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Feasibility of desensitizing children highly allergic to peanut by high-dose oral immunotherapy

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Abstract

Background: There are limited data on the feasibility, efficacy and safety of high-dose oral immunotherapy (OIT) in children highly allergic to peanuts.

Objective: In children highly allergic to peanut, we primarily aimed to determine the feasibility of reaching the maximum maintenance dose (MMD) of 5000 mg peanut protein or, alternatively, a lower individual maintenance dose (IMD), by OIT up-dosing. Secondarily, we aimed to identify adverse events (AEs) and determine factors associated with reaching a maintenance dose.

Methods: The TAKE-AWAY peanut OIT trial enrolled 77 children 5-15 years old, with a positive oral peanut challenge. Fifty-seven were randomized to OIT with biweekly dose step-up until reaching MMD or IMD and 20 to observation only. Demographic and biological characteristics, AEs, medication and protocol deviations were explored for associations with reaching maintenance dose.

Results: All children had anaphylaxis defined by objective symptoms in minimum two organ systems during baseline challenge. The MMD was reached by 21.1%, while 54.4% reached an IMD of median (minimum, maximum) 2700 (250, 4000) mg peanut protein, whereas 24.5% discontinued OIT. During up-dosing, 19.4% experienced anaphylaxis. Not reaching the MMD was caused by distaste for peanuts (66.7%), unacceptable AEs (26.7%) and social reasons (6.7%). Increased peanut s-IgG$_4$/s-IgE ratio (OR [95% CI]: 1.02 [1.00, 1.04]) was associated with reaching MMD.

Conclusion: Although 75.5% of children with peanut anaphylaxis reached a maintenance dose of 0.25-5 g, only 21.1% reached the MMD. Distaste for peanuts and AEs, including high risk of anaphylaxis, limited the feasibility of reaching MMD.

KEYWORDS
adverse events, desensitization, feasibility, oral immunotherapy, peanut allergy

Abbreviations: AEs, adverse events; BAT, basophil activation test; CAPT, conjunctival allergen provocation test; DBPCFC, double-blind placebo-controlled food challenge; EoE, eosinophilic oesophagitis; FC, food challenge; IMD, individual maintenance dose; LOAEL, lowest observed adverse effect level; MMD, maximum maintenance dose; OIT, oral immunotherapy; OPAS, Oslo Peanut Allergy Study; PPI, proton pump inhibitor; RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; sIgE/sIgG/sIgG□, specific immunoglobulin E, G, G□; SPT, skin prick test; SU, sustained unresponsiveness; TAKE-AWAY trial, The "Take-Away food allergy; inducing tolerance in children allergic to peanut" trial.

Clinical trial registration: ClinicalTrials.gov number NCT02457416.
The study was performed within the ORAACLE (Oslo Research group of Asthma and Allergy in Children; the Lung and Environment), Oslo University Hospital and the University of Oslo.

1 | INTRODUCTION

Peanut allergy affects 1%-2% of the paediatric population,[1] is seldom resolved[2] and is the main cause of life-threatening allergic reactions in the Western World.[3] The only established treatment is dietary restrictions and rescue medication including epinephrine auto-injectors. However, the possibility of accidental exposure[4] causes anxiety and reduced quality of life.[5–7]

