Original Article

Efficacy, Safety, and Quality of Life in a Multicenter, Randomized, Placebo-Controlled Trial of Low-Dose Peanut Oral Immunotherapy in Children with Peanut Allergy

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What is known already about the topic? Only 2 small placebo-controlled trials on peanut oral immunotherapy using a relatively high maintenance dose of peanut protein have been published so far showing good efficacy. But safety concerns have been raised.

What does this article add to our knowledge? With this placebo-controlled trial we could show that low-dose oral immunotherapy in children with peanut-allergy is effective, has an excellent safety profile, and leads to improvement in quality of life, a low burden of treatment, and immunologic changes showing tolerance development.

How does this study impact current management guideline? Low-dose oral immunotherapy is effective and safe and thus might be a promising treatment option for children with peanut allergy.

BACKGROUND: Only 2 small placebo-controlled trials on peanut oral immunotherapy (OIT) have been published.
OBJECTIVE: We examined the efficacy, safety, immunologic parameters, quality of life (QOL), and burden of treatment (BOT) of low-dose peanut OIT in a multicenter, double-blind, randomized placebo-controlled trial.
METHODS: A total of 62 children aged 3 to 17 years with IgE-mediated, challenge-proven peanut allergy were randomized (1:1) to receive peanut OIT with a maintenance dose of 125 to 250 mg peanut protein or placebo. The primary outcome was the proportion of children tolerating 300 mg or more peanut protein at oral food challenge (OFC) after 16 months of OIT. We measured the occurrence of adverse events (AEs), immunologic changes, and QOL before and after OIT and BOT during OIT.
RESULTS: Twenty-three of 31 (74.2%) children of the active group tolerated at least 300 mg peanut protein at final OFC compared with 5 of 31 (16.1%) in the placebo group ($P < .001$).

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Abbreviations used
AE- Adverse event
BOT- Burden of treatment
FAQLQ-PF- Food Allergy Quality of Life Questionnaire-Parent form
FAQLQ-CF- Food Allergy Quality of Life Questionnaire-Child form
FAQLQ-TF- Food Allergy Quality of Life Questionnaire-Teenage form
HRQOL- Health-related quality of life
IQR- Interquartile range
ITT- Intention to treat
MCID- Minimum clinically important difference
OFC- Oral food challenge
OIT- Oral immunotherapy
QOL- Quality of life
SAE- Severe adverse event
SPT- Skin prick test

Thirteen of 31 (41.9%) children of the active versus 1 of 31 (3.2%) of the placebo group tolerated the highest dose of 4.5 g peanut protein at final OFC ($P < .001$). There was no significant difference between the groups in the occurrence of AE-related dropouts or in the number, severity, and treatment of objective AEs. In the peanut-OIT group, we noted a significant reduction in peanut-specific IL-4, IL-5, IL-10, and IL-2 production by PBMCs compared with the placebo group, as well as a significant increase in peanut-specific IgG_4 levels and a significant improvement in QOL; 86% of children evaluated the BOT positively.
DISCUSSION: Low-dose OIT is a promising, effective, and safe treatment option for peanut-allergic children, leading to improvement in QOL, a low BOT, and immunologic changes showing tolerance development. **© 2018 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2019;7:479-91)**

Key words: *Oral immunotherapy; Tolerance; Induction; Children; Peanut allergy; Desensitization*

INTRODUCTION

Peanut allergy is a common disease in childhood, with estimated prevalence rates ranging from 0.4% in Europe[1] to 3% in Australia.[2] Ingestion of only small quantities of the allergen may lead to potentially life-threatening allergic reactions.[3] Thus, peanut is the most common allergen to induce food-induced anaphylaxis in childhood.[4] Patients are advised to strictly avoid peanut, but accidental reactions are common due to the widespread use of peanut in the food industry.[5] Thus, patients are also advised to carry self-administered epinephrine at all times. Overall, quality of life (QOL) in patients with peanut allergy is reduced.[6,7] Therefore, there is a need for an allergen-specific therapy in this group of patients.

Recent research has focused on the therapeutic option of oral allergen-specific immunotherapy. Published trials on peanut oral immunotherapy (OIT) have demonstrated clinical desensitization of most of the patients, although different doses for maintenance were used.[8-18] However, all trials were small and only 2 were placebo-controlled. Mild to moderate adverse reactions were reported in most patients. Some patients even suffered from anaphylactic reactions associated with OIT dosing. Although OIT seems an effective treatment option for patients with peanut allergy, safety has to be evaluated more carefully.

Hypothetically, using a low maintenance dose and a long updosing period in peanut OIT might lead to the same efficacy but better safety profile than using a higher maintenance dose for a shorter updosing period. The aim of this double-blind, placebo-controlled study was to assess efficacy for clinical desensitization and safety of OIT as well as possible changes in immunologic parameters, QOL after OIT, and the burden of treatment (BOT) in children with peanut allergy using the lowest maintenance dose so far reported. It is one of the first placebo-controlled peanut-OIT trials where oral food challenges (OFCs) were conducted before and after OIT, where a high enough top dose of peanut protein was included into the final OFC to define a proper threshold after OIT in individual patients, where safety was assessed thoroughly, and the first where changes in QOL and BOT were investigated in a placebo-controlled way.

METHODS

Study overview

This investigator-initiated, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial was conducted at 7 German sites (see this article's Study centers section in the Online Repository at www.jaci-inpractice.org). We recruited patients consecutively in the outpatient clinics or from a list of peanut-sensitized children followed within these tertiary care clinics. The study protocol and consent forms were approved by all ethics committees. All caregivers of the study participants gave written informed consent before the start of the study. The study was registered with the German Clinical Trials Register (DRKS00004553).

Study population

Eligible patients were aged 3 to 17 years with a serum peanut-specific IgE level of more than 0.35 kU/L and challenge-proven clinically relevant peanut allergy. Parents of the patients had to be capable of understanding the proposed intervention of the study as well as being able to follow written emergency instructions. Patients were excluded if they had participated in another trial, if they were receiving any other form of immunotherapy including immunotherapy using inhalant allergens, or if they suffered from a severe disease (eg, uncontrolled asthma despite proper treatment). Children with controlled asthma or a history of severe allergic reaction (severity grade V[19] like respiratory arrest, bradycardia, arterial hypotension, cardiac arrest, or loss of consciousness) after peanut consumption were not excluded.

Study end points

This study compared active peanut OIT with placebo OIT in children with peanut allergy. The primary end point was defined as the proportion of children tolerating a single dose of greater than or equal to 300 mg peanut protein at the final OFC after a maximum of 14 months of updosing and 2 months of a maintenance phase of OIT in both groups. Secondary outcomes for efficacy were full clinical desensitization defined as the proportion of children tolerating the top, single dose of 4.5 g peanut protein at the final OFC, median changes in the maximum tolerated single dose at initial and final OFCs, and comparison of the severity of reaction between

initial and final OFCs. Other secondary outcomes included safety measurements such as severity and number of adverse events (AEs), number of accidental allergic reactions to peanut, change in the severity of other atopic diseases as well as changes in immunologic parameters, QOL, and the BOT.

Randomization

After the initial OFC, study participants were randomly assigned (1:1) to the active group or the placebo group via block randomization with a size of 4 using Dat Inf, Rand List, version 1.2. A stratification for age (≤ or >6 years) and peanut-specific IgE (≤ or >50 kU/L) was performed by an independent statistician.

Study design

During the screening visit, the patient's history was obtained (doctor's diagnosed asthma, allergic rhinitis, atopic dermatitis, and other primary food allergies), a physical examination, and screening for peanut sensitization was conducted. After approximately 8 weeks, children were admitted to our ward for an open oral peanut challenge (=initial OFC). After this OFC, patients were eligible to be randomized. OIT was started the next day on the ward. On the day of the initial OFC as well as on the day of the final OFC—"post-OIT" (after the maintenance phase of OIT)—patients received a physical examination including a SCORing Atopic Dermatitis, a spirometry if compliance allowed, a skin prick test (SPT) performed as a prick-to-prick test with the natural, roasted whole peanut, and blood samples for analysis of B-cell markers (peanut-, Ara h 2-, timothy-, birch-, mugwort-, dermatophagoides pteronyssinus-, cladosporium herbarum-, dog- and cat-specific IgE, and peanut-specific IgG_4 [CAP-System FEIA, Thermo Fisher]) and T-cell cytokine production in cell culture supernatants (described in Blumchen et al[19]).

Open OFCs

Before the start of OIT—at the initial OFC—as well as after the maintenance phase at the final OFC, children received an open oral peanut challenge using a modified PRACTALL protocol[20] with 2-hour time intervals between dose steps as previously described.[19] In summary, patients received whole crushed roasted peanuts in boiled apple sauce as a matrix in increasing titration steps for a maximum of 3 days (first day: 3 mg - 10 mg - 30 mg - 100 mg; second day: 100 mg - 300 mg - 1000 mg - 3000 mg; third day: 4500 mg peanut protein). The procedure was stopped if objective clinical symptoms were observed. This dose was considered to be the eliciting dose. The last single dose the patient tolerated just before the eliciting dose was defined as the maximum tolerated single dose.

Procedures for OIT

Peanut flour (light roasted, 12% fat, 50% protein) from the Byrd Mill Company (Ashland, Va) was used as the peanut protein source for OIT mixed in a vehicle of chocolate pudding for masking (see this article's Preparation and dosing of OIT section; and Figure E1 for peanut protein quantification and homogeneity testing of pudding bases in this article's Online Repository at www.jaci-inpractice.org). The placebo group received the vehicle without peanut flour. Patients received the first dose of peanut/placebo OIT on the ward. The starting dose of peanut/placebo OIT varied depending on the eliciting dose patients reacted to at the initial OFC. If patients had an eliciting dose of 3, 10, 30, 100, or greater than or equal to 300 mg peanut protein at the initial OFC, they started OIT on a dose of 0.5, 1, 3, 10, or 30 mg peanut protein, respectively. The same OIT dose was administered again the next day. After 2 hours of monitoring, patients were instructed to take this dose daily, approximately at the same time. Updosings were planned every 2 weeks under medical monitoring in the outpatient clinics of the study centers (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). The updosing phase lasted a maximum of 14 months or shorter if the patients reached their individual planned maintenance dose. The planned final maintenance dose was determined by the eliciting dose patients had reacted to at the initial OFC: The doses of patients with an eliciting dose of 3 mg to 100 mg peanut protein at the initial OFC were gradually increased to 125 mg, whereas patients with an eliciting dose of 300 mg to 4500 mg peanut protein were dosed up to 250 mg peanut protein as an OIT-maintenance dose. The maintenance phase lasted for 8 weeks (±2 weeks).

Safety outcomes

AEs were recorded daily by parents in a diary and were assessed every 1 to 2 weeks by the blinded study physician during either updosing visits or a telephone interview. AEs were recorded as possibly related or related to peanut/placebo OIT if symptoms occurred within 2 hours after ingestion. AEs were also categorized as being either objective (eg, hives, flush, angioedema, vomiting, diarrhea, conjunctivitis, rhinitis, sneezing, coughing, wheezing, and shortness of breath) or subjective symptoms (eg, pruritus, abdominal pain, nausea, oral itching, hawking, globus sensation, or diverse symptoms [joint, ear, and throat pain, headache, fever]). Severity of possible allergic reactions was determined by the investigator using a modified grading system for food-induced anaphylaxis.[19,21] As judged by the study physician, AEs were also categorized as being a possible allergic reaction after accidental peanut exposure. By assessing the parents' diary, patient's spirometry, peak flow, and SCORing Atopic Dermatitis score, the study physician determined whether an atopic comorbidity as asthma, allergic rhinitis, and atopic dermatitis improved, worsened, or remained stable during the study on the day of the final OFC.

