy context, does so in the absence of oral exposure. We postulated that targeting newly diagnosed young peanut-allergic children would provide the best opportunity to enhance the clinical effectiveness of OIT as an immunomodulatory and disease-modifying treatment by interrupting allergic priming before its full maturation. We termed this approach early intervention oral immunotherapy (E-OIT).

To test whether E-OIT would safely enhance favorable long-term outcomes and explore an effective dose range, we designed a randomized, double-blinded clinical trial of low-dose and high-dose peanut E-OIT among recently diagnosed peanut-allergic children aged 9 to 36 months and compared outcomes to a control group of untreated peanut-allergic patients. Our primary hypothesis was that 70% or more participants receiving low-dose E-OIT would achieve SU to 5 g of peanut protein during a double-blinded, placebo-controlled food challenge (DBPCFC) performed 4 weeks after discontinuing OIT.

METHODS

Study design

This single-center clinical trial was appropriately registered¹⁷ and carried out in accordance with the principles of the Declaration of Helsinki and the local ethics committee. Following written informed parental consent, eligible participants underwent a qualifying baseline open oral food challenge (OFC) to 4 g of peanut protein (see this article's [Methods](#) section in the Online Repository at www.jacionline.org). Those who demonstrated clear objective evidence of an IgE-mediated allergic reaction were block-randomized 1:1 to receive low-dose (target maintenance dose, 300 mg/d peanut protein) or high-dose (3000 mg/d peanut protein) E-OIT. All randomized subjects represent the intent-to-treat (ITT) population. After an initial-day escalation, all subjects in both groups uposed to a 3000 mg/d target maintenance dose in

a double-blinded fashion before undergoing up to 2 exit DBPCFCs. Study product for the low-dose group consisted of 300 mg peanut flour plus 2700 mg of placebo filler. Further details about the investigational product and dosing schedule can be found in this article's [Methods](#) section. All participants, site investigators, and study coordinators were blinded to treatment assignment. Efficacy, safety, and immunological data were all analyzed in blinded fashion.

The primary end point was the proportion of ITT subjects achieving sustained unresponsiveness at 4 weeks after discontinuing early intervention oral immunotherapy (4-SU), defined as the ability to consume 5 g of peanut protein without dose-limiting symptoms during an exit DBPCFC followed by 1 additional serving size feeding of peanut fed openly. As discussed further in this article's [Methods](#) section, we prespecified an analysis of a matched standard-care control group to compare the frequency of peanut consumption in the diet following OIT or standard care (ie, allergen avoidance). Key secondary end points included the proportion of subjects achieving desensitization, the frequency of treatment-related adverse events (AEs) in each group, and longitudinal immunologic changes.

Study population

We recruited children aged 9 to 36 months inclusive who were peanut-allergic or peanut-sensitized. Peanut-allergic children were enrolled within 6 months of a convincing first allergic reaction following oral exposure to a peanut-containing food, and had a psIgE level of more than 0.35 kU_A/L and/or a peanut skin prick test (SPT) wheal diameter of 3 mm or more above that with the negative control. Children with no known history of peanut ingestion and psIgE level of 5 kU_A/L or more were also eligible. Exclusion criteria included life-threatening peanut anaphylaxis (eg, involving hypoxia, hypotension, or neurological compromise); wheat/oat allergy; severe atopic dermatitis according to the clinical judgment of the investigator (eg, requiring systemic therapy); asthma requiring more than medium-dose inhaled corticosteroids as per the National Heart, Lung, and Blood Institute asthma guidelines; and participation in an interventional food allergy study within 1 year.

Standard-care control group

A control cohort (N = 154), matched on inclusion and exclusion criteria, was retrospectively collected from a pediatric allergy clinic database at Johns Hopkins (see this article's [Methods](#) section). These children were treated consistent with standard of care National Institute of Allergy and Infectious Disease clinical guidelines¹⁸ and the routine practice patterns of the attending physician(s). For example, not all diagnoses were routinely confirmed with OFC when the history was suggestive, and open OFCs were offered according to the judgment of the attending physician when he or she deemed natural tolerance likely to have occurred. Key clinical and immunologic variables were extracted from case histories by research assistants and were verified by the same pediatric allergist (C.K.), who was unaware of the trial results. IgE levels at Johns Hopkins were measured by ImmunoCAP (Thermo Fisher, Waltham, Mass).

Food challenge assessments

OFC techniques are described further in this article's [Methods](#) section. End points were assessed with two 5-g exit DBPCFCs, the first at the end of treatment to confirm desensitization. If successful, the OIT was stopped and the DBPCFC repeated after 4 weeks of peanut abstinence to test for 4-SU. The protocol allowed for end-point assessment on achievement of prespecified benchmarks (at least 12 months in the maintenance phase; psIgE ≤ 15 kU_A/L; SPT ≤ 8 mm; and no severe peanut-related symptoms in the previous 6 months). All subjects not meeting these benchmarks were assessed for 4-SU once they completed a 36-month maintenance phase.

Mechanistic studies

SPTs were performed and PsIgE, total IgE, and peanut-specific IgG₄ (psIgG₄) levels were measured as previously described.^{19,20}

Analysis plan

We computed averages, variances, frequencies, proportions, and graphical displays for all variables and examined them to ensure that parametric distributional assumptions were met. Nonparametric test statistics were used as appropriate. Baseline demographic characteristics and categorical peanut consumption outcomes were compared between E-OIT and controls using Fisher exact test. Analyses were performed with GraphPad Prism 6 for Mac (La Jolla, Calif) or Stata/SE 13.1 (College Station, Tex). To achieve approximate normality and variance stabilization for longitudinal immune analyses, pIgE and pIgG₄ were log-transformed, whereas for SPT raw data were used. Models were fit separately for each group in R (www.r-project.org) for each outcome with functions of time using generalized estimating equations.²¹ Linear and quadratic, and cubic models in time, models were considered, with the best-fitting model selected for each group for each outcome selected using QIC. All hypothesis tests were 2-sided, with a *P* value of less than .05 considered significant.