Peanut oral immunotherapy (OIT) trials are promising for inducing desensitization with acceptable safety profiles,[8–14] but evidence of sustained unresponsiveness (SU) after OIT discontinuation is limited.[8,14] The optimal starting dose of peanut OIT is not clear, and there is limited documentation of what maintenance dose would be safe and provide the greatest likelihood of inducing sustained unresponsiveness (SU). The ongoing "Take-Away food allergy; inducing tolerance in children allergic to peanut" trial (the TAKE-AWAY trial) is an open randomized controlled trial which primarily aims to assess SU after 4 years of peanut OIT. At the onset of the TAKE-AWAY trial, peanut OIT trials reported maintenance doses ranging from 125 to 4000 mg peanut protein,[9,12,13] with no adverse events (AEs) requiring epinephrine reported during a biweekly step-up protocol to 4000 mg peanut protein.[13] A high maintenance dose confers an increased likelihood of SU in subcutaneous immunotherapy (SCIT) trials for inhalant and venom allergies,[15,16] while this issue has not been adequately addressed for OIT. However, in a recent peanut OIT study,[17] maintenance dose was not decisive for SU 4 weeks after cessation of OIT. A fixed starting dose and a long-term step-up protocol have been associated with fewer AEs and higher retention rate.[9,18] Even though a recent workshop concluded that severe reactions occur unpredictably at any dose,[19] a possible relationship between allergen dose and the occurrence of anaphylaxis[20] may suggest a low OIT starting dose.

The feasibility of OIT is likely to be influenced by AEs,[21] while other factors are less well known. A low starting dose with a high maintenance dose increases the number of dose steps in an already time-consuming long-term protocol,[9,18] thereby excluding patients with less time resources.[22]

Therefore, the primary aim of the present study was to determine the feasibility of reaching the predefined maximum maintenance dose (MMD) of 5000 mg peanut protein or, alternatively, a lower individual maintenance dose (IMD), by OIT up-dosing in children highly allergic to peanut. Secondarily, we aimed to identify AEs and determine factors associated with reaching a maintenance dose, and in particular the MMD.

What is known on this subject

Peanut oral immunotherapy (OIT) is promising for inducing desensitization with acceptable safety profiles, but children highly allergic to peanuts and susceptible of severe systemic reactions to peanut are often excluded from OIT trials. Hence, there is limited information on the feasibility of performing OIT in this group of patients.

This study adds

The present peanut OIT study in children proven highly allergic to peanut during food challenge demonstrates that only 21% reached the predefined maintenance dose of 5000 mg peanut protein, mostly due to reported distaste for peanuts or adverse events. However, 75% of the children were able to reach an individual maintenance dose. Anaphylaxis occurred in 19.4% during up-dosing, causing discontinuation of OIT in 36.3% of these children.

Impact on current management guidelines

High-dose peanut OIT may be initiated in children highly allergic to peanut, but distaste for peanuts and adverse events may limit the likelihood of successful OIT. The high risk of anaphylaxis during treatment questions the safety of OIT in these children.

2 | METHODS

2.1 | Study design

The TAKE-AWAY trial, conducted at the Department of Paediatric and Adolescent Medicine, Oslo University Hospital, Ullevål, Norway, consists of four phases: the screening phase (3 days of eligibility screening), up-dosing phase (50-78 weeks), maintenance phase (36 months) and follow-up phase (12 months). The present study explored the up-dosing phase.

Children were recruited from February 2014 to June 2015 from the Oslo Peanut Allergy Study[23] and from in-house or other paediatric allergy clinics in Oslo and the surrounding area.

Inclusion criteria for screening were age 5-15 years, with a history of systemic reactions to peanut and/or sensitization to peanut by a peanut skin prick test (SPT) $\geq$ 3 mm or a peanut sIgE $\geq$ 0.35 kUA/L. Exclusion criteria were noncontrolled asthma or severe chronic disease (further details in Appendix S1).

Screening included a structured interview, blood samples for serological and immunological analyses, lung function measurements, SPT, conjunctival allergen provocation test (CAPT) and basophil activation test (BAT), followed by a DBPCFC. The DBPCFC was defined positive with at least two moderate objective symptoms in one or more organ systems according to Bock's criteria.[24–26] Cumulated peanut protein (mg) intake at positive DBPCFC was recorded as the reactivity threshold, whereas the lowest observed adverse effect level (LOAEL) was calculated post hoc and defined as the amount of peanut protein ingested eliciting mild, objective symptoms.[22] Enrolment in the TAKE-AWAY trial required a positive DBPCFC with a reactivity threshold > 3 mg peanut protein.[22] Of the 213 children referred for screening, 113 did not wish to enter the study, did not fulfil the screening inclusion and exclusion criteria, withdrew during

screening, and had a negative DBPCFC or a positive DBPCFC but with a reactivity threshold ≤3 mg peanut protein.[22]

Randomization to OIT vs observation followed an initial 2:1 block size, and restarted by approval from the Regional Committee for Medical and Health Research Ethics (the ethical committee) when the OIT starting dose was lowered (further details in Table S1).