Health-related quality of life and BOT

To measure changes in health-related quality of life (HRQOL), the German translation of the Food Allergy Quality of Life Questionnaire (FAQLQ) was sent out to mothers (FAQLQ-PF,[22] parental form, proxy measurement), children (FAQLQ-CF,[23] child form), and teenagers (FAQLQ-TF,[24] teenage form) 4 weeks before the initial OFC and 4 weeks after the final OFC (see this article's HRQOL measures section in the Online Repository at www.jaci-inpractice.org). For comparison of changes in HRQOL before and after OIT in both study groups, only complete data sets were considered for analysis (per-protocol analysis). Results represent the median change in total score and each domain score for each study group before and after OIT. The greater the negative change in score, the better was the improvement in HRQOL.

The BOT questionnaire was sent out to the families 3 to 4 months after starting OIT. Mothers of children (3-12 years), children (8-12 years), and teenagers (13-17 years) were asked to rate the advantages and disadvantages of OIT treatment on a 7-point scale ranging from 1 (=extremely positive) through 4 (=neutral) to 7 (=extremely negative).[25,26] Mothers and patients were also asked whether they would perform OIT again. Results are presented for each treatment group as numbers of mothers or children who reported on a positive (score 1-3) or a negative BOT (score 4-7) and who would and would not perform OIT once more. HRQOL data and BOT data of teenagers were not included in data analysis due to the small number of teenagers within the study.

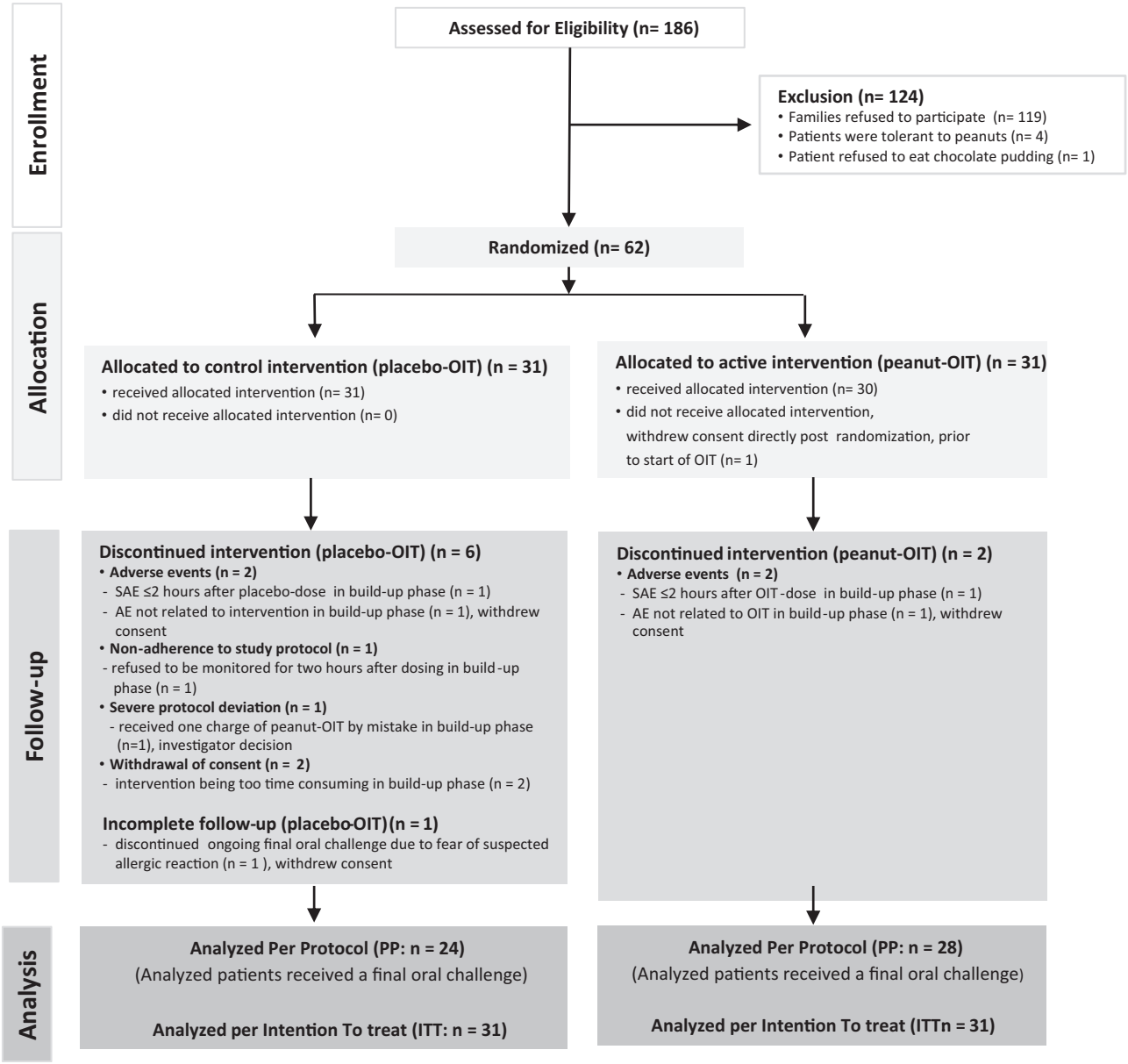


FIGURE 1. Consolidated Standards of Reporting Trials diagram. *PP*, Per protocol.

Statistical analysis

Values are expressed as median and interquartile ranges (IQRs) unless otherwise indicated, or counts and percentages as appropriate. For primary and secondary end points, data are presented as either proportions or as the median change between pre- and post-OIT values (median of post-OIT minus pre-OIT values). All patients randomized were included for the analysis of the primary end point as the intention-to-treat (ITT) population. For the robustness of the statistical analysis of the primary end point, a worst-case analysis was also conducted where all dropouts of the placebo group were considered to reach the primary end point and all dropouts of the active group were considered to fail the primary end point. Data of the primary end point as well as all other secondary end points were also analyzed per protocol including all patients who received the intervention and completed the final OFC. Safety outcomes were analyzed from all patients within the ITT population receiving at least 1 dose of placebo/peanut OIT, also including all dropout patients until the time they discontinued the study. Group comparisons between randomization arms of continuous variables were performed using the Kruskal-Wallis test. The primary end point and other categorical variables were compared between randomization arms using the chi-square test for contingency tables (Fisher exact test). All statistical tests were 2-tailed, and a 2-sided *P* value of .05 was considered for significance. The statistical analyses were performed using R version 2.5.1 (R Core Team, Vienna, Austria) and SPSS version 22.0 (SPSS, Inc, Chicago, Ill).

RESULTS

Study population

Of 186 children with suspected peanut allergy approached for the study, 119 refused to participate, 4 were tolerant to peanut at the initial OFC, and the youngest patient vigorously refused to eat the

TABLE I. Baseline characteristics of study participants

Baseline Characteristic	Placebo OIT (n = 31)	Peanut OIT (n = 31)
Age (y), median (IQR)	7.9 (4.6-10.7)	6.6 (4.8-9.8)
Sex, male, n (%)	19 (61.3)	19 (61.3)
Weight (kg), median (IQR)	22.4 (18.2-36.4)	24.0 (18.7-31.8)
Positive family history of atopy, n (%)	29 (93.5)	26 (83.9)
Asthma/increased airway reactivity, n (%)	20 (64.5)	13 (41.9)
Atopic dermatitis, n (%)	22 (71.0)	19 (61.3)
Allergic rhinitis, n (%)	18 (58.1)	14 (45.2)
Further systemic food allergies,* n (%)	12 (38.7)	9 (29.0)
History of accidental allergic reaction to peanut and to unknown cause, n (%)	29 (93.5)	31 (100.0)
History of accidental allergic reaction to peanut and to unknown cause with severity grade ≥IV,† n (%)	16 (51.6)	18 (58.1)
Eliciting single dose of peanut protein (mg) at the initial OFC, median (IQR)	100 (10-200)	100 (30-1000)
Cumulative eliciting dose (mg peanut protein) consumed at day of allergic reaction of OFC, median (IQR)	143 (13-272)	143 (43-1400)
Maximum tolerated single dose of peanut protein (mg) at the initial OFC, median (IQR)	30 (3-65)	30 (10-300)
Patients tolerating ≥300 mg peanut protein at the initial OFC,‡ n (%)	4 (12.9)	10 (32.3)
Severity† of reaction at OFC, n (%)		
Grade I	1 (3.2)	1 (3.2)
Grade II	13 (41.9)	11 (35.5)
Grade III	11 (35.5)	10 (32.3)
Grade IV	6 (19.4)	9 (29.0)
Peanut SPT (mm), median (IQR)	8 (7.0-9.8)	8 (6.5-9.5)
Total IgE (kU/L), median (IQR)	434 (267-758)	347 (193-766.5)
Peanut-specific-IgE (kU/L), median (IQR)	73.1 (31.3-197)	89.5 (6.9-217)
Ara h 2−specific IgE (kU/L), median (IQR)	48.8 (20.5-85.7)	44.6 (6.4-99.7)
Peanut-specific IgG_4 (mgA/L), median (IQR)	0.38 (0.15-0.97)	0.63 (0.18-0.89)

Continuous values are presented as medians with IQR. Kruskal-Wallis test was used for statistical analysis. Categorical variables are presented as number of participants and percentage using the χ^2 test for statistical analysis.
*Defined as either historical or challenge-proven systemic reaction to food allergens other than peanut.
†For detailed definition of grading the severity of allergic reactions, see Blumchen et al.[19]
‡Number of patients with an eliciting single dose of 1, 3, or 4.5 g peanut protein at the initial OFC.

vehicle (chocolate pudding) (see Figure 1, Consolidated Standards of Reporting Trials flow diagram). Thus, 62 participants with a median age of 6.8 years (range, 3.2-17.8 years), median peanut-specific IgE of 81.5 kU/L (range, 0.57-624 kU/L), median Ara h 2−specific IgE of 44.7 kU/L (range, 0.04-256 kU/L), and median maximum tolerated single dose at the initial OFC of 30 mg peanut protein (range, 1-3,000 mg) were randomized to receive either active, peanut OIT (n = 31) or placebo OIT (n = 31). Ten of 62 patients discontinued during the study (see Consolidated Standards of Reporting Trials diagram): 1 patient of the peanut-OIT group withdrew consent after randomization but before receiving the allocated intervention. This patient was still included in the ITT analysis (n = 62 in ITT). See Figure 1 and this article's Dropouts section in the Online Repository at www.jaci-inpractice.org for further explanations of all dropouts. There were no significant differences between the peanut-OIT and the placebo-OIT groups in demographical and immunologic baseline characteristics (Table I).