RESULTS

Subject enrollment and disposition

On the basis of our prestudy power calculations (see this article's [Methods](#) section) to compare E-OIT against standard-care controls, we consented and enrolled 40 participants (31 clinically allergic and 9 sensitized/never exposed). Study progression is shown in [Fig 1](#). Baseline demographic characteristics, and those of the control group, are presented in [Table I](#). The study population was predominantly white and atopic, with median age of 28.5 months (interquartile range [IQR], 22-35 months) at enrollment. The ITT population consisted of 37 participants who had a reaction during the entry OFC at a median (IQR) of 21 (21-171) cumulative milligram of peanut protein (see [Fig E1](#) in this article's Online Repository at www.jacionline.org). Three (8%) of the 37 subjects were withdrawn from the study for treatment-related AEs. Two additional subjects withdrew for nonadherence, leaving 32 participants with evaluable outcomes with respect to the primary end point. Four of the 5 withdrawals were from the high-dose arm.

SU was achieved at high rates with both low-dose and high-dose OIT in young peanut-allergic children

In the ITT analysis, 30 of 37 (81%) overall were desensitized at the end of treatment (low-dose, 17 of 20 [85%]; high-dose, 13 of 17 [76%]). A total of 29 of 37 (78%) achieved 4-SU (low-dose, 17 of 20 [85%]; high-dose, 12 of 17 [71%]; *P* = .43 by Fisher exact test; difference in proportions 0.14; 95% CI, -0.12 to 0.40) ([Fig 2, A](#)). In the per-protocol analysis, the rate of desensitization was 30 of 32 (94%), with 29 of 32 (91%) achieving 4-SU (low-dose, 17 of 19 [89%]; high-dose, 12 of 13 [92%]).

Peanut exposure, not avoidance, suppresses pIgE and permits dietary consumption

Among 154 matched standard-care controls from the pediatric allergy clinic at Johns Hopkins, the median (IQR) baseline pIgE level was 21.9 kU_A/L (6.9-73 kU_A/L), compared with 14.4 kU_A/L (3.3-51 kU_A/L) in trial participants (*P* = .12). However, over time, median (IQR) pIgE level significantly declined in OIT subjects to 1.6 kU_A/L (0.5-4.9 kU_A/L), whereas in controls it significantly increased to 57.4 kU_A/L (9-101 kU_A/L) ([Fig 2, B](#)). On the basis of standard-of-care treatment, 20 (13%) control patients were deemed OFC-eligible over an average follow-up of 3.6 years

(95% CI, 3.3-3.8). Consistent with generally accepted clinical indications for OFC in this situation,^{22,23} the median pIgE level at OFC in the control cohort was 3.02 kU_A/L (range, 0.48-13.5 kU_A/L). A total of 19 of 20 OFCs were completed, and 6 of 19 (32%) passed. The remaining 13 had a reaction at a cumulative eliciting dose of 1150 mg (range, 250-5000 mg), with 3 patients requiring epinephrine. No other control patients were noted to have developed spontaneous peanut tolerance. Therefore, the known overall proportion of controls who successfully introduced peanut in the diet was 4%, compared with 78% in the OIT group (relative risk, 19.42; 95% CI, 8.7-43.7; Fisher exact test *P* < .001) ([Fig 2, C](#)).

We performed a worst-case analysis of these outcomes based on well-established predictive values of peanut allergy. Nine of 37 (24%) of the randomized group began the study with pIgE values of less than 5 kU_A/L, one of whom subsequently withdrew for nonadherence. In the control group, there were serial IgE values available for 147 subjects, of which 46 (31%) had a pIgE value of less than 15 kU_A/L at the end of the follow-up period. For the purposes of this secondary analysis, we assumed that all 9 subjects with a pIgE level of 5 kU_A/L did not benefit from the intervention but would have outgrown it regardless,²⁴ and were considered failures. We also assumed that all controls with a pIgE level of 15 kU_A/L or more at the end of follow-up were allergic, whereas all those with a pIgE level of less than 15 kU_A/L were tolerant.²⁵ In this scenario, the proportion of successes was still significantly higher (57%) in the OIT group than among controls (31%) (relative risk, 1.8; 95% CI, 1.3-2.6; *P* = .007) ([Fig 2, D](#)).

Treatment length and outcome are determined by baseline pIgE levels

The 8 ITT failures had significantly higher median baseline pIgEs and pIgE:total IgE ratios than the 29 successes (90.1 kU_A/L [IQR, 55.4-288.8 kU_A/L] vs 9.3 kU_A/L [2.3-32 kU_A/L], *P* < .001; and 0.39 kU_A/L [0.25-0.6 kU_A/L] vs 0.16 kU_A/L [0.05-0.3 kU_A/L]; *P* = .04, respectively) ([Fig 3, A](#)). As a result of the conditional end-point assessment strategy, the median (IQR) duration of treatment was 29.1 months (25.3-47.3 months), and there was a significant stepwise increase in treatment duration from lowest to highest tertile of baseline pIgE ([Fig 3, B](#)).

Low-dose and high-dose peanut OIT both modulate allergic immune responses

As expected, the baseline SPT, pIgE, and pIgG₄ data were not normally distributed and were analyzed with nonparametric test statistics. Overall medians (IQR) for baseline pIgE level and SPT wheal size were 14.4 kU_A/L (3.4-48.6 kU_A/L) and 11.5 mm (8-16.5 mm), respectively, and not different between treatment arms ([Table I](#)). We analyzed changes in these immunological outcomes with longitudinal mixed models for each group with functions of time. These models demonstrated strong temporal trends in the decline in pIgE levels and SPT wheal size, and the amplification of pIgG₄ production, all of which are statistically significant in their change from baseline ([Fig 4, A-C](#)). Notably, there were no significant differences in the rate of change between treatment arms.