Written informed consent was obtained from both parents after oral and written study information.

TAKE-AWAY was approved by the ethical committee (number 2013/430) with regular communications in case of severe or unexpected AEs, and registered at ClinicalTrials.gov (number NCT02457416).

2.2 | Study population

The present study includes the 57 children (5-15 years of age) randomized to peanut OIT. Anaphylaxis was defined as objective symptoms from at least two organ systems in line with European Academy of Allergy and Clinical Immunology (EAACI) task force position papers,[27,28] modified for children by Vetander et al[29]

2.3 | Immunological investigations

Specific IgE, IgG and IgG_4 were analysed using the Phadia CAP System FEIA (Thermo Fisher, Uppsala, Sweden), with positive tests defined as sIgE ≥ 0.35 kUA/L, IgG > 2.0 mg_A/L and IgG4 > 0.07 mg_A/L. The BAT is described in the Appendix S1.

2.4 | Up-dosing protocol of the oral immunotherapy

The peanut OIT followed a biweekly step-up long-term protocol with a fixed starting dose and a predefined MMD of 5000 mg peanut protein (details in the Appendix S1 and Table S2). The OIT starting dose was initially 5 mg peanut protein based on previously published studies[9,18] and results from the OPAS trial,[23] but lowered to 1 mg due to low reactivity thresholds in the referred patients.[22] For the lowest doses, the allergen source was peanut flour (Golden Peanut Company, Alpharetta, GA, USA). Because larger amounts of peanut flour mixed with other food became too sticky to eat, all but one patient switched to roasted peanuts at OIT doses of 65-500 mg peanut protein. Each increasing OIT dose was discussed with the patient and their guardian and ingested under observation at the hospital, followed by daily intake of this dose at home for 14 days.

In case of intolerable distaste or AEs, or if AEs resulted in three consecutive unsuccessful attempts to dose step-up, the IMD was considered reached (further details in Appendix S1). Withdrawal followed self-discontinuation of OIT, intolerable or severe AEs or more than two anaphylactic reactions. All unexpected severe AEs were reported to an independent safety board. In case of ongoing infections, asthma exacerbations, excessive tiredness or vaccinations, children were advised to postpone the daily OIT dose to the next day. The OIT was resumed at home if less than three consecutive doses were missing, and in hospital if three or more doses were missed. Exercise within 2 hours after the OIT dose was discouraged.

Registration of peanut intake, AEs, use of medication and accidental exposure to peanut were based upon daily symptom diary recordings. Grading AEs followed the modified Bock's criteria,[24,25] as described in the Appendix S1.

All participants received prescriptions of epinephrine auto-injectors and antihistamines and a written treatment plan for AEs and had around-the-clock access to the study paediatricians.

2.5 | Outcomes and explanatory factors

The primary outcome was the feasibility of reaching MMD, defined by the proportion of children who reached the predefined MMD of 5000 mg peanut protein. The secondary outcome was the proportion of children who reached the IMD (<5000 mg peanut protein).

Potential explanatory factors of reaching the MMD or the lower IMDs were AEs characterized by the involved organ(s) and classified into either subjective and mild objective, moderate or severe (including anaphylaxis) in line with the modified Bock's criteria,[25] baseline characteristics, biological markers, LOAEL, severity grade of anaphylaxis at screening DBPCFC, medication for AEs and protocol deviations (dose reduction or postponed up-dosing due to social events, AEs or infections).