Efficacy

After a median of 13 months (10-14 months) of the updosing and 9.5 weeks (8.5-11.4 weeks) of the maintenance phase, 24 patients of the placebo-OIT group and 28 patients of the peanut-OIT group finished the study with a final OFC; 50% in each randomization group reached their planned maintenance dose. The median maintenance dose was 125 mg peanut protein (50-250 mg) in the peanut-OIT group and "125 mg placebo" (31.3-225 mg) in the placebo-OIT group. Within the ITT population, 23 of 31 patients (74.2%) of the peanut-OIT group tolerated greater than or equal to 300 mg peanut protein, whereas only 5 of 31 patients (16.1%) within the placebo-OIT group tolerated this dose at the final OFC ($P < .001$) (Table II; Figure 2). Also, in the worst-case analysis ($P = .01$) as well as in the per-protocol analysis ($P < .001$), the primary end point was met (Table II). As a secondary end point, 13 patients of the peanut-OIT group (41.9% of the ITT population) tolerated the maximum dose of 4.5 g peanut protein at the final OFC compared with only 1 patient (3.2%) within the placebo-OIT group ($P < .001$). With a median of 20 mg (10-100) peanut protein, the maximum tolerated single dose at the final OFC remained unchanged (fold change = 1 [0.33-4.3]) when compared with the median maximum tolerated single dose at the initial OFC (30 mg [8.3-100] peanut protein) within the placebo group. In comparison, the maximum tolerated single dose increased by a factor of 12.1 (4.3-97) from a median of 30 mg (10-300) to a median of 1000 mg (825-4500) peanut protein at the final OFC within the peanut-OIT group.

Within the first 6 of 8 dose steps of the final OFC, the patients of the placebo group experienced more and more severe reactions than did the peanut-OIT group (Figure 3). However, comparing the number of grade IV reactions during all dose steps (3-4.5 g peanut protein) at the final OFC, there was no difference between the peanut-OIT (n = 7) and the placebo-OIT (n = 7) groups (Figure 3).

TABLE II. Clinical efficacy end points

Clinical efficacy end points	Placebo OIT	Peanut OIT	*P* value
Primary end point			
Primary end point: ITT analysis	n = 31	n = 31	
Patients tolerating ≥300 mg peanut protein at the final OFC, n (%)	5 (16.1)	23 (74.2)	<.001
Patients newly tolerating ≥300 mg peanut protein at the final OFC,* n (%)	1 (3.2)	13 (41.9)	<.001
Primary end point: Worst-case analysis	n = 31	n = 31	
Patients tolerating ≥300 mg peanut protein at the final OFC, n (%)	12 (38.7)	23 (74.2)	.01
Primary end point: PP analysis	n = 24	n = 28	
Patients tolerating ≥300 mg peanut protein at the final OFC, n (%)	5 (20.8)	23 (82.1)	<.001
Secondary end points			
Secondary end point: ITT analysis	n = 31	n = 31	
Patients tolerating the maximum dose of 4500 mg peanut protein at the final OFC, n (%)	1 (3.2)	13 (41.9)	<.001
Secondary end point: PP analysis	n = 24	n = 28	
Patients tolerating the maximum dose of 4500 mg peanut protein at the final OFC, n (%)	1 (4.2)	13 (46.4)	.002
Maximum tolerated single dose of peanut protein (mg) at the final OFC, median (IQR)	20 (10 to 100)	1000 (825 to 4500)	<.001
Change in maximum tolerated single dose of peanut protein (mg) at the final OFC, median (IQR)	0 (−7.5 to 13.5)	997 (592.5 to 4200)	<.001

Data present the primary and secondary clinical end points within the ITT and per-protocol (PP) population. For primary and secondary clinical end points, data are presented as proportions of patients within a randomization arm at the final OFC after OIT and were statistically analyzed by using the χ^2 test for contingency tables (Fisher exact test). Within the PP population, the median change in maximum tolerated peanut dose between the initial OFC and the final OFC was calculated and statistically analyzed using the Kruskal-Wallis test. For analysis of the primary end point, a worst-case imputation was also used.

*Number of patients who did not tolerate ≥300 mg peanut protein (single eliciting dose of 3-300 mg) at the initial OFC but tolerated it at the final OFC.

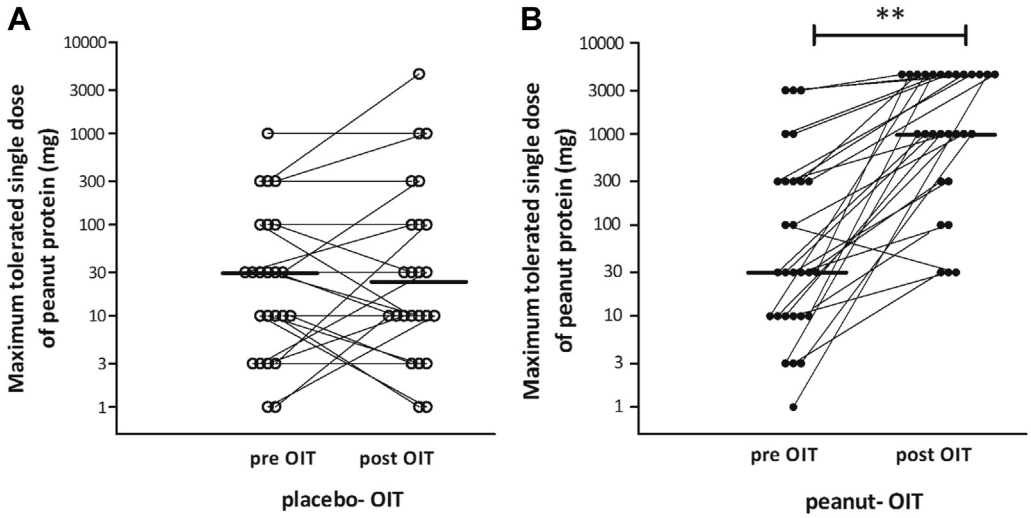


FIGURE 2. Maximum tolerated single dose of peanut protein before and after OIT. Shown are the maximum tolerated single doses of peanut protein at initial and final OFCs in (**A**) individual placebo-OIT patients and (**B**) peanut-OIT patients of the per-protocol population. The horizontal lines represent the median of the maximum tolerated single dose in each group. For the statistical analysis of the comparison of data before and after treatment within a randomization group, the Wilcoxon-test was used. $**P < .01$.

Safety

Two patients in each group discontinued because of AEs (6.5% of the total ITT population), 1 of these patients in each group because of a severe adverse event (SAE) being judged to be related to the OIT dose (Figure 1; for details, see this article's Dropouts section in the Online Repository and Table E2 in this article's Online Repository at www.jaci-inpractice.org).

All patients suffered from AEs. But only a small number of all placebo-OIT doses (1.2%) and 4.3% of all peanut-OIT doses were associated with AEs (=AEs related to OIT = occurring within 2

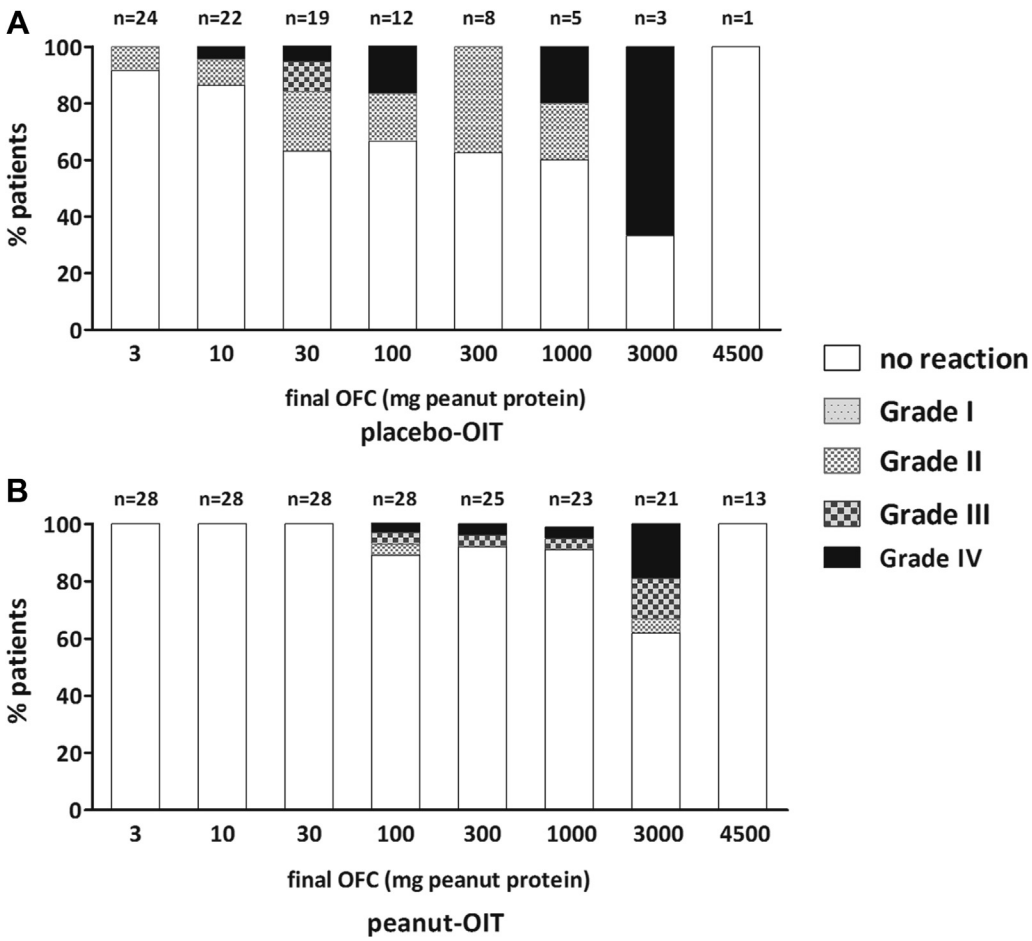


FIGURE 3. Grade of severity of allergic reactions during the final OFC at individual dose steps. Shown are the proportions of patients of (**A**) the placebo-OIT group and (**B**) the peanut-OIT group with their individual severity of symptoms at each dose step during the final OFC within the per-protocol population. Severity was graded using a modified grading system for food-induced anaphylaxis.[19,21]

hours after OIT ingestion; Table E3). There was a significantly higher proportion of OIT doses associated with AEs in the peanut-OIT group than in the placebo-OIT group ($P = .001$) mainly due to a significantly higher number of mild, subjective AEs related to peanut OIT (Table E3). Thus, significantly more patients of the peanut-OIT group (83%) suffered from subjective AEs related to OIT than patients of the placebo group (45%) ($P = .002$). Especially subjective symptoms such as tingling in the mouth, globus sensation, hawking, and abdominal pain were reported in a significantly higher number of patients receiving peanut OIT than in those receiving placebo (Table III; see Table E3). None of the subjective symptoms related to OIT had to be treated.

More than half the patients in both groups suffered from objective symptoms within 2 hours after ingestion of OIT (Table III). However, less than 1% of all OIT doses were associated with objective symptoms related to OIT (Table E3), mainly skin symptoms (hives and angioedema), vomiting, diarrhea, and coughing. There was no significant difference in the number of OIT doses associated with objective AEs, the number of patients suffering from objective AEs related to OIT, and the severity or the treatment of these symptoms between randomization groups (Tables III and E3).