E-OIT was overall safe and well tolerated

There were no treatment-related, protocol-defined severe AEs, hospitalizations, or deaths. Overall, 95% of the subjects were

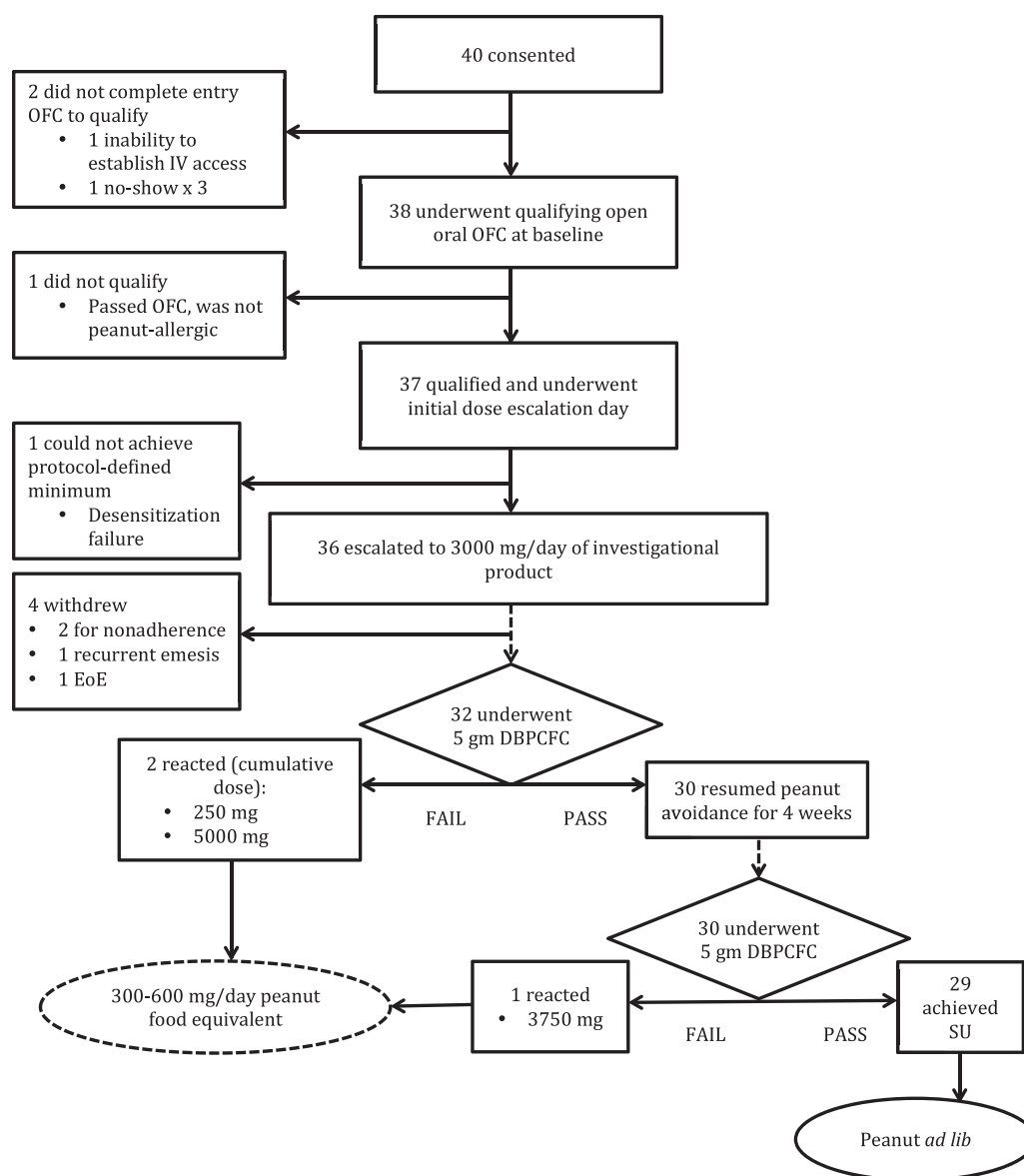


FIG 1. Progression of subjects through the study. *EoE*, Eosinophilic esophagitis; *IV*, intravenous.

affected by AEs that were likely related to OIT, with an average per-dose rate of 0.8% (95% CI, 0.3% to 1.4%) overall (see [Table E3](#) in this article's Online Repository at www.jacionline.org). Reported treatment-related AEs occurred significantly more frequently during the buildup phase, compared with the maintenance phase, and involved predominantly the gastrointestinal tract and the upper airway (see [Fig E2](#) in this article's Online Repository at www.jacionline.org). A total of 85% of these AEs were mild, with 15% considered moderate and none severe. Two subjects withdrew with persistent gastrointestinal tract–predominant AEs. Withdrawing OIT resulted in prompt resolution of abdominal pain in the first. The other subject, who reported a history of “gastroesophageal reflux,” before starting OIT, underwent esophagogastroduodenoscopy while on OIT because of persistent regurgitation and vomiting refractory to high-dose ranitidine. Mucosal furrowing and approximately 30 eosinophils per hpf were noted, which persisted at repeat esophagogastroduodenoscopy 3 months later despite stopping OIT and resuming a peanut-free diet.

Moderate-severity AEs were significantly more likely in the low-dose compared with the high-dose group overall ($P = .04$) and during the buildup phase ($P = .02$) ([Table E3](#)). Overall, 25% of events (47% of subjects) required treatment, with the vast majority being antihistamines only. No epinephrine was administered during a dose escalation visit, and once at home following a dose reaction (see [Table E4](#) in this article's Online Repository at www.jacionline.org).

DISCUSSION

This study is the first to target peanut-allergic children younger than 3 years for OIT treatment and also the first to prospectively study 2 peanut OIT doses in a randomized, blinded fashion. We show here that overall 78% of subjects receiving E-OIT demonstrated SU to peanut 4 weeks after stopping E-OIT and reintroduced peanut into the diet, the highest rate reported to date, after a median of only 29 months of treatment. Compared with a

TABLE I. Baseline demographic characteristics by treatment arm

Characteristic	All subjects	High dose	Low dose	Controls
Total	37 randomized	17	20	154
Sex: female	12 (32)	4 (24)	8 (40)	47 (31)
Age (mo) at starting OIT or observation (controls)				
9-12	9 (24)*	4 (24)	5 (25)	15 (10)
13-24	17 (46)	9 (53)	8 (40)	67 (44)
25-36	11 (30)	4 (24)	7 (35)	72 (47)
Race				
White	33 (89)†	16 (94)	17 (85)	92 (60)
Black	3 (8)	0	3 (15)	24 (16)
Other	1 (3)	1 (6)	0	38 (25)‡
History of				
Asthma/recurrent wheeze	10 (27)§	6 (35)	4 (20)	20 (13)
Atopic dermatitis	26 (70)	14 (82)	12 (60)	130 (84)
Allergic rhinitis	8 (22)	4 (24)	4 (20)	51 (33)
Peanut SPT (mm)	11.5 (8-16.5)	12.5 (8-17.5)	10.5 (8-15.3)	NA
Peanut IgE (kU _A /L)	14.4 (3.4-48.6)	12.3 (3.2-61.5)	22.4 (5.4-43.4)	21.9 (6.9-73)
Cumulative eliciting dose, entry OFC (mg)	21 (21-171)	21 (21-221)	21 (9.8-152)	NA
Peanut IgG ₄ (μg/mL)	0.5 (0.2-1.0)	0.5 (0.2-1.0)	0.5 (0.1-1.1)	NA

Values are n (%) or median (IQR).