2.6 | Statistical analyses

The statistical power analyses at study onset were based upon studies reporting that up to 80% of peanut-allergic children were desensitized using a step-up peanut OIT[12,13] and development of spontaneous tolerance in 20%.[2] In children with severe peanut allergy, we expected desensitization in 57%. A treatment group of 40 and a control group of 20 subjects would provide a statistical power of 80% at a five per cent significance level.

Due to nonnormal distribution, continuous baseline characteristics are presented by geometric mean with 95% confidence intervals (CI) and categorical data as number of cases (n) with percentage (%), while potential differences between groups were analysed using the Mann-Whitney U test for continuous data and the Pearson's chi-square test for categorical data.

To determine the statistical significance of desensitization based upon the individual difference in peanut daily maintenance dose to the reactivity threshold and LOAEL at baseline, we used a paired-sample *t* test. The associations between explanatory factors and feasibility of desensitization were assessed using bivariate logistic regression analyses with the proportion of children who reached the MMD versus the proportion who reached either IMD or discontinued OIT as the dependent variable. The analyses were duplicated with the proportion of children who reached either MMD or IMD as the dependent variable versus the proportion who discontinued OIT.

A one-way ANOVA was used to analyse the overall difference between the three groups of children who reached the MMD, those

who reached the IMD and those who discontinued OIT with the latter group as reference. One-way ANOVA was also used to analyse the overall difference between AEs occurring in the three dose intervals of the up-dosing phase (1-65, 66-800 and 801-5000 mg peanut protein). In the case of a significant overall *P*-value, the Dunnett's post hoc test was used to confirm between which groups the statistically significant difference had occurred.

Statistical analyses were performed using the Statistical Analysis System (SAS, version 9.3; SAS Institute Inc., Chapel Hill, NC, USA) and IBM Statistical Package for the Social Sciences (IBM SPSS Statistics, version 21.0.1.; IBM Corp, Armonk, NY, USA).

A 2-tailed *P*-value of ≤0.05 was considered statistically significant.

3 | RESULTS

All 57 children randomized to active peanut OIT were primary sensitized to peanut with geometric mean (min, max) sIgE to Ara h 2 of 56.2 (0.82, 492.0) kUA/L and had a LOAEL of 18.4 (11.8, 28.6) mg peanut protein, and 78.9% had a history of a anaphylaxis to peanut. During baseline DBPCFC, all children randomized to OIT, as well as the control children in the TAKE-AWAY trial, reacted with anaphylaxis.[22] The baseline characteristics including grading of anaphylaxis are reported in Table 1 for children reaching MMD or IMD or those who discontinued peanut OIT, as well as for the controls.

The predefined MMD of 5000 mg peanut protein was reached by 21.1% (n = 12) of the children, while 54.4% (n = 31) reached a lower IMD and 24.5% (n = 14) discontinued (Table 2). The median (min, max) IMD reached was 2700 (250, 4000) mg of peanut protein, which was 207 (3.1, 1666.7) ($P < 0.001$ for both) times higher than LOAEL at screening.

The most common reasons for not reaching the MMD were distaste for peanuts in 66.7% (n = 28 within IMD and 2 discontinued) of the children and AEs in 26.7% (n = 3 within IMD and 9 discontinued) and social reasons in 6.7% (n = 3 discontinued; two found the treatment too time-consuming, while one discontinued due to parents' divorce). Distaste for peanuts was reported as a daily challenge in 77.2% of the children.

Mild AEs were reported in relation to 13.9% of the OIT doses. One child only did not report any AEs. The AEs occurred more often in the first (1-65 mg peanut protein), compared with the second (66-800 mg) and third (801-5000 mg peanut protein) dose interval steps (overall $P = 0.03$), with a statistically significant difference between the first and the last dose intervals (Figure 1). The AEs, mostly oral itching (43.5%) or other gastrointestinal (GI)-related (42.5%) symptoms, occurred more frequently during the first two, compared with the remaining days in each up-dosing period ($P = 0.001$; Figure 1). Dyspeptic symptoms were reported as the main reason for discontinuation in two children, while six children with dyspeptic symptoms had spontaneous (n = 2) or proton pump inhibitor (PPI)-related (n = 4) symptom relief and continued treatment throughout the up-dosing phase.