Regarding individual objective symptoms, wheezing was the only symptom related to OIT reported significantly more often in the peanut-OIT group (in all 8 times by 6 patients) than in the placebo-OIT group (once by 1 patient; $P = .045$) (Tables III and E3). However, there was no difference between groups concerning all other individual symptoms, for example, coughing or shortness of breath (Tables III and E3). There were more OIT doses associated with objective AEs during the updosing phase than during maintenance, but to a similar extent in both groups (Table E3). Dose reductions due to AEs could be a sign of more severe AEs during OIT. However, 12 of 30 patients within the placebo-OIT group (40%) and 14 of 31 patients within the peanut-OIT group (45%) needed at least 1 dose reduction due to AEs during the course of OIT.

Five patients within the placebo-OIT group and 3 patients within the peanut-OIT group experienced an SAE (Table III; see Table E2 in this article's Online Repository at www.jaci-inpractice.org). In each group, 1 patient suffered from an SAE related to OIT and leading to study discontinuation as mentioned in more detail in this article's Online Repository at www.jaci-inpractice.org.

Within the placebo group, 14 patients experienced 24 allergic reactions, which were considered to be caused by an accidental ingestion of peanut. In contrast, only 5 patients of the peanut-OIT group experienced 8 accidental reactions ($P < .001$; Table III).

TABLE III. Patients with AEs related to OIT in the placebo-OIT and peanut-OIT groups

Patients with adverse events and treatment	Placebo-OIT group (n = 31)	Peanut-OIT group (n = 30)	*P* value
Total no. of AEs, n (%*)	2866 (20.7)	2515 (20.3)	0.71
Total no. of SAEs, n (%*)	5 (0.04)	3 (0.02)	0.73
No. of SAEs related to OIT, n (%*)	1 (0.007)	1 (0.008)	1.0
No. of patients who discontinued the study because of AEs, n (%†)	2 (6.5)	2 (6.7)	1.0
No. of patients with …/receiving …			
AEs related to OIT, n (%†)	24 (77.4)	27 (90.0)	0.3
Subjective AEs related to OIT, n (%†)	14 (45.2)	25 (83.3)	**0.002**
OAS related to OIT, n (%†)	8 (25.8)	18 (60.0)	**0.007**
Abdominal pain related to OIT, n (%†)	6 (19.4)	20 (66.7)	**<0.001**
Nausea related to OIT, n (%†)	2 (6.5)	7 (23.3)	0.06
Skin itching related to OIT, n (%†)	7 (22.6)	7 (23.3)	0.94
Joint pain/headache/throat pain related to OIT, n (%†)	2 (6.5)	6 (20)	0.12
Objective AEs related to OIT, n (%†)	21 (67.7)	19 (63.3)	0.72
Skin symptoms related to OIT (contact urticaria, flush, generalized hives, angioedema), n (%†)	8 (25.8)	12 (40.0)	0.24
GI symptoms related to OIT (vomiting, diarrhea), n (%†)	7 (22.6)	8 (26.7)	0.71
URT symptoms related to OIT (conjunctivitis, rhinitis, sneezing, rhinoconjunctivitis), n (%†)	10 (32.3)	9 (30.0)	0.85
Laryngeal symptoms related to OIT (hoarseness, stridor), n (%†)	1 (3.2)	1 (3.3)	0.98
Lower respiratory tract symptoms related to OIT (coughing, wheezing, shortness of breath), n (%†)	9 (29.0)	13 (43.3)	0.25
Coughing related to OIT, n (%†)	6 (19.4)	11 (36.7)	0.13
Wheezing related to OIT, n (%†)	1 (3.2)	6 (20.0)	**0.04**
Shortness of breath related to OIT, n (%†)	4 (12.9)	3 (10.0)	0.72
Cardiovascular symptoms (drop in blood pressure, unconsciousness) related to OIT, n (%†)	1 (3.2)	0 (0.0)	1.0
AEs related to OIT of severity grade I, n (%†)	5 (16.1)	7 (23.3)	0.48
AEs related to OIT of severity grade II, n (%†)	10 (32.2)	11 (36.7)	0.72
AEs related to OIT of severity grade III, n (%†)	13 (41.9)	10 (33.3)	0.49
AEs related to OIT of severity grade IV, n (%†)	4 (12.9)	7 (23.3)	0.29
AEs related to OIT of severity grade V, n (%†)	1 (3.2)	0 (0.0)	0.32
Treatment for AEs related to OIT, n (%†)	9 (29.0)	12 (40.0)	0.37
Systemic antihistamines for AEs related to OIT, n (%†)	6 (19.4)	8 (26.7)	0.55
Systemic steroids for AEs related to OIT, n (%†)	4 (12.9)	4 (13.3)	1.0
Inhalant salbutamol for AEs related to OIT, n (%†)	5 (16.1)	6 (20.0)	0.69
Adrenaline for AEs related to OIT, n (%†)	0 (0.0)	0 (0.0)	1.0
New sensitization to inhalant allergens after OIT, n	(n = 24) 10	(n = 28) 11	1.0
New diagnosed atopic diseases after OIT, n	(n = 24) 4	(n = 28) 5	1.0
Worsening of atopic diseases after OIT, n	(n = 24) 8	(n = 28) 4	0.1
Accidental reactions, total n (average per person)	24 (0.77)	8 (0.27)	**<0.001**
No. of patients with accidental reactions, n (%†)	14 (45.2)	5 (16.7)	**0.026**

GI, Gastrointestinal; *OAS*, oral allergy syndrome; *URT*, upper respiratory tract.

Data present the occurrence of AEs and the number of patients with AEs related to OIT during the study in both randomization groups. Severity was graded using a modified grading system for food-induced anaphylaxis.[19,21]

Bold indicates statistical significance ($P < .05$).

*% of all OIT doses within the randomization group.

†% of all patients within the randomization group.

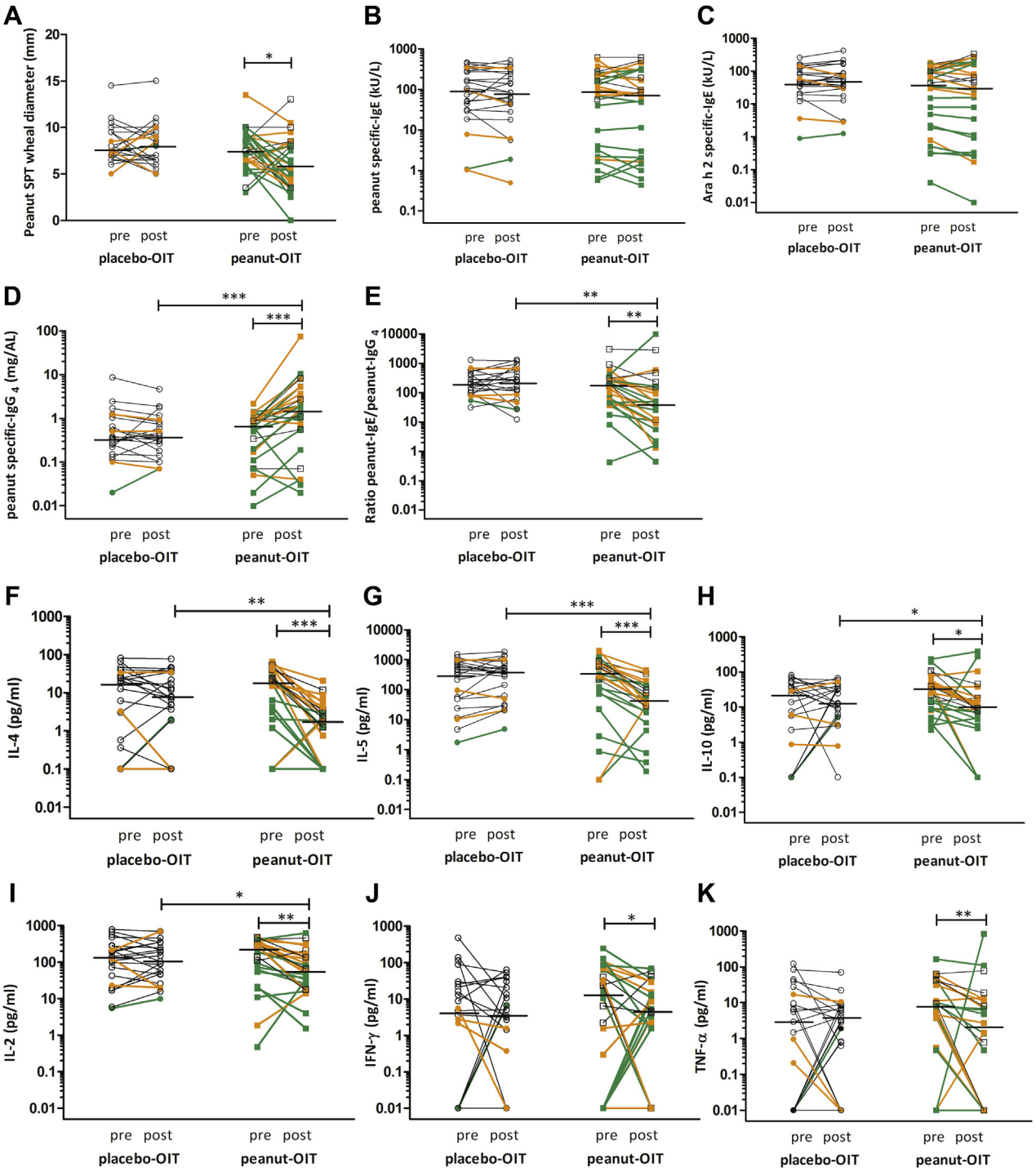
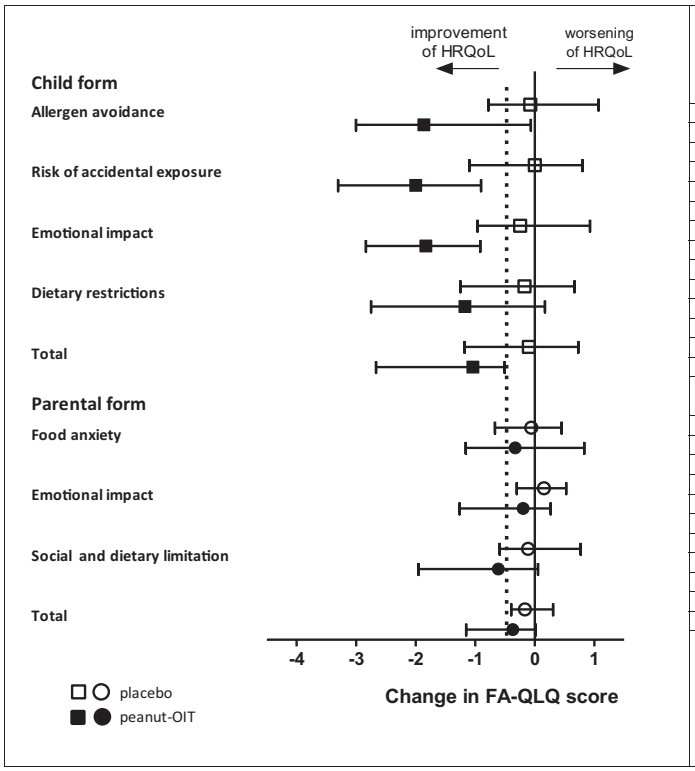


FIGURE 4. Immunologic changes from baseline (pre-OIT) to post-OIT at the final OFC of the per-protocol population. Shown are wheal size diameter of peanut SPT (**A**), peanut-specific IgE (**B**), Ara h 2–specific IgE (**C**), peanut-specific IgG_4 (**D**), ratio of peanut-specific IgE/peanut-specific IgG_4 (**E**), IL-4- (**F**), IL-5- (**G**), IL-10- (**H**), IL-2- (**I**), IFN-γ- (**J**), and TNF-α production (**K**) after *in vitro* stimulation of PBMCs with peanut extract minus the amount of cytokine production after stimulation with medium. Black lines represent median values. Black circles/squares represent patients tolerating a maximum dose of up to 100 mg, orange circles/squares represent patients tolerating a maximum dose of 300 to 3000 mg, and green circles/squares represent patients tolerating a maximum dose of 4500 mg peanut protein at the final OFC. For the statistical analysis of the comparison of data before and after treatment within a randomization group, the Wilcoxon-test was used. For the intergroup comparison, the median changes from baseline in each group were calculated and analyzed by the Kruskal-Wallis test (*$P < .05$; **$P < .01$; ***$P < .001$).