NA, Not available/applicable.

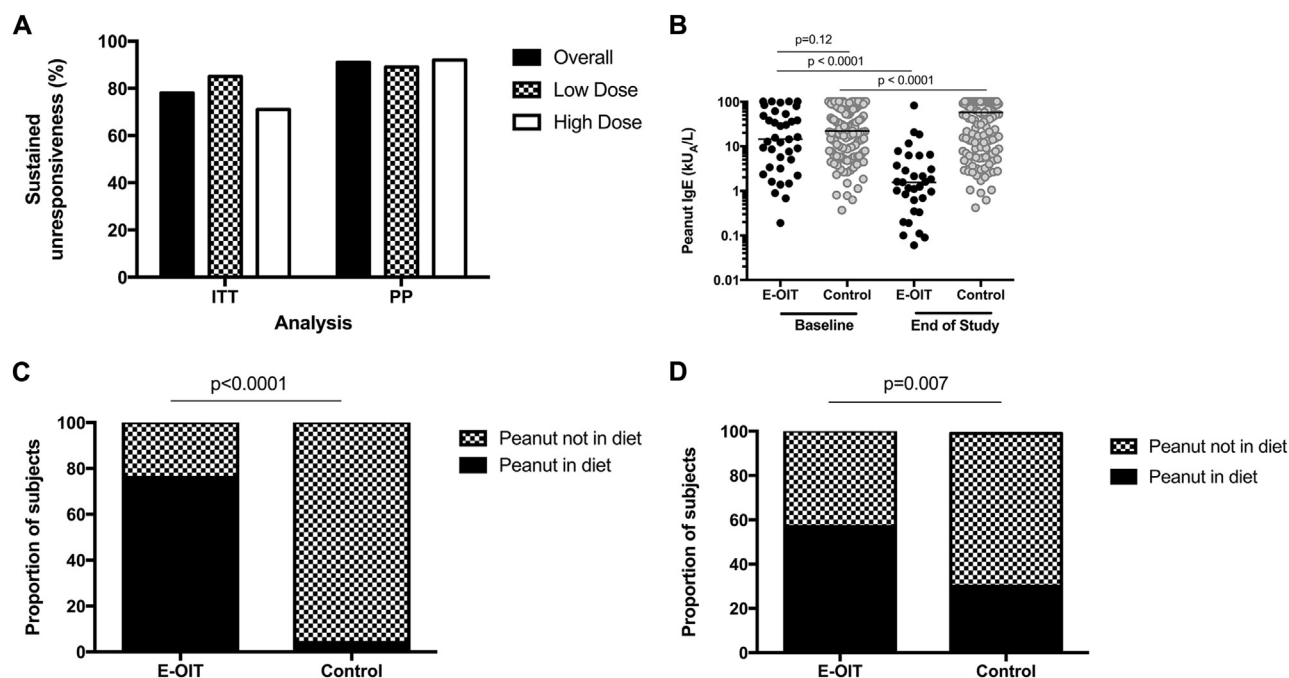
**P* = .03 vs controls.†*P* = .0005 vs controls.‡*P* = .001 vs all E-OIT.§*P* = .04 vs controls.

FIG 2. Outcomes of E-OIT and standard-care treatment. **A**, Clinical outcomes of E-OIT. The proportion of overall subjects, and those in each treatment arm, achieving SU are shown for both intent-to-treat and per-protocol analyses. **B**, The distributions of pslgE among E-OIT participants and matched controls practicing allergen avoidance at baseline and end-of-study periods (median 29 and 43 months, respectively). Note that all pslgE levels of more than 100 were transformed to 101 for these analyses because dilutional analysis was not available for all high-titer samples. **C**, The proportions of E-OIT and control participants able to reintroduce peanut-containing foods in the diet at the end of the study period. **D**, The imputed proportions able to reintroduce peanut-containing foods in the diet with evidence-based worst-case assumptions.

matched standard-care control group practicing avoidance, subjects receiving E-OIT had significantly lower pslgE levels and were estimated to be 19 times more likely to consume peanut in

the diet over approximately a 3-year period. Importantly, 300 mg/d was as effective as 3000 mg/d at regulating the allergic immune response, and produced 4-SU among 85% of the intent-to-treat

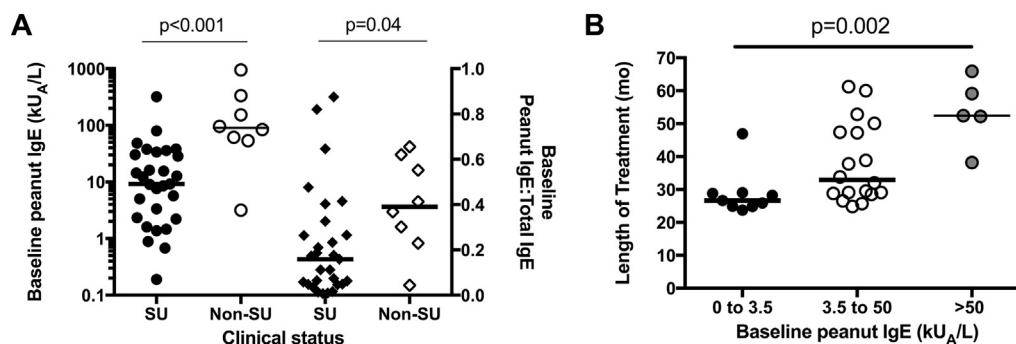


FIG 3. Association of baseline psIgE characteristics and outcomes. **A**, Both the baseline psIgE and the ratio of peanut-specific to total IgE are significantly lower among successes than among failures in the ITT population. **B**, Length of treatment broken down by tertiles of baseline psIgE. Significance testing by 1-way ANOVA.

and 89% of the per-protocol population. Confirming our previous results,⁸ we observed that SU was clearly associated with low baseline psIgE levels and psIgE:total IgE ratio. Allowing those with low psIgE level to qualify early for exit challenges appeared to facilitate rapid introduction of peanut back into the diet. Taken together, these findings support our hypothesis that early intervention effectively disrupts peanut allergy and enhances outcomes, perhaps due to the lower average psIgE levels typically seen in young children and/or the plasticity of a relatively immature immune response, which we are exploring in greater detail in ongoing experiments.