Moderately graded AEs constituted 0.6% of all AEs (Table 3), and 11 anaphylactic events classified as moderate occurred in 11 children (0.06% of the doses), with epinephrine administered in six of the episodes (Table S3). All but two anaphylactic reactions were preceded by known augmenting factors: exercise within two hours of a dose,[5] ongoing infection,[1] excessive tiredness,[1] impaired compliance to OIT[1] or asthma treatment.[1] In comparison, the control group did not experience any anaphylactic events to peanut.

Children discontinuing OIT reported significantly more AEs per dose step per child than children who reached any maintenance dose (MMD or IMD) median (min, max) 2.45 (0.27, 10.50) vs 1.04 (0, 12.90), respectively ($P = 0.01$), whereas moderately graded AEs were similarly reported in these two groups ($P = 0.61$).

The only identified significant predictor of reaching a maintenance dose was the peanut $sIgG_4$/sIgE ratio ratio that was associated with MMD in the bivariate (Table 4) and the multivariate logistic regression model (not shown). Including Sampson's anaphylaxis severity grading did not influence the results (not shown). We found nonsignificant trends for associations between LOAEL and MMD, and between sIgE to peanut, sIgE to Ara h 2, the peanut sIgE/total IgE ratio and AEs and any maintenance dose (MMD + IMD) ($P = 0.06$–0.08) (Table 4).

4 | DISCUSSION

In the randomized controlled peanut OIT TAKE-AWAY trial, desensitization to peanut was feasible for most children highly allergic to peanut and reacting with anaphylaxis at baseline food challenge. The high predefined MMD of 5000 mg peanut protein was reached by 21.1%, whereas 54.4% reached the lower IMD. Failure to reach the MMD was most often due to distaste for peanuts, whereas AEs were the main reason for discontinuation. Anaphylaxis occurred in 19.3% of the children during the up-dosing phase. Peanut $sIgG_4$/sIgE ratio was the only significant predictor of reaching MMD, while AEs, baseline sIgE to peanut or Ara h 2 and LOAEL showed a nonsignificant tendency to be associated with the maintenance dose reached.

Desensitizing children with anaphylaxis to peanut by reaching the MMD of 5000 mg peanut protein was feasible in 21.1% only, while 73.7% reached a maintenance dose of at least 500 mg, in line with the 63.6% to 86.9% previously reported.[8–11,13,21,30,31] Based upon the limited experience with peanut OIT and MMD varying from 125 mg to 4000 mg of peanut protein trial,[8–11,13,21,30,31] our high MMD was chosen to increase the likelihood of SU in children with severe peanut allergy. However, 5000 mg peanut protein represents approximately 25 whole peanuts, a quantity that was challenging for many children as they developed distaste for peanuts. Few reports have addressed this issue previously, except one study[9] reporting distaste for peanuts as the reason for withdrawal of one patient and reduction of maintenance dose in two patients.

The 24.5% discontinuation of OIT in our cohort of children highly allergic to peanut is in line with previously published peanut OIT studies, ranging from 10% to 32%.[32] Experiencing AEs

TABLE 1 Baseline characteristics of children randomized to peanut OIT and controls in the TAKE-AWAY trial