Median [IQR] change	n/n possible patients to analyze	p-value
-0.1 [-0.8-1.1]	8/9	.08
-1.9 [-3- -0.1]	9/11	
0 [-1.1-0.8]	8/9	**.02**
-2.0 [-3.3- -0.9]	9/11	
-0.3 [-1.0-0.9]	8/9	**.02**
-1.8 [-2.8- -0.9]	9/11	
-0.2 [-1.3-0.7]	8/9	.23
-1.2 [-2.8-0.2]	9/11	
-0.1 [-1.2-0.7]	8/9	.10
-1.0 [-2.7- -0.5]	9/11	
-0.1 [-0.7-0.5]	18/21	.61
-0.3 [-1.2-0.8]	20/27	
0.2[-0.3-0.5]	18/21	.17
-0.2 [-1.3-0.3]	20/27	
-0.1 [-0.6-0.8]	18/21	.16
-0.6 [-2.0-0.1]	20/27	
-0.2 [-0.4-0.31]	18/21	.20
-0.4 [-1.2-0.02]	20/27	

FIGURE 5. Change in HRQOL after OIT. Presented is the median change in total and each domain score for the FAQLQ-CF and FAQLQ-PF for each study group after OIT in the per-protocol population. Open symbols represent the placebo group, filled symbols the peanut-OIT group, and dotted the MCID. The greater the negative change in score the better is the improvement in HRQOL. The Kruskal-Wallis test was used for a group comparison. *P*, Statistical significance, bold values represent a significant change in HRQOL after OIT when placebo and active groups are compared.

After the course of OIT, no difference was found concerning the number of patients in the 2 groups with newly diagnosed atopic diseases (bronchial asthma, atopic dermatitis, allergic rhinoconjunctivitis), with new sensitization to 1 of the inhalant allergens tested or with worsening of established atopic diseases at baseline (Table III).

Immunologic parameters

There were no significant differences between the peanut-OIT and placebo-OIT groups concerning the baseline levels of immunologic parameters (Table I; Figure 4). Comparing immunologic markers within 1 randomization arm before and after OIT, a significant reduction in the wheal size of the peanut SPT and peanut-specific IL-4, IL-5, IL10, IL-2, IFN-γ, and TNF-α production by PBMCs, a significant increase in peanut-specific-IgG_4 levels, and decrease in the ratio of peanut-specific-IgE to IgG_4 could be noted for the peanut-OIT group but not for the placebo-OIT group (Figure 4). There was no significant change before and after OIT within 1 randomization arm for peanut- and Ara h 2—specific IgE. When comparing the median changes from baseline between randomization arms, a significant increase in peanut-specific-IgG_4 and decrease in the ratio of peanut-specific-IgE/IgG_4 as well as a significant reduction in production of IL-4, IL-5, IL-10, and IL-2 could be demonstrated for the peanut-OIT group in comparison to the placebo-OIT group (Figure 4). There were no significant differences between groups for the changes in wheal size of peanut SPT, peanut-specific IgE, Ara h 2—IgE, and production of IFN-γ and TNF-α (Figure 4).

HRQOL and BOT

Before start of OIT, baseline HRQOL did not differ between the placebo and active groups in all domains except for the domain of "risk of accidental exposure" in children (see Table E4 in this article's Online Repository at www.jaci-inpractice.org). After the final OFC, mothers of both study groups (n = 38) filled out the FAQLQ-PF after a median of 9.5 weeks (IQR, 5-15.3 weeks) and children (n = 17) filled out the FAQLQ-CF after a median of 11 weeks (IQR, 7-16 weeks) after the final OFC. Taking a minimum clinically important difference (MCID) of 0.5 for a significant clinical improvement in HRQOL after an intervention,[27] mothers of the peanut-OIT group but not the placebo-OIT group reported a median improvement in HRQOL of greater than 0.5 in score within the domain of "social and dietary limitations" after OIT (Figure 5). There was no meaningful median change in HRQOL reported by mothers within the total score and the domains of emotional impact and food-related anxiety in the placebo group or the peanut-OIT group (Figure 5). However, on comparing the placebo and active groups, we found that there was no significant

group difference in median change in HRQOL for all domains of the FA-QLQ-PF reported by mothers after OIT.

When children reported on a possible change in HRQOL before and after OIT (Figure 5), the median improvement for the total score as well as for each domain of the FAQLQ-CF exceeded the MCID of 0.5 in the peanut-OIT group. Within the placebo group, median changes ranged between 0 and 0.25. By group comparison, children of the peanut-OIT group reported a statistically significant improvement in HRQOL within the 2 domains of "risk of accidental exposure" and "emotional impact" when compared with the placebo group.

BOT measures during OIT could be analyzed from 50 of 56 mothers and 21 of 23 children, which were answered a median of 20.5 weeks (IQR, 19-23 weeks) after starting OIT. Twenty-two of 27 mothers (82%) of the peanut-OIT group and all mothers of the placebo group (n = 23) reported a positive BOT (=BoT score, 1-3). Only 1 mother from the peanut-OIT group (3.7%) and 2 from the placebo group (8.7%) would not perform OIT again. Nine of 11 children of the active group (82%) and 9 of 10 children of the placebo group (90%) were positive about their treatment. One child of each group spoke against performing OIT again.

DISCUSSION

Efficacy

This study is the first study to target highly sensitive patients with peanut allergy with a low-dose peanut OIT in a randomized, placebo-controlled fashion showing a good efficacy for clinical desensitization, an excellent safety profile, a prevention of accidental reactions, immunomodulatory capacity, improvement in HRQOL, and a low BOT. Efficacy was highly significant, with 74% of the active group meeting the primary end point in tolerating a dose of at least 300 mg peanut protein at final challenge in contrast to only 16% of the placebo group. For the first time ever, we report also on a significant reduction in the number of accidental reactions during OIT within the active group (n = 8) versus the placebo group (n = 24).

Even with a slow, long-term updosing period (median, 13 months) and a low maintenance dose (median, 125 mg peanut protein), efficacy in this placebo-controlled trial on peanut OIT is similar to that in other studies on OIT using higher maintenance doses and a shorter updosing period, challenging the hypothesis that a higher maintenance dose may lead to better efficacy. Comparing efficacy for desensitization in studies on peanut OIT is difficult because of the variations in recruited study populations, maintenance doses, duration of updosing and maintenance, and the definition of the end point for desensitization.

However, our result of the primary end point is almost equal to 2 recently published trials on peanut OIT that recruited a similar risk group of children of a similar age and degree of sensitization who were highly allergic to peanut, also including children with a history of anaphylaxis.[15,18] Using a higher maintenance dose of 300 mg peanut protein than in our study, Bird et al[18] reported on 79% of patients within the active group tolerating at least 300 mg peanut protein at final challenge in comparison to 19% of the placebo group. Choosing an even higher maintenance dose of 800 mg peanut protein, Kukkonen et al[15] were able to demonstrate in a noncontrolled trial that 67% of the children in their peanut-OIT group tolerated a maximum cumulative dose of 1255 mg peanut protein at final challenge,[15] which might be comparable to our results, with 68% of the active group tolerating a cumulative dose of 1443 mg peanut protein (data not shown) at the final OFC. Recently published in a direct comparison, Vickery et al[16] also demonstrated that using a very high maintenance dose (eg, 3000 mg peanut protein) does not lead to a better efficacy than using a lower maintenance of 300 mg.

Interestingly, in this study, we could also show that even a lower maintenance dose than the planned one of 125 mg/250 mg peanut protein lead to a reasonable efficacy: 14 of the active patients did not reach their planned maintenance dose but had a median maintenance dose of 50 mg peanut protein (range, 2.5-225 mg peanut protein). Nine of these 14 (64%) tolerated at least 300 mg peanut protein at the final OFC. In contrast, only 1 of 12 patients of the placebo group who did not reach their planned maintenance dose reached the primary end point with a median maintenance dose of "32.5 mg peanut protein" (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

In choosing the dose of at least 300 mg peanut protein to be tolerated at the final OFC as the primary end point we aimed for protection from severe allergic reactions to accidental ingestion of peanut in most of the patients within the active group, after OIT. Recently, Baumert et al[28] demonstrated in a model for quantitative risk assessment that an increase in the eliciting dose to greater than or equal to 300 mg peanut protein after OIT or even more—as in our case to greater than or equal to 1000 mg as the eliciting dose—would lead to a significantly higher and clinically meaningful reduction in the risk of experiencing an accidental allergic reaction after eating snack chips mixes, cookies, doughnuts, or ice cream in patients with peanut allergy.[28] Our results strengthen this risk assessment. This is the first report directly demonstrating a protection from accidental reaction by OIT with a significant reduction in the number of accidental reactions within the peanut-OIT group in comparison to the placebo group (Table III). Thus, we could demonstrate that low-dose OIT clinically desensitizes most of the patients with peanut allergy to an extent that they are protected from severe allergic reaction after unintended exposure.

This study included 14 patients who tolerated greater than or equal to 300 mg peanut protein at the initial OFC (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). Although receiving a low maintenance dose of only 225 to 250 mg peanut protein, this group of patients also seemed to profit from OIT. Eighty percent of the patients of the active group with a maximum tolerated dose of 300 mg peanut protein and 100% of the active patients tolerating 1000 mg or 3000 mg peanut protein at the initial OFC passed the final OFC with a maximum dose of 4500 mg peanut protein. Immunologic modulation and a reduction in accidental reactions seemed to occur in the active treated patients. More moderate AEs related to OIT such as wheezing seemed to be a rare event. These results generate the hypothesis that this group of patients might be a good target population for peanut OIT outside of specialized OIT centers. But further studies with a larger population with this kind of patients have to confirm this hypothesis.

Safety

Similar to other published studies on peanut-OIT[8,10,11,29] including the 2 placebo-controlled trials,[17,18] in our study 90% of the patients of the active group suffered from AEs related to OIT, mainly mild to moderate in severity (Table III). Also, most of these symptoms were of subjective nature. About two-thirds of

patients in the peanut-OIT group suffered at least once from symptoms of the oral cavity and/or abdominal pain. However, more than three-quarters of the placebo group (77%) also experienced treatment-related AEs.