Safety data from young children treated with OIT are sparse. We observed a favorable safety profile with E-OIT, with a side-effect profile similar to that in other studies.⁷ Virtually all subjects experienced AEs likely related to OIT, but generally AEs were mild and required antihistamines, if any treatment was required. None was graded as severe. Like many other studies,²⁶ gastrointestinal allergic side effects were common and their persistence led to 2 withdrawals, 1 of which had eosinophilic esophagitis that importantly did not improve on a peanut-free diet, suggesting that peanut was not the specific trigger. Given his medical history of self-reported “gastroesophageal reflux,” and failure to respond to peanut elimination, it is most likely that his eosinophilic esophagitis was preexisting. Importantly, there were no AEs that met serious AE criteria, and only 1 participant required epinephrine for 1 systemic reaction at home.

Almost 80% of the randomized study population was able to successfully introduce peanut-containing foods into the diet *ad libitum* 4 weeks after stopping treatment. This improvement has been termed “sustained unresponsiveness,”^{8,27} and in part because we cannot be certain that these children have achieved permanent tolerance, we are continuing to follow them to better assess their long-term clinical outcomes. Although we acknowledge that the lack of a placebo group in this first-in-preschoolers OIT study limits a precise estimate of the effect size, we believe that the high rates of success in dietary reintroduction are largely due to E-OIT. This conclusion is supported by the reduction in psIgE to very low levels that was sustained 4 weeks after stopping OIT, which has been previously associated with OIT success.^{8,28} Although it is possible that spontaneous resolution may have occurred in the E-OIT group, several studies have shown that only a small minority of peanut-allergic children acquire natural tolerance.^{24,29-31} Most recently, the HealthNuts study demonstrated, with high methodological rigor, a 22% rate

of peanut allergy resolution by age 4 years in an unselected population.²⁴ The baseline characteristics of the active group, especially the low baseline OFC thresholds, as well as those of the controls in this study leave little reason to believe that we over-sampled milder patients likely to spontaneously resolve.^{15,24} We chose to use open challenges, rather than DBPCFCs, to confirm the diagnosis at baseline, and we required the presence of objective allergic signs in judging challenges to be positive. In other recent studies, including Learning Early About Peanut Allergy (LEAP) and HealthNuts,^{2,32} open OFCs were shown to be valid and sufficient for classifying food allergy in infants and young children.³³ The prespecified primary efficacy outcome variable was based on the exit DBPCFC results only and did not include a comparison to the entry challenge.

Despite the similarities of the 2 participating food allergy centers and actively matching on inclusion and exclusion criteria, the control cohort was more ethnically diverse and was evaluated by standard-care criteria rather than required OFCs at the entry and exit of their observation period. Thus, during the period of observation 13% of the control patients were offered OFCs by their treating allergist on the basis of clinical criteria suggesting the development of tolerance.²¹ Only one-third of those selected for challenge passed, suggesting that the treating physicians were aggressively evaluating for tolerance. Although the selection of control patients for tolerance OFCs could introduce bias, our worst-case analysis showed a statistically significant effect favoring E-OIT even when we conservatively assumed that all patients with sIgE level predictive values of less than 95% were tolerant. It should be noted that we understood in advance that we would be underpowered for a primary comparison of the 2 doses head-to-head. Given limited resources, we were unable to execute a study large enough to show what we assumed would be small between-group differences. Given how small the actually observed clinical and immunologic differences were in this study, this concern was justified. Our findings raise the possibility that the effective dose range in young children may be even lower than 300 mg.

Recently, the LEAP trial provided high-quality experimental evidence³² supporting data obtained from other cohort studies^{9,11} that together construct a new paradigm concerning the early-life origins of peanut allergy.³⁴ In this paradigm, allergic sensitization to peanut begins in the first few months of life and progresses to production of psIgE and expression of clinical disease in a high proportion of high-risk infants. In the LEAP study, properly timed oral exposure appeared to interrupt this progression and prevent