	Total patients receiving OIT (n = 57)	Patients reaching MMD (n = 12)	Patients reaching IMD (n = 31)	Patients discontinued OIT (n = 14)	Overall *P*-value between MMD, IMD and dis-continued	Controls (n = 20)	*P*-value between OIT patients and controls
Age (median, min-max)	10.1 (5.2, 15.2)	10.7 (7.2, 15.2)	8.5 (5.2, 14.4)	10.2 (5.4, 15.1)	**0.02**[##]	8.9 (5.1, 13.3)	0.28
Male	31 (54.4)	7 (58.3)	14 (45.2)	10 (71.4)	0.26	13 (65.0)	0.41
History of anaphylaxis to peanut	45 (78.9)	9 (75.0)	23 (74.2)	13 (92.8)	0.82	18 (90.0)	0.63
Current asthma	24 (42.1)	5 (41.2)	11 (35.4)	8 (57.1)	0.37	9 (45.0)	0.78
Allergic rhinitis	15 (26.3)	5 (41.7)	8 (25.8)	2 (14.3)	0.53	8 (40.0)	0.83
Atopic dermatitis	47 (82.5)	11 (91.7)	25 (80.6)	11 (78.6)	0.64	14 (73.9)	0.41
Allergy to tree-nuts	20 (35.1)	5 (41.7)	15 (48.4)	0 (0.0)	0.15	7 (36.8)	0.99
Allergy to other food than nuts	27 (47.4)	6 (50.0)	19 (61.3)	2 (14.3)	**0.02**[#]	11 (57.9)	0.65
Parental atopic disease[a]	50 (87.7)	9 (75.0)	27 (87.1)	14 (100.0)	0.16	16 (80.0)	0.40
Parental food allergy[b]	21 (36.8)	4 (33.3)	10 (32.3)	7 (50.0)	0.51	6 (30.0)	0.58
FEV1% predicted	101.2 (97.6, 105.0)	101.0 (91.2, 112.2)	101.9 (97.7, 104.7)	99.7 (94.0, 105.8)	0.86	95.5 (88.3, 107.2)	0.22
Pos sIgE (≥0.35 kUA/L)							
Tree-nuts[c]	52 (91.2)	10 (83.3)	30 (96.7)	12 (85.7)	0.08	16 (80.0)	0.11
Other food[d]	54 (94.7)	12 (100.0)	29 (96.7)	13 (92.9)	0.63	19 (95.0)	0.50
Peanut SPT (mm)	9.8 (8.6, 11.0)	8.7 (7.0, 10.9)	9.7 (8.4, 11.3)	10.3 (7.3, 14.6)	0.64	9.3 (7.4, 11.7)	0.94
sIgE (kUA/L)							
Peanut	110.6 (70.4, 173.8)	21.9 (4.9, 97.8)	129.3 (88.9, 188.0)	175.7 (55.0, 561.6)	**0.003**[#]	52.2 (20.3, 134.4)	0.12
Ara h2	56.2 (37.2, 87.1)	13.5 (3.1, 59.1)	67.0 (47.8, 94.0)	89.6 (33.9, 235.9)	**0.004**[#]	22.4 (8.4, 58.9)	0.09
Peanut sIgE/total IgE (kUA/L)	0.4 (0.0, 1.5)	0.3 (0.1, 0.6)	0.3 (0.1, 0.6)	0.5 (0.4, 0.7)	**0.002**[#]	0.2 (0.1, 0.6)	0.12
Peanut sIgG_4/sIgE (ng/mL)	5.7 (3.7, 8.9)	15.5 (3.4, 60.3)	4.9 (2.9, 8.3)	3.3 (1.4, 7.8)	**0.04**[#]	5.3 (2.6, 10.9)	0.46
CAPT pos level[e]	2.6 (2.3, 3.0)	3.0 (2.2, 4.1)	2.6 (2.3, 3.1)	2.3 (1.7, 3.1)	0.41	3.1 (2.7, 3.4)	0.19
BAT (%$CD63^+$)	68.0 (61.6, 75.1)	34.4 (15.5, 75.9)	49.6 (34.7, 70.8)	63.7 (46.0, 88.2)	0.28	51.2 (32.0, 85.4)	0.48
At baseline DBPCFC							
Number of anaphylaxis	57 (100.0)	12 (100.0)	31 (100.0)	14 (100.0)	0.11	20 (100.0)	0.51
Anaphylaxis severity grade							
Modified EAACI	1.6 (1.4, 1.7)	1.4 (1.1, 1.8)	1.7 (1.5, 1.9)	1.6 (1.3, 1.9)	0.22	1.7 (1.5, 2.0)	0.33
Sampson	2.6 (2.4, 2.8)	2.8 (2.4, 3.4)	2.5 (2.3, 2.8)	2.6 (2.3, 3.1)	0.49	2.8 (2.5, 3.2)	0.23