On comparing the active and placebo groups, there was no difference in the number of dropouts due to AEs, occurrence of SAEs and objective, OIT-related AEs, severity of symptoms, treatment of symptoms, or worsening of preexisting atopic diseases. The only highly significant difference between the groups could be demonstrated for the 2 subjective symptoms of oral allergy syndrome and abdominal pain. "Wheeze" was the only objective, OIT-related symptom that occurred significantly more often in the active group versus the placebo group in this study. But with only a lower significance ($P = .04$) the clinical significance is debatable because there was no difference when treatment with salbutamol was analyzed in both groups (Tables III and E3).

Our excellent safety profile might result from the slow updosing and the low maintenance dose used in this protocol. Looking at the proportion of dropouts (13%-21%) in other studies recruiting a similar study population but using faster updosing and a higher maintenance dose,[14,15,18] the proportion of dropouts due to AEs (6.7%) in this study is much lower. There was no need of epinephrine treatment for AEs related to OIT and absence of development of eosinophilic esophagitis. Moreover, antihistamine and steroid treatment was lower than previously reported by others.[15]

Immunologic changes

Similar to results of studies published previously, we were able to demonstrate a reduction in peanut SPT and a marked increase in peanut-specific IgG_4 after OIT in comparison to the placebo group.[8,16-18] Uniquely, like in our pilot trial[8] but now shown for the first time in comparison to a placebo group, we again found not only an *in vitro* peanut-specific suppression of T_H2 cytokines such as IL-4 and IL-5 but also a general suppression of cytokine production for IL-2, IL-10, IFN-γ, and TNF-α in the peanut-OIT group after OIT. No change was noted in the placebo-OIT group. Similar results for the possible induction of anergy but not for a shift to T_H1 cytokine upregulation were also reported by Gorelik et al.[30] They demonstrated a reduction not only in IL-5- and IL-13- but also in IFN-γ-, IL-10-, and TNF-α production of $CD4^+$ T cells cocultured with myeloid dendritic cells after 12 months of a maintenance peanut OIT with 2 g of peanut protein ingested daily.

HRQOL and BOT

After peanut OIT there was a significant improvement in HRQOL (decrease in score) for the domain of "risk of accidental exposure" and "emotional impact" in children when compared with the placebo group approximately 11 weeks after the final OFC. If one considers an improvement of more than 0.5 MCID as significant,[27] the HRQOL even improved for all domains in children and for the domain of "social and dietary limitations" in mothers' proxy reports of the active group. This is the first trial on OIT showing a significant improvement in HRQOL after OIT in a placebo-controlled study design. Two previously published studies on peanut OIT showed a significant improvement in HRQOL after OIT in parents' proxy reports[13,31] and in children and teenagers reports[31] using the same questionnaires but not comparing their results to a control group.

To our knowledge, this is the first time that BOT has been analyzed for an OIT study. Although patients and parents had to cope with a daily therapy that might have also elicited disgust, AEs, and included also a daily 2-hour interval of parental monitoring of their children, most mothers and children reported (after a median of 4 months on OIT) being positive (=low BOT) about this treatment and would start this kind of therapy again.

Study limitations

Because an unblinded OFC protocol was used in this study, overreporting of allergic reactions during baseline OFCs and underreporting at final OFCs due to change in attitude of the children toward peanut ingestions might have occurred. However, efficacy results are so robust and similar to other efficacy data on peanut OIT published so far,[15,18] this effect seems marginal. In addition, the OFC protocol used in this study—with a 2-hour interval between dose steps[19]—differs from other OFC protocols used in OIT trials, possibly changing the sensitivity of threshold and severity of reactions during OFC, which might impact the efficacy data of this trial. However, the eliciting dose for peanut-induced allergic reactions in 5% of this study population (ED_{05})[19] is comparable to the ED_{05} of other published peanut-allergic populations being challenged with 15- to 30-minute intervals.[32-34] Therefore, the sensitivity for threshold might not be too different from that in other published studies on peanut OIT. Because of differences in the reporting of the severity of reaction during OFC, the data of this current study cannot be compared with others. Therefore, it might well be that because of a 2-hour interval between dose steps more severe reactions could have been avoided.

Summary

We have been able to demonstrate for the first time in a placebo-controlled way that using a low maintenance dose in peanut OIT has a very good safety profile with an efficacy similar to that reported by other studies using higher maintenance doses. Treatment with low-dose peanut OIT leads to immunologic changes, pointing to the possible development of immunologic anergy due to OIT. Despite daily treatment and daily monitoring for 2 hours, children showed a significant improvement in HRQOL after OIT, which was demonstrated here for the first time in a placebo-controlled manner. Furthermore, the overall BOT seems to be very low for this kind of therapy. However, further placebo-controlled, long-term studies with a larger number of patients, especially including more teenagers, are needed to verify the reduction in allergic reaction after accidental exposure due to OIT and to further evaluate safety.

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ONLINE REPOSITORY

METHODS

Study centers

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Preparation and dosing of OIT

For proper blinding of OIT, a special chocolate pudding vehicle was used during this study developed by the EuroPrevall project by the Institute of Food Research (Norwich, UK) based on a system devised by Unilever R&D BV (Vlaardingen, Netherlands).[E1] It is a well-standardized vehicle and shows good reproducibility, homogenicity, and blinding capacities, and a long shelf life (up to 6 months as the pudding base). Three sets of chocolate peanut/placebo pudding bases were produced every 4 to 5 months: (1) "high-dose" recipe (5 mg peanut protein/mL in final "ready-to-eat" pudding), (2) "low-dose" recipe (1 mg peanut protein/mL in final "ready-to-eat" pudding), and (3) an allergen-free recipe (placebo). All materials for the pudding bases were stored in a microbiologically stable manner. The pudding bases during the study were prepared in a food-grade environment (the main hospital kitchen of the Charité, Berlin). All equipment was thoroughly washed with detergent before use so that any dust or allergenic material was removed. The following ingredients were used for the chocolate pudding bases: cold swelling starch (ULTRA-TEX 4; National Starch, Hamburg, Germany), cocoa powder (Cebe Cacao, lightly defatted; Wilhelm Reuss, Berlin, Germany), rapeseed oil (Karl Heidenreich GmbH, Mannheim, Germany), icing sugar (sweet family Nordzucker, Braunschweig, Germany), sweetener (Huxol, Nutrisun, Seevetal, Germany), and Tween 60 (Croda, Singapore). Because the vehicle contains Tween 60 (polysorbat 60, E435), all study participants had to weigh at least 13 kg. Peanut flour (light roasted, 12% fat, 50% protein) from Byrd Mill Company was used as the peanut protein source; 128.57 g of the chocolate peanut/placebo pudding bases was transferred into a container and was stored in a cool dark condition (20°C) for up to 6 months.

Before distribution to the patient, the microbiological safety of each batch of the chocolate peanut/placebo pudding base was checked by Institute Fresenius (Berlin, Germany) according to national and international standards. Testing included total bacterial counts, tests for yeasts, molds, and lactic acid bacteria as well as surveillance for indicator microorganisms (Enterobactereriacae, sulfite-reducing clostridia) and pathogens (*Salmonella spp*, *Bacilli spp, Staphylococcus aureus*, *Clostridium perfringens*, *Listeria monocytogenes*, *Escherichia coli*, *Campylobacter spp*, *Vibrio cholerae*, and *Yersinia enterocolitica*). Each batch was also tested for peanut protein quantification and homogeneity verification determining the allergen-free status of the chocolate placebo pudding, the homogeneity of the chocolate peanut pudding, and the stability of protein doses between batches.

Every 7 to 14 days, parents had to prepare the "ready-to-eat," hydrated pudding themselves. Parents were thoroughly instructed and taught how to prepare the "ready-to-eat pudding" to ensure good homogeneity. They had to pour 300 mL of bottled water into each container of the pudding bases and mix it thoroughly with an electric mixer. This freshly made pudding was divided into smaller portions that were then frozen at home for a maximum of 40 days. Every 2 days a storage box of frozen "ready-to-eat" pudding was defrosted. The patient's individual dose of pudding was measured using different sized spoons. The volumes were exact if the whole spoon was filled with the pudding, and leveled off by a flat edge knife and extra pudding being removed from the sides. The exact dosing schedule is outlined in Table E1.

Peanut protein quantification and homogeneity testing of pudding bases

Using a Kjeldahl total nitrogen method,[E2] 51.0% (0.6% coefficient of variation [CV]) total protein was determined in defatted peanut flour (Byrd Mill Company) used for the preparation of low- and high-dose dessert bases, confirming the manufacturer's information of a total protein content of 50% within the peanut flour. Accordingly, for further investigation of peanut protein quantity and homogeneity using ELISA, 50% peanut protein in peanut flour was assumed. Thus, according to the recipe, the high- and low-dose pudding bases should contain 1.7% or 0.34% peanut protein, respectively. Using a previously described peanut-specific ELISA,[E3] the presence and quantity of peanut protein was investigated in 10 placebo batches, 11 low-dose pudding bases, and 15 high-dose pudding bases. From each of these, a total of ten 4-g subsamples were randomly drawn, individually extracted, and analyzed in each triplicate dilution and triplicate wells per dilution. In placebo pudding bases, peanut protein was not detectable (with a limit of detection of 0.1 ppm or 0.00001% peanut protein). Considering that final, "ready-to-eat" chocolate pudding portions are made of 1:3.333 dilution of pudding base in water, peanut protein is absent or below 0.03 ppm in placebo meals. As a worst-case calculation, peanut protein at the limit of detection would theoretically translate to a peanut protein dose of 1.5 μg for the largest portion (50 mL) given to patients.

With a median recovery (ratio of protein quantified and protein added according to recipe) of 88% (range, 73%-115%), the amount of peanut protein of 0.34% and 1.7% was analytically confirmed in all batches of low- and high-dose pudding (Figure E1, *A*). Furthermore, all batches of high-dose pudding showed homogeneous distribution of peanut protein with mean CV of less than 15% (Figure E1, *B*). In 10 of 11 low-dose pudding bases, a homogeneous peanut protein distribution with mean CV of less than 15% was determined. With 15.3% CV in 1 of 11 low-dose dessert bases, the upper limit of the 95% CI slightly exceeded the set limit of 15% mean CV but was still interpreted as presenting acceptable homogeneity. Statistical significance was achieved in most cases in which the *P* value was less than .0001. For this above-described batch and all the following batches, patients had to step 1 step down in their dosing schedule and be monitored when consuming a new batch for the first time. Ready-to-eat chocolate pudding stored frozen

showed 91.5% of detectable peanut protein compared with freshly made chocolate pudding.

Statistical analyses: Power calculation

For the primary end point, efficacy rates were assumed to be 65% in the peanut-OIT group and 15% in the placebo-OIT group on the basis of our previously published data.[E4] With an assumed dropout rate of 20%, a target sample size of 56 patients (randomized 1:1 to both groups) was calculated to provide at least 90% power ($\alpha/2 = 0.025$; 1-sided Fisher exact test).

Standard operating procedures for safety

During the inpatient phase (at challenge and start of OIT), emergency training for the emergency kit was repeated. The emergency kit included 2 epinephrine autoinjectors, oral antihistamine, an oral corticosteroid or suppository, and beta2-agonist for inhalation. Families were advised that the kit should be available at all times. A 24-hour-telephone hotline by medical doctors was available to answer questions regarding dosing and AEs. Parents were instructed to monitor their children for 2 hours after the intake of peanut/placebo OIT. Patients were advised to avoid strenuous physical activity during this time, to carry the emergency medication (eg, 2 epinephrine autoinjectors) at all times, and to strictly avoid peanuts otherwise.