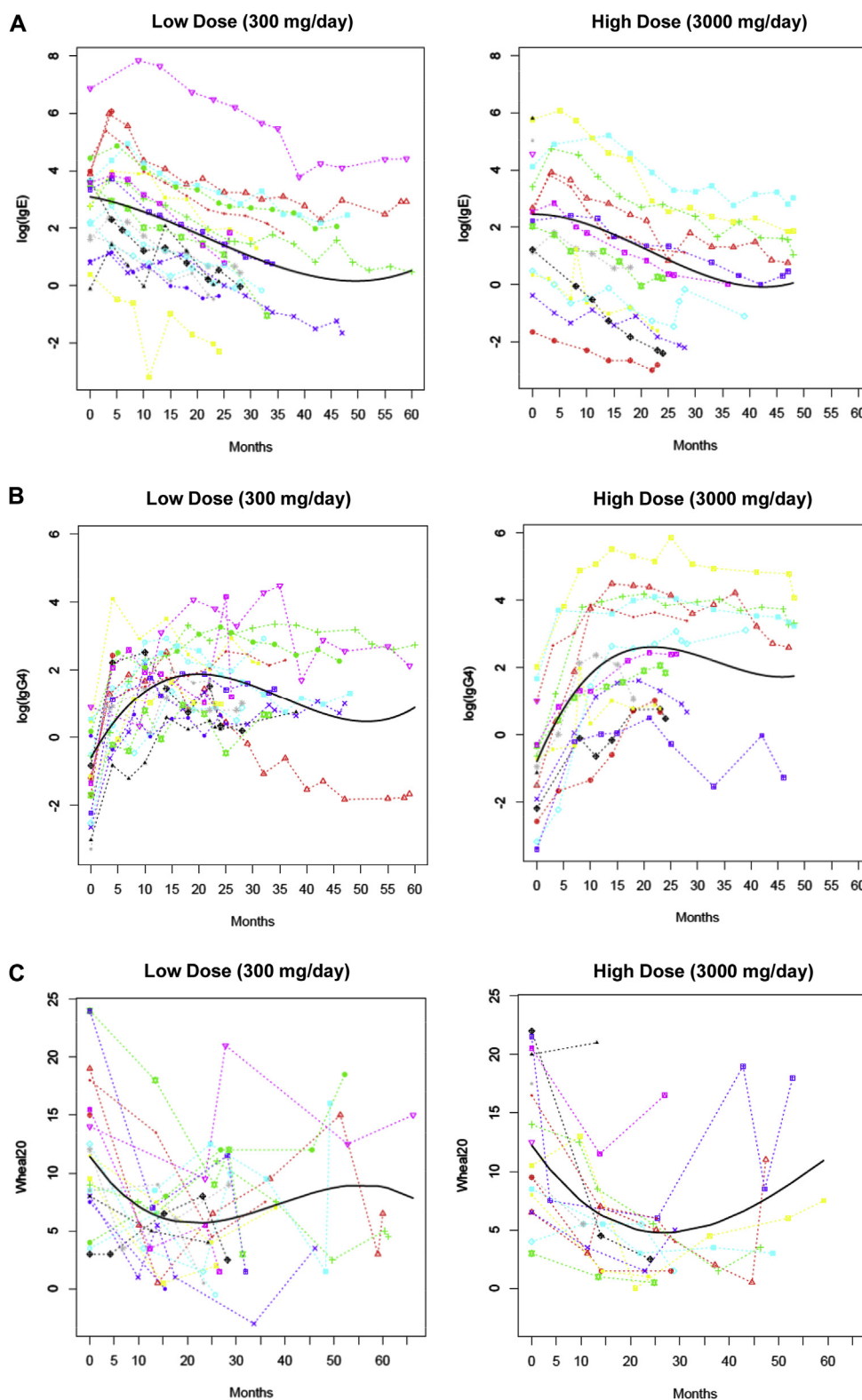


FIG 4. Immunoregulation during E-OIT at both doses tested. Log-transformed pslgE (**A**) and IgG₄ (**B**), and raw data for mean wheal diameter of peanut skin tests (**C**) are plotted separately by group, with data from individuals connected by colored lines and the fitted time trajectory curve displayed with the raw data for these models. *P* values comparing the parameter estimates for the 2 groups for each outcome are also provided.

peanut allergy from developing in most of the selected population, which consisted of unexposed atopic infants with absent or minimal sensitization to peanut. However, children known to, or likely to, already have peanut allergy were deemed unlikely to benefit from primary or secondary prevention strategies, and were thus excluded from the LEAP study; and in a small proportion, the preventative intervention failed. The population of interest for treatment with E-OIT is this group of infants and toddlers whose sensitization to peanut has progressed to clinical disease. We show here that even after allergic hypersensitivity is apparent, immunological programming to peanut may still be effectively disrupted through oral exposure in the form of E-OIT.

In summary, E-OIT was immunoregulatory and resulted in a very high rate of 4-SU at 1/13th of the maintenance dose previously used in older peanut-allergic children,⁸ and in as little as half the time. This suggests that allergic responses may be more easily and durably corrected in young children, and that in this context relatively low OIT doses are sufficiently potent in suppressing IgE responses and stimulating IgG₄ production. We are further exploring these concepts in ongoing mechanistic studies. Within an average of 2.5 years, children receiving E-OIT were able to stop treatment and begin eating peanut-containing foods at approximately 19-fold higher rates than did similar peanut-allergic controls continuing to avoid peanut. If the promise of E-OIT is confirmed in other studies, one of which is ongoing with a randomized, placebo-controlled, multicenter design,³⁵ we believe it has the potential to further transform the standard of care in the post-LEAP era. When initiated soon after the initial diagnosis, controlled oral peanut exposure through E-OIT may safely and effectively rescue many young children whose peanut allergy has already progressed to clinical disease expression.

We thank the children and their families for their gracious participation in this trial. We are indebted to the Duke Clinical Research Institute and the North Carolina Translational and Clinical Sciences Institute for the use of clinical research facilities. J. Kamilaris, A. Edie, J. Hainline, D. Hamilton, and L. Herlihy provided nurse coordinator support. X. Yue, H. Zhang, N. Kamilaris, C. Oppen, A. Beavers, and N. Szczepanski provided invaluable laboratory and investigational drug manufacturing assistance. A. Kazatsky and B. Krueger assisted in extraction of clinical case histories at Johns Hopkins.

Clinical implications: Treating peanut-allergic preschool children with OIT is feasible and may enhance long-term outcomes. In this study, relatively short, low-dose therapy achieved immunoregulation and a high rate of SU.

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METHODS

Intervention

Participants were randomly assigned to receive peanut OIT at 300 mg or 3000 mg/d target maintenance doses. To maintain allocation concealment, unblinded laboratory personnel kept the randomization table and manufactured and labeled the study product. We purchased 12% lightly roasted, partially defatted peanut flour (Golden Peanut Co, Alpharetta, Ga) and manufactured it at the MSRB Duke Manufacturing Facility and subsequently at the University of North Carolina Manufacturing Facility under 21 CFR 211 Good Manufacturing Practice. Release testing of the investigational drug product was performed in accordance with US Pharmacopeia standards and described in the Chemistry, Manufacturing, and Control section of our Investigational New Drug Application filing with the Food and Drug Administration (IND-13665, PI: Burks). For the low-dose arm, oat flour was purchased (Arrowhead Mills, Boulder, Colo) and toasted and mixed in with peanut at all dose steps above 300 mg to maintain blinding. Doses were packaged in polystyrene cups (Solo Corp, Lake Forest, Ill) and individually labeled with the subject's study ID. Participants consumed 1 dose per day by mixing the investigational product in a vehicle food of their choice (eg, applesauce and pudding). They otherwise maintained a peanut-free diet. We advised but did not require participants to dose at approximately the same time every day on a full stomach, and we recommended limited activity such as quiet play for approximately 2 hours after dosing. On the basis of previously published work, we provided standard anticipatory guidance about the withholding of doses for illnesses common to this age group such as febrile infections and gastroenteritis.^{E1} A caregiver for each participant filled out a daily dosing log, noting whether the dose was given or held and any AEs. Each participant had an up-to-date food allergy action plan, an in-date epinephrine autoinjector, and around-the-clock access to an on-call allergy physician.