(Continues)

TABLE 1 (Continued)

	Total patients receiving OIT (n = 57)	Patients reaching MMD (n = 12)	Patients reaching IMD (n = 31)	Patients discontinued OIT (n = 14)	Overall *P*-value between MMD, IMD and dis-continued	Controls (n = 20)	*P*-value between OIT patients and controls
Use of adrenaline	30 (52.6)	5 (41.7)	17 (54.8)	8 (57.1)	0.70	5 (25.0)	**0.03**
LOAEL (mg peanut protein)	18.4 (11.8, 28.6)	45.9 (10.2, 207.1)	15.1 (10.3, 22.1)	36.2 (15.4, 84.4)	0.05	5 (25.0)	0.19
Reactivity threshold (mg peanut protein)	46.2 (29.7, 72.0)	108.7 (29.3, 402.9)	32.1 (22.0, 46.9)	93.3 (40.0, 222.4)	**0.01**[##]	75.9 (33.1, 173.8)	0.63

MMD, subjects who reached the maximum maintenance dose; IMD, subjects who reached the individual maintenance dose; SPT, skin prick test; Ig, immunoglobulin; BAT, basophil activation test; CAPT, conjunctival allergen provocation test; LOAEL, lowest observed adverse effect level; OIT, oral immunotherapy; DBPCFC, double-blind placebo-controlled food challenge.

Variables are given as geometric mean (95% CI) or n (%), except age which is given as median (min, max).

Bold values are statistically significant ($P < 0.05$).

One-way ANOVA was applied to determine statistically significant differences between group means and the Dunnett's post hoc test to confirm which groups differed.

Anaphylaxis severity was graded by two grading systems according to the modified EAACI position papers[27,28] ranging from 1 to 3 and the method of Sampson (Grading of Food-Induced Anaphylaxis According to Severity of Clinical Symptoms)[42] ranging from 1 to 5.

LOAEL is defined as the cumulated peanut protein (mg) ingested eliciting mild, objective symptoms.

Reactivity threshold is defined as the cumulated peanut protein (mg) ingested at positive DBPCFC, with at least two moderate objective symptoms in one or more organ systems according to Bock's criteria.[24–26]

[a]Atopic disease includes asthma, allergic rhinitis, atopic dermatitis and allergic conjunctivitis.

[b]All food allergy including peanut and tree nut allergy.

[c]Hazelnut, almond, cashew nut, pistachio nut, walnut, pecan nut, brazil nut and macadamia nut.

[d]Fenugreek, soya bean, pea, red kidney bean, lupin seed and wheat.

[e]The CAPT was recorded positive ranging from dilution level 1 (1:160) to 5 (1:1).

[#]Statistically significant difference between MMD and discontinued.

[##]Statistically significant difference between MMD and IMD.

TABLE 2 Characteristics of children who discontinued oral immunotherapy without reaching a maintenance dose

Patient no.	Age years	Peanut sIgE kUA/L	Ara h 2 sIgE kUA/L	LOAEL mg peanut protein	Reactivity threshold mg peanut protein	Dose at discontinuation mg peanut protein	Reason for discontinuation mg peanut protein
1	8.8	93.2	82.7	110.8	110.8	5	Social
2	11.3	493.0	221.0	35.8	35.0	5	AEs
3	14.3	26.2	14.6	110.8	243.0	450	AEs
4	15.1	179.0	77.0	13.0	13.0	10	AEs
5	14.8	951.0	457.0	443.0	943.0	45	AEs
6	6.5	63.9	32.4	43.0	43.0	20	Distaste
7	10.9	271.0	158.0	43.0	43.0	350	AEs
8	13.8	2311.0	475.0	43.0	43.0	45	AEs
9	11.7	114.0	87.4	3.0	43.0	1000	Distaste
10	10.1	629.0	179.0	3.0	13.0	20	AEs
11	9.8	352.0	210.0	13.0	143.0	1	Social
12	5.4	0.6	0.8	143.0	443.0	1	Social
13	7.3	92.8	61.6	143.0	943.0	65	AEs
14	11.6	285.0	131.0	13.0	443.0	5	AEs