Reasons and procedure for OIT-dose reductions

- If symptoms were considered to be a viral or bacterial infection, the advice was to continue with 50% of the previous daily OIT dose. This 50% of the dose was given for 3 days, followed by another 3 days with 75% of the dose. After that the full dose could be ingested again (ie, "dosing scheme for infections"). This reduction and updosing was done at home. Patients had to be stable on this dose for further 14 days until another updosing to a new dose could occur in the clinic.
- If symptoms were considered to be due to an accidental reaction or the patient received a vaccination or an elective operation, the OIT dose was skipped that day and for the following days the "dosing scheme for infections" was applied.
- For safety reasons, doses were reduced by 1 dose step if a new charge of chocolate peanut/placebo-pudding bases was used.
- If a mild related or nonrelated AE (severity grade I) or a mild AE at updosing or a subjective AE occurred, the same dose was given the next day at home.
- If an objective, moderate related AE (severity grades II-IV) or an objective, moderate AE at updosing occurred, either the "dosing scheme for infections" or a reduction in dose (1 step down) was applied at home as determined by the study physician. The subsequent updosing was performed in the study center.
- If a moderate nonrelated AE (severity grades II-IV) occurred, either the "dosing scheme for infections" or a reduction in dose (1 step down) was applied or the same dose was given for another 14 days before updosing.
- If recurrent mild related or recurrent nonrelated AEs (especially gastrointestinal symptoms) were detected, the dose was reduced by 1 step.
- If recurrent related or nonrelated pulmonary symptoms at a certain dose occurred, a more vigorous dose reduction was performed (2-12 dose steps down) as was determined by the study physician. The doses were then increased every 14 days at home until the former dose was reached.

Early termination of the treatment

- OIT treatment was terminated if a patient showed objective symptoms related to OIT (within 2 hours of the OIT dose) repeatedly, every time the dose was increased above a certain level. A maximum of 3 trials for updosings were tried before early termination was considered.
- OIT treatment was terminated if there was an SAE related or possibly related to OIT. This was defined as an SAE occurring within 2 hours of OIT ingestion. Events were categorized as SAEs if they were life-threatening, resulted in any kind of hospitalization (included if only for monitoring), disability, congenital anomaly, and death or were otherwise deemed an important medical event.
- OIT treatment was terminated by or on behalf of the patient's decision.
- OIT treatment was terminated by the study physician because of safety concerns (eg, insufficient adherence to protocol, or recurrent gastrointestinal AEs possibly related to OIT).

HRQOL measures

To measure changes in HRQOL, the German translation of the FAQLQ was sent out to parents (FAQLQ-PF,[E5] parental form, proxy measurement), children (FAQLQ-CF,[E6] child form), and teenagers (FAQLQ-TF,[E7] teenage form) 4 weeks before the initial OFC and 4 weeks after the final OFC. Mothers of children 3 to 12 years old, children 8 to 12 years old, and teenagers 13 to 17 years old were asked to fill out the forms at home and to send them back to the study unit. FAQLQ-TFs were not included in data analysis due to the small number of teenagers in the study (active group: $n = 1$; placebo group: $n = 5$). Depending on the age of the child, the FAQLQ-PF included 26 to 30 items in 3 domains (emotional impact, food-related anxiety, and social and dietary limitations). It measured the parent's report on the child's HRQOL from the child's perspective. The FAQLQ-CF included 24 items in 4 domains (allergen avoidance, risk of accidental exposure, emotional impact, and dietary restrictions). The scoring system was a 7-point Likert scale ranging from either 0 in the FAQLQ-PF or 1 in the FAQLQ-CF (= no impact on HRQOL) to 6 in the FAQLQ-PF or 7 in the FAQLQ-CF (= extreme impact on HRQOL). To harmonize both scales in data analysis, the raw scores 0 to 6 in the FAQLQ-PF were recorded as 1 to 7, as in other studies.[E6,E8] For comparison of changes in HRQOL before and after OIT in both study groups, only complete data sets were considered for analysis (per-protocol analysis). The mean total and mean domain scores were calculated for each child/mother.

RESULTS

Dropouts

Ten of 62 patients discontinued during the study (see Figure 1): 1 patient of the peanut-OIT group withdrew consent after randomization but before receiving the allocated intervention. Two patients of each randomization group discontinued because of AEs: Within the placebo-OIT group, 1 patient suffered from sudden abdominal pain, sleepiness, followed by rhinoconjunctivitis, vomiting, and unconsciousness 75 minutes after intake of the placebo-OIT dose and 15 minutes after eating a cookie from a friend. Because of the severity of symptoms (severity grade V), this event was considered an SAE related to OIT (and thus—following the protocol—the patient had to be excluded). Another patient in the placebo-OIT group

experienced a worsening of known episodes of recurrent obstructive bronchitis in the winter not related to OIT. Although the pulmonary situation stabilized after a reduction of the placebo-OIT dose, the mother decided to discontinue the study. One patient of the peanut-OIT group suffered from abdominal pain, rhinoconjunctivitis, swelling of the eyes and lips, generalized hives, and dry cough (severity grade III) 45 minutes after ingestion of 125 mg peanut protein-OIT dose during physical activity outside during the summer. After treatment with inhalant salbutamol, systemic antihistamines, and steroids, the patient was admitted to hospital for monitoring, and per protocol, the patient had to be excluded from the study. The patient was known to suffer from seasonal allergic rhinoconjunctivitis due to grass pollen sensitization and bronchial asthma. Before this event the patient had had to be downdosed due to gastrointestinal symptoms. In the winter, 1 patient in the peanut-OIT group experienced recurrent infections of the upper airways and coughs, rhinoconjunctivitis, and shortness of breath not related to OIT. After a 50% reduction in the OIT dose, symptoms remained. The family decided to stop OIT. The patient was highly sensitized to house dust mite and suffered from bronchial asthma and perennial rhinoconjunctivitis before starting OIT.

In the placebo group, 1 patient did not adhere to the study protocol; 2 patients withdrew consent during the build-up phase; 1 patient refused to finish the OFC because of fear of allergic reactions during the final oral OFC; and 1 patient experienced a severe protocol deviation. This patient suffered from worsening of gastrointestinal symptoms during the build-up phase of the placebo OIT. Although receiving a 75% stepdown in dosing, the symptoms remained. The chocolate pudding vehicle was sent back to the study center, where it was noticed that the patient received 1 charge of the wrong peanut-chocolate pudding vehicle. The investigator decided that the patient should be excluded.

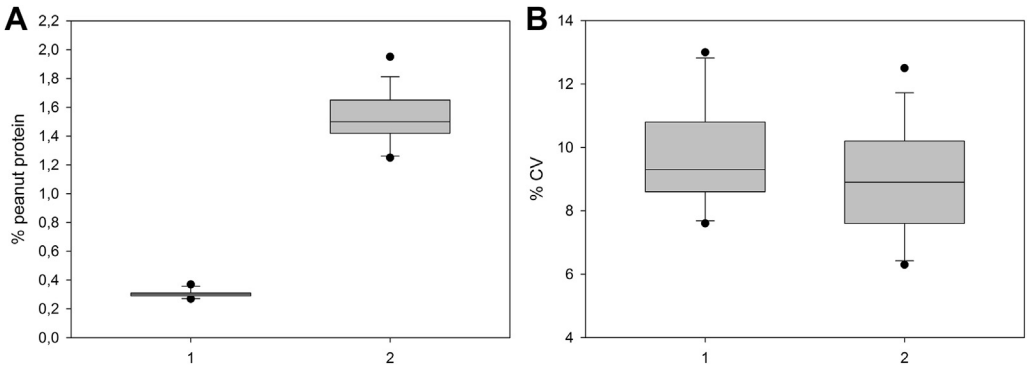

FIGURE E1. Peanut protein quantification and homogeneity in different batches of low-dose and high-dose pudding bases. Box-plot analysis of low-dose (1) and high-dose (2) pudding bases. Percentage of peanut protein quantified (**A**), and variation of homogeneity expressed as mean % CV (**B**).

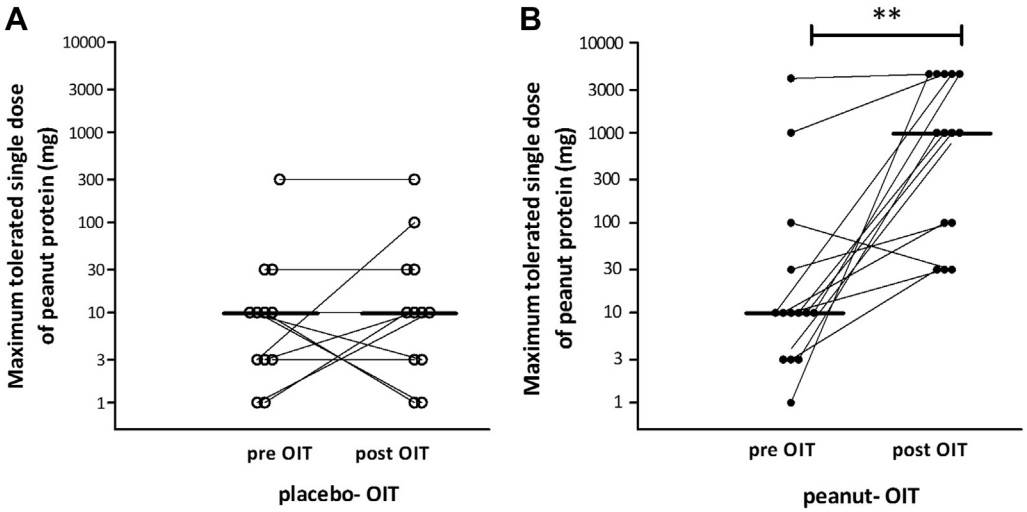

FIGURE E2. Maximum tolerated single dose of peanut protein before and after OIT of patients not reaching their planned maintenance dose. Shown are the maximum tolerated single doses of peanut protein at initial and final OFCs in (**A**) individual placebo-OIT patients not reaching the planned maintenance dose with a median maintenance dose of "32.5 mg placebo (range, 3.5-150 mg)" and (**B**) peanut-OIT patients not reaching the planned maintenance dose with a median maintenance dose of 50 mg peanut protein (range, 2.5- 225 mg) of the per-protocol population. The horizontal lines represent the median of the maximum tolerated single dose in each group. For the statistical analysis of the comparison of data before and after treatment within a randomization group, the Wilcoxon-test was used. $**P < .01$.