Dosing schedule

All participants underwent an initial-day escalation phase, and those able to tolerate a minimum of 3 mg proceeded to an approximately 42-week buildup phase, to a goal maintenance dose of 3000 mg/d, which was continued until the end of the maintenance period. Tables E1 and E2 present the schedules for initial-day escalation and buildup phases.

Food challenge assessments

At screening, eligible participants underwent an open OFC to 4 g of peanut protein, using peanut butter. Challenges were judged positive only when participants demonstrated clear objective evidence of an allergic reaction (urticaria, angioedema, respiratory distress/wheeze/cough, vomiting/diarrhea, anaphylaxis).

At the end of the maintenance period upon qualifying for end-point assessment, subjects presented to the clinical research unit for assessment of clinical desensitization with a DBPCFC to a cumulative total of 5 g of peanut protein. Before the DBPCFC, subjects were asked to restrict the use of antihistamines (short-acting, 72 hours; long-acting, 7 days), beta-agonists (12 hours), theophylline (12 hours), and cromolyn (12 hours). One part of the DBPCFC consisted of 6 doses of peanut given every 10 to 20 minutes in increasing amounts up to a total weight of 5 g of peanut protein. The other part of the challenge consisted of equal amounts of placebo (oat) material given also in 6 doses. The cumulative dose of peanut protein given is 5 g (10 g weight of peanut flour), and all doses were mixed thoroughly and delivered in a nonallergenic vehicle of the subject's choice, usually applesauce or pudding. Both challenges started by first touching the patient's lip/tongue with a small amount of the test material. The first ingested dose was 0.5 g (5%), then increasing to 1 g (10%), 2 g (20%), 2 g (20%), 2 g (20%), and 2.5 g (25%). Randomization and preparation of the challenge materials were performed by an unblinded research nutritionist or a representative from Dr Burks' laboratory. If all the challenge material was consumed without dose-limiting symptoms, OIT was stopped for 4 weeks, and the DBPCFC was repeated, using the same procedure, to assess for SU. SU was confirmed with an open feeding of 5 to 8 g of peanut butter in 1 serving 1 to 2 hours after the completion of the DBPCFC. Such subjects were then instructed to add peanut to their diets *ad libitum*.

Mechanistic studies

Serologic and cell-based assays. Peripheral blood was collected in serum-separator or sodium-heparin tubes. Serum and plasma were collected by whole-blood centrifugation, and stored frozen until analysis. PBMCs were isolated and cultured under various conditions; the results of these experiments will be reported separately. A subset of subjects had blood drawn in sodium-heparin tubes to assess basophil activation at the time of both exit DBPCFCs, using previously described assay methods.^{E2}

Total-IgE and pslgE and IgG₄ quantification. PsIgE and IgG₄, as well as total-IgE, levels were measured via ImmunoCAP 100 (Thermo Fisher, Uppsala, Sweden) according to manufacturer's specifications.

Power/statistical considerations

No placebo-controlled studies have been published that evaluated the development of tolerance/SU after years of treatment with peanut OIT. Published data from our own uncontrolled pilot study in older children with long-standing disease suggest that SU developed in 12 of 24 (50%) peanut-allergic subjects completing high-dose OIT.^{E3} On the basis of preliminary data that were available to us at the time this study was conceived in 2008, and according to our hypothesis, we predicted before the study that 70% of low-dose subjects would develop SU, compared with the expected rate of spontaneous peanut allergy resolution of 20% as shown in multiple cohort studies. At a 2-sided significance level of .05, 15 subjects in each treatment arm would have at least 80% power to detect a 50% absolute average difference between the proportion of subjects in each arm passing the exit SU OFC and the 20% rate of spontaneous tolerance expected in untreated controls. On the basis of a pre-study assumption of 15% to 20% dropout, we enrolled 20 subjects per arm to ensure adequate power.

Practical considerations prevented a trial large enough to show definitive comparisons of high- and low-dose therapy directly. Twenty subjects in each arm would have 63% power to identify a 40% difference in SU acquisition between regimens. Even if underpowered to show a difference between low-dose and high-dose therapy, we reasoned *a priori* that a type II error in this setting may still be clinically meaningful so long as the proportion achieving SU in the low-dose group significantly exceeded 20%. This would be especially true if low-dose therapy offers other advantages (fewer visits, better safety profile, improved palatability, etc).

Control cohort

We collaborated with the pediatric allergy group at Johns Hopkins (C.K. and R.A.W.), whose practices consist of peanut-allergic patients of similar age and severity as that of the lead site where the trial occurred. In addition, the clinic cohort at Johns Hopkins has formed the basis of several seminal and highly cited studies of the natural history of food allergies in US children,^{E4-E8} and importantly was not recruiting young children in peanut OIT at the time our study was enrolling. In retrospective fashion, we recruited a standard-care control cohort that was matched for age between 9 and 36 months at enrollment, clinical history (eg, both sensitized-not-ingested and clinically allergic), peanut allergy severity, absence of severe atopic dermatitis, severe/uncontrolled asthma, oat allergy, and eosinophilic disorders. Additional criteria for inclusion in the control cohort included having at least 2 visits separated by at least 6 months, as well as absence of recent immunomodulatory drugs or participation in a clinical trial. Although the standard of care for peanut allergy has not changed for young children since the initiation of this project, we did perform contemporaneous and consecutive enrollment into the control cohort; for example, every qualifying clinical patient who was seen at Johns Hopkins during the period of trial enrollment 2009-2011 was included. We aimed to enroll at least 120 subjects to give at least 3 controls for each "case" receiving OIT in the trial.