TABLE E1. Dosing schedule of "ready-to-eat" chocolate peanut/placebo pudding for OIT

	Active				Placebo
Incremental steps	Peanut protein concentration of "ready-to-eat" pudding (mg protein/mL)	Whole peanut (mg)	Peanut protein (mg)	Volume of pudding (mL)	Peanut protein concentration of "ready-to-eat" pudding (mg protein/mL)
1	1.0	2.0	0.5	0.5	0
2	1.0	4.0	1.0	1.0	0
3	1.0	6.0	1.5	1.5	0
4	1.0	10.0	2.5	2.5	0
5	1.0	12.0	3.0	3.0	0
6	1.0	14.0	3.5	3.5	0
7	1.0	18.0	4.5	4.5	0
8	1.0	22.0	5.5	5.5	0
9	1.0	26.0	6.5	6.5	0
10	1.0	32.0	8.0	8.0	0
11	1.0	38.0	9.5	9.5	0
12	1.0	44.0	11.0	11.0	0
13	1.0	52.0	13.0	13.0	0
14	1.0	60.0	15.0	15.0	0
15	1.0	70.0	17.5	17.5	0
16	1.0	80.0	20.0	20.0	0
17	1.0	90.0	22.5	22.5	0
18	1.0	100.0	25.0	25.0	0
19	1.0	120.0	30.0	30.0	0
20	5.0	140.0	35.0	7.0	0
21	5.0	160.0	40.0	8.0	0
22	5.0	180.0	45.0	9.0	0
23	5.0	200.0	50.0	10.0	0
24	5.0	240.0	60.0	12.0	0
25	5.0	280.0	70.0	14.0	0
26	5.0	340.0	85.0	17.0	0
27	5.0	420.0	105.0	21.0	0
28	5.0	500.0	125.0	25.0	0
29	5.0	600.0	150.0	30.0	0
30	5.0	700.0	175.0	35.0	0
31	5.0	800.0	200.0	40.0	0
32	5.0	900.0	225.0	45.0	0
33	5.0	1000.0	250.0	50.0	0

TABLE E2. SAEs during placebo/peanut OIT*

Patient/ randomization	Days on OIT	OIT dose (mg)	Time to reaction after OIT dose	Cause for SAE/possible augmentation factor	Symptoms	Severity	Treatment/early termination
Placebo OIT	118	4.5	75 min	Possible accidental reaction after cookie from friend	Abdominal pain, tiredness, allergic rhinoconjunctivitis, vomiting, unconsciousness	V	Antihistamine *po*, corticosteroid rectal → monitoring for 2 h in ER → PP early termination: SAE related to OIT
Placebo OIT	270	150	24 h	Accidental reaction after peanut sauce at barbeque	OAS, angioedema, abdominal pain, coughing, generalized hives	III	Antihistamine *po*, corticosteroid rectal, inhalative salbutamol → hospitalization
Placebo OIT	106	3.5	24 h	Possible accidental reaction after mucosal contact with peanut/physical activity	Conjunctivitis, hoarseness, coughing, shortness of breath, flush	IV	No medication applied → hospitalization
Placebo OIT	88	20	17 h	Possible accidental reaction after eating snack	Abdominal pain, generalized hives, coughing, wheezing	IV	Antihistamine *po*, corticosteroid *po*, inhalative adrenaline → hospitalization
Placebo OIT	168	1.75	16 h	Ingestion of raw carrot/viral infection	OAS, coughing	III	Antihistamine *po*, corticosteroid *po* → hospitalization
Peanut OIT	342	125	45 min	Physical activity (running around in garden)	Abdominal pain, rhinoconjunctivitis, angioedema, pruritus, generalized hives, coughing	III	Inhaled salbutamol, antihistamine *po*, corticosteroid IV → hospitalization → PP early termination: SAE related to OIT and hospitalization
Peanut OIT	230	4.5	3.5 h	Possible accidental reaction after Chinese meal/URI	Coughing, somnolence	V	Adrenaline IM, antihistamine *po*, corticosteroid rectal → hospitalization
Peanut OIT	15	1	23 h	Possible accidental reaction after Sushi meal	OAS, coughing, allergic rhinoconjunctivitis, itching	III	Antihistamine IV, corticosteroid IV → hospitalization

ER, Emergency room; *IM*, intramuscular; *IV*, intravenous; *OAS*, oral allergy syndrome; *po*, *per os* (by mouth); *URI*, upper respiratory infection.
*Defined as AEs that were leading to death, hospitalization, disability, were life-threatening, or otherwise deemed an important medical event.

TABLE E3. Number of OIT doses associated with AEs in the placebo-OIT and peanut-OIT groups

OIT doses	Placebo-OIT group	Peanut- OIT group	
Total OIT doses, n	13,813	12,412	
OIT doses during updosing, n	11,838	10,323	
OIT doses during maintenance, n	1,975	2,089	
No. of OIT doses associated with …			***P* value***
AEs in total, n (%)	170 (1.2)	534 (4.3)	**0.001**
Subjective AEs, n (%)	72 (0.52)	459 (3.7)	**<0.001**
OAS, n (%)	29 (0.21)	281 (2.26)	**0.003**
Abdominal pain, n (%)	20 (0.14)	111 (0.89)	**<0.001**
Nausea, n (%)	8 (0.06)	13 (0.1)	0.07
Skin itching, n (%)	23 (0.17)	10 (0.1)	1.0
Joint pain/headache/throat pain, n (%)	5 (0.04)	70 (0.56)	0.11
Objective AEs, n (%)	107 (0.77)	85 (0.68)	0.98
Objective AEs during updosing, n (%)	99 (0.84)	81 (0.78)	0.99
Objective AEs during maintenance, n (%)	8 (0.41)	4 (0.19)	0.79
Skin symptoms (contact urticaria, flush, generalized hives, angioedema), n (%)	23 (0.17)	24 (0.19)	0.44
GI symptoms (vomiting, diarrhea), n (%)	10 (0.07)	26 (0.21)	0.63
URT symptoms (conjunctivitis, rhinitis, sneezing, rhinoconjunctivitis), n (%)	58 (0.42)	10 (0.08)	0.64
Laryngeal symptoms (hoarseness, stridor), n (%)	14 (0.1)	1 (0.01)	1.0
Lower respiratory tract symptoms (coughing, wheezing, shortness of breath), n (%)	20 (0.14)	52 (0.42)	0.11
Coughing, n (%)	15 (0.11)	41 (0.33)	0.09
Wheezing, n (%)	1 (0.01)	8 (0.06)	**0.045**
Shortness of breath related to OIT, n (%)	4 (0.03)	3 (0.02)	0.8
Cardiovascular symptoms (drop in blood pressure, unconsciousness), n (%)	1 (0.01)	0 (0.0)	0.33
AEs of severity grade I, n (%)	6 (0.04)	12 (0.1)	0.46
AEs of severity grade II, n (%)	54 (0.39)	12 (0.1)	0.81
AEs of severity grade III, n (%)	28 (0.2)	50 (0.4)	0.73
AEs of severity grade IV, n (%)	19 (0.14)	11 (0.1)	0.28
AEs of severity grade V, n (%)	1 (0.01)	0 (0.0)	0.33
Treatment for AEs related to OIT, n (%)	12 (0.09)	23 (0.19)	0.261
Application of systemic antihistamines for AEs related to OIT, n (%)	9 (0.07)	12 (0.1)	0.531
Application of systemic steroids for AEs related to OIT, n (%)	4 (0.03)	5 (0.04)	0.922
Application of inhalant salbutamol for AEs related to OIT, n (%)	6 (0.04)	10 (0.08)	0.561
Application of adrenaline for AEs related to OIT, n (%)	0 (0.0)	0 (0.0)	1.0

GI, Gastrointestinal; *URT*, upper respiratory tract.
Bold indicates statistical significance ($P < .05$).
**P* value comparing the percentage of OIT doses associated with AEs per patient between groups using the Kruskal-Wallis test.

TABLE E4. Baseline median scores of FAQLQ before the start of OIT as measure of HRQOL

Baseline scores for FAQLQ	Placebo OIT	Peanut OIT
FAQLQ-PF (IQR)		
Median total score	n = 23/26 3.6 (3.1-5.2)	n = 22/30 4.0 (3.4-4.7)
Median emotional impact score	n = 23/26 3.4 (2.8-5.2)	n = 22/30 3.8 (2.9-4.4)
Median food anxiety score	n = 23/26 4.7 (2.6-5.1)	n = 22/30 4.0 (3.2-4.3)
Median social and dietary limitation score	n = 23/26 4.7 (3.1-5.2)	n = 22/30 4.6 (3.6-5.7)
FAQLQ-CF (IQR)		
Median total score	n = 10/10 5.0 (4.1-5.4)	n = 9/13 5.3 (4.7-5.8)
Median allergen avoidance score	n = 10/10 4.0 (3.4-5.2)	n = 9/13 4.7 (4.0-5.6)
Median risk of accidental exposure score	**n = 10/10 4.9 (4.3-5.7)**	**n = 9/13 6.2 (5.3-6.4)***
Median emotional impact score	n = 10/10 6.3 (4.5-6.7)	n = 9/13 5.7 (5.5-6.2)
Median dietary restrictions score	n = 10/10 4.7 (3.6-5.8)	n = 9/13 4.7 (4.1-5.7)

Results are reported as the median (IQR) baseline scores of total and specific domains of the distributed questionnaire for HRQOL (FAQLQ).
Bold indicates statistical significance ($P < .05$).
*$P = .035$.

TABLE E5. Characteristics of patients who tolerated a maximum dose of ≥300 mg peanut protein at baseline OFC (PP population)

Patient no.	Randomization of OIT	Maximum tolerated dose* at baseline OFC	Baseline peanut SPT (mm)	Baseline peanut-specific IgE (kU/L)	Baseline peanut-specific IgG_4 (mgA/L)	Reached maintenance dose*	Maximum tolerated dose* at final OFC	Delta peanut SPT (mm)†	Delta peanut-specific IgE (kU/L)†	Delta peanut-specific IgG_4 (mgA/L)†	No. of wheezing episodes related to OIT, n	No. of accidental reactions, n
5	Placebo	300 mg	7.5	1.08	0.02	"250 mg"	4500 mg	+0.5	+0.79	+0.05	0	1
28	Placebo	1000 mg	5	1.02	ND	"250 mg"	1000 mg	+3.5	−0.53	ND	0	1
53	Placebo	300 mg	7	7.79	0.1	"150 mg"	300 mg	+3	−1.7	−0.03	0	0
62	Placebo	300 mg	7.5	93.8	1.22	"250 mg"	1000 mg	−2.5	−50.4	−0.3	0	1
1	Peanut	1000 mg	5	4.1	0.11	250 mg	4500 mg	+0.5	−1.09	+0.43	0	0
2	Peanut	3000 mg	3	2.21	0.01	250 mg	4500 mg	+4.5	−0.15	+0.03	0	0
7	Peanut	300 mg	5.5	68.9	1.39	250 mg	4500 mg	−2.5	−20.2	+0.52	0	0
16	Peanut	300 mg	6	1.86	0.05	250 mg	1000 mg	+2.5	−0.27	−0.01	1	0
29	Peanut	1000 mg	8	0.98	0.02	225 mg	4500 mg	−4.5	−0.55	+0.17	0	0
46	Peanut	300 mg	7	40.2	0.62	250 mg	4500 mg	+1	+10.9	+4.7	0	0
50	Peanut	3000 mg	6	1.63	0.2	225 mg	4500 mg	−6	−1.02	+1.17	0	0
55	Peanut	300 mg	9	0.57	1.32	250 mg	4500 mg	−6.5	+0.86	−0.43	0	0
64	Peanut	300 mg	8.5	3.15	0.07	250 mg	4500 mg	−4	−2.15	−0.05	0	0
69	Peanut	3000 mg	9.5	0.63	ND	250 mg	4500 mg	−4.5	+1.41	ND	0	0

ND, Not done; *PP*, per-protocol.
*Dose of peanut protein.
†"Delta" represents the change from baseline to posttreatment (post-OIT value minus pre-OIT value).

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