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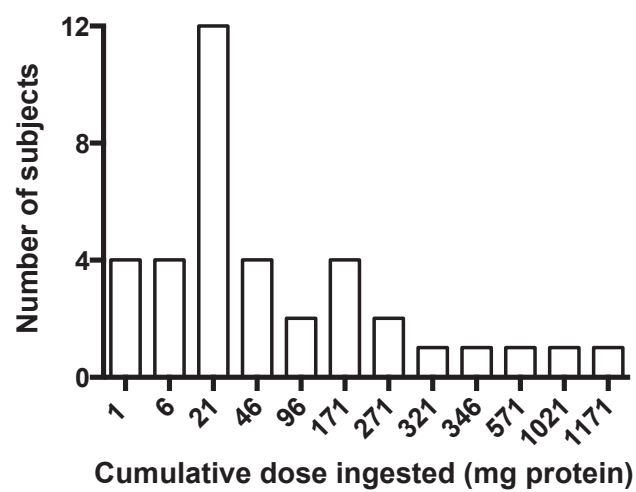


FIG E1. Cumulative dose ingested during entry open OFCs in the E-OIT ITT population.

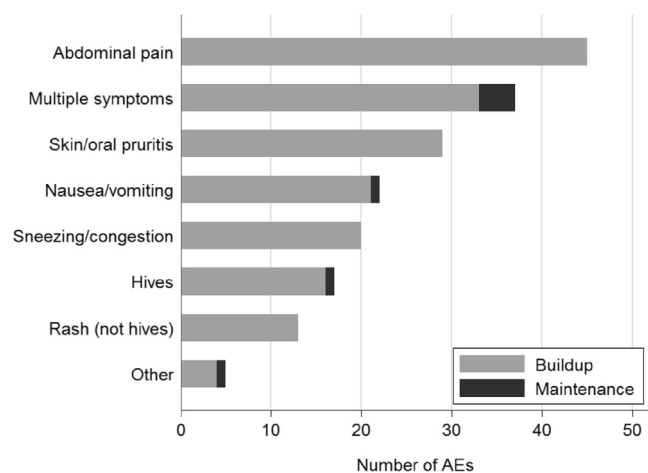


FIG E2. Distribution of all allergic AEs during buildup and maintenance phases. Multiple symptoms included any single reaction that involved multiple systems (skin/gastrointestinal/upper respiratory/lower respiratory). This group does not overlap with the other groups that involved isolated symptoms in each specified category. The “Other” category included isolated symptoms that occurred with less than 5% frequency (isolated cough at 2%, isolated angioedema at 1%, and isolated eye-tearing at 0.5%).

TABLE E1. Initial-day escalation

Dose no.	Dose (mg)	Interval (min)	% Increase
1	0.1	30	NA
2	0.2	30	100
3	0.4	30	100
4	0.8	30	100
5	1.5	30	87.5
6	3	30	100
7	6	30	100

NA, Not available/applicable.

TABLE E2. Buildup phase

Dose no.	Dose (mg)	Interval (wk)	% Increase
7	6		As above
8	12	2	100
9	25	2	108
10	50	2	100
11	75	2	50
12	100	2	33
13	125	2	25
14	156	2	25
15	195	2	25
16	245	2	25
17	306	2	25
18	383	2	25
19	479	2	25
20	599	2	25
21	749	2	25
22	936	2	25
23	1170	2	25
24	1463	2	25
25	1829	2	25
26	2286	2	25
27	3000	2	31

TABLE E3. Safety data by treatment arm

Population	Overall	Buildup	Maintenance
Subjects affected by AEs			
All subjects	95% (35 of 37)	92% (34 of 37)	27% (9 of 33)
High dose	100% (17 of 17)	100% (17 of 17)	43% (6 of 14)
Low dose	90% (18 of 20)	85% (17 of 20)	16% (3 of 19)
Average rate of AEs per person per dose (95% CI)			
All subjects*	0.8% (0.3%-1.4%)	1.5% (0.9%-2.2%)	0.06% (0%-0.1%)
High dose*	1.1% (0%-2.3%)	1.9% (0.6%-3.2%)	0.06% (0.01%-0.1%)
Low dose	0.6% (0.3%-0.9%)	1.2% (0.5%-2.0%)	0.05% (0%-0.2%)
Total number of AEs			
All subjects	211	195	16
High dose	133	126	7
Low dose	78	69	9
Proportion of moderate-severity AEs†			
All subjects	17% (36 of 211)	17% (33 of 195)	19% (3 of 16)
High dose	13% (17 of 133)	12% (15 of 126)	29% (2 of 7)
Low dose	24% (19 of 78)‡	26% (18 of 69)§	11% (1 of 9)
Study withdrawals			
All subjects	14% (5 of 37)	11% (4 of 37)	3% (1 of 33)
High dose	24% (4 of 17)	18% (3 of 17)	7% (1 of 14)
Low dose	5% (1 of 20)	5% (1 of 20)	0% (0 of 19)

*Rate of AE = number of AEs/d on therapy. Because subject 36 was never able to start therapy because of inability to complete the modified rush, this subject was excluded from these calculations.

†All AEs were either mild or moderate (no severe AEs reported).

‡ $P = .04$, compared with high-dose group.

§ $P = .02$, compared with high-dose group.

TABLE E4. Treatment of likely related AEs

Treatment	Events requiring treatment, n (%)			Subjects requiring treatment, n (%)		
	Overall	Buildup	Maintenance	Overall	Buildup	Maintenance
Treated (all subjects)	54 (26)	47 (24)	7 (44)	20 (54)	16 (43)	5 (15)
Antihistamines	52 (25)	46 (24)	6 (38)	20 (54)	16 (43)	5 (15)
Albuterol	3 (1)	1 (0.5)	2 (13)	3 (8)	1 (3)	2 (6)
Epinephrine	1 (0.5)	1 (0.5)	0 (0)	1 (3)	1 (3)	0 (0)
Treated (high dose)	39 (29)	36 (29)	3 (43)	9 (53)	7 (41)	3 (21)
Antihistamines	38 (29)	35 (28)	3 (43)	9 (53)	7 (41)	3 (21)
Albuterol	1 (0.8)	0 (0)	1 (14)	1 (6)	0 (0)	1 (7)
Epinephrine	1 (0.8)	1 (0.8)	0 (0)	1 (6)	1 (6)	0 (0)
Treated (low dose)	15 (19)	11 (16)	4 (44)	11 (55)	9 (45)	2 (11)
Antihistamines	14 (18)	11 (16)	3 (33)	11 (55)	9 (45)	2 (11)
Albuterol	2 (3)	1 (1)	1 (11)	2 (10)	1 (5)	1 (5)
Epinephrine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)