AEs, adverse events; LOAEL, lowest observed adverse effect level.

were the cause of OIT discontinuation in 55% of our children (three with anaphylaxis and two with dyspeptic symptoms), in line with pooled data of three OIT studies including 104 children in which 20% discontinued treatment mostly due to AEs (65%) and logistic reasons (35%).[21]

Our finding that 13.9% of the doses elicited mild AEs is in line with previously published OIT studies,[10,32] including the 13.5% AEs reported in the STOP II study[10] of 99 children with allergy severity ranging from a mild allergic reaction in one organ system (24.2%) to severe respiratory symptoms (5.1%). Our children most frequently reported GI-related AEs including oral itching and stomach ache in line with previous studies,[21,30–32] as well as effect of oral antihistamines if simultaneous dyspeptic symptoms were absent.[10] Dyspepsia, reported by eight (14%) of our children, may be a symptom of OIT-related eosinophilic oesophagitis (EoE),[21,33] estimated to develop in 2.7% undergoing OIT.[32,33] In two children, OIT was discontinued due to dyspepsia, while three of the four children treated with PPI became asymptomatic and the fourth reported decreasing symptoms. Mild AEs occurred significantly more often during the first two days of each up-dosing period and in the first third of the dose steps, as previously described.[10]

The reported 0.6% of moderate AEs is somewhat lower than the 2.6% objective AEs reported in a German study of 23 children highly sensitized to peanut.[9] This may be explained by the German study's use of a rush OIT protocol with a tailored starting dose reported to be associated with more AEs.[9,18] In contrast, anaphylactic events occurred in every fifth child in our study, which is significantly higher than in comparable peanut OIT studies with MMDs (range) 300-1400 mg peanut protein,[9,10,31] reporting no systemic reactions,[9] one anaphylactic event[10] or use of epinephrine once only.[31] Although the high proportion of children who reacted with anaphylaxis throughout up-dosing was equally distributed by OIT dose, most anaphylactic reactions occurred at OIT doses above 300 mg of peanut protein and none among the controls. Recently, Baumert et al[34] showed that increasing the reactivity threshold from 100 to 300 mg reduced the risk of allergic reactions from accidental exposure by 95%. Hence, a high-dose OIT may not be clinically meaningful, but it remains unclear if a higher treatment dose is required to achieve SU. The patients in the TAKE-AWAY trial will be analysed for SU in follow-up studies. Nevertheless, even if children with anaphylaxis to peanut would benefit the most from a successful OIT,[13,14,18,35] it might be that the risk of severe systemic reactions outweighs the potential benefit of the treatment.[36,37]

Peanut $sIgG_4$/sIgE was significantly associated with reaching MMD with an absolute OR value almost similar to the nonsignificant OR for reaching any maintenance dose. Hence, the clinical value of this biological marker in predicting MMD versus any maintenance dose is limited. The lack of a significant association between AEs, LOAEL, peanut sIgE/total IgE ratio and the sIgE to peanut and Ara h 2, and reaching maintenance dose may be explained by distaste for peanuts being the main reason for not reaching MMD as well as the limited sample size.

4.1 | Strengths and limitations

To our knowledge, the TAKE-AWAY children had sIgE to peanut higher and LOAELs lower than in previous OIT trials[8–11,13,21,30,31] with more than half of them experiencing anaphylaxis already at the LOAEL. These findings are in line with previously published reports that suggest an association with high sIgE to peanut and low LOAEL, and severity of allergic reactions.[38–41] All our children, older than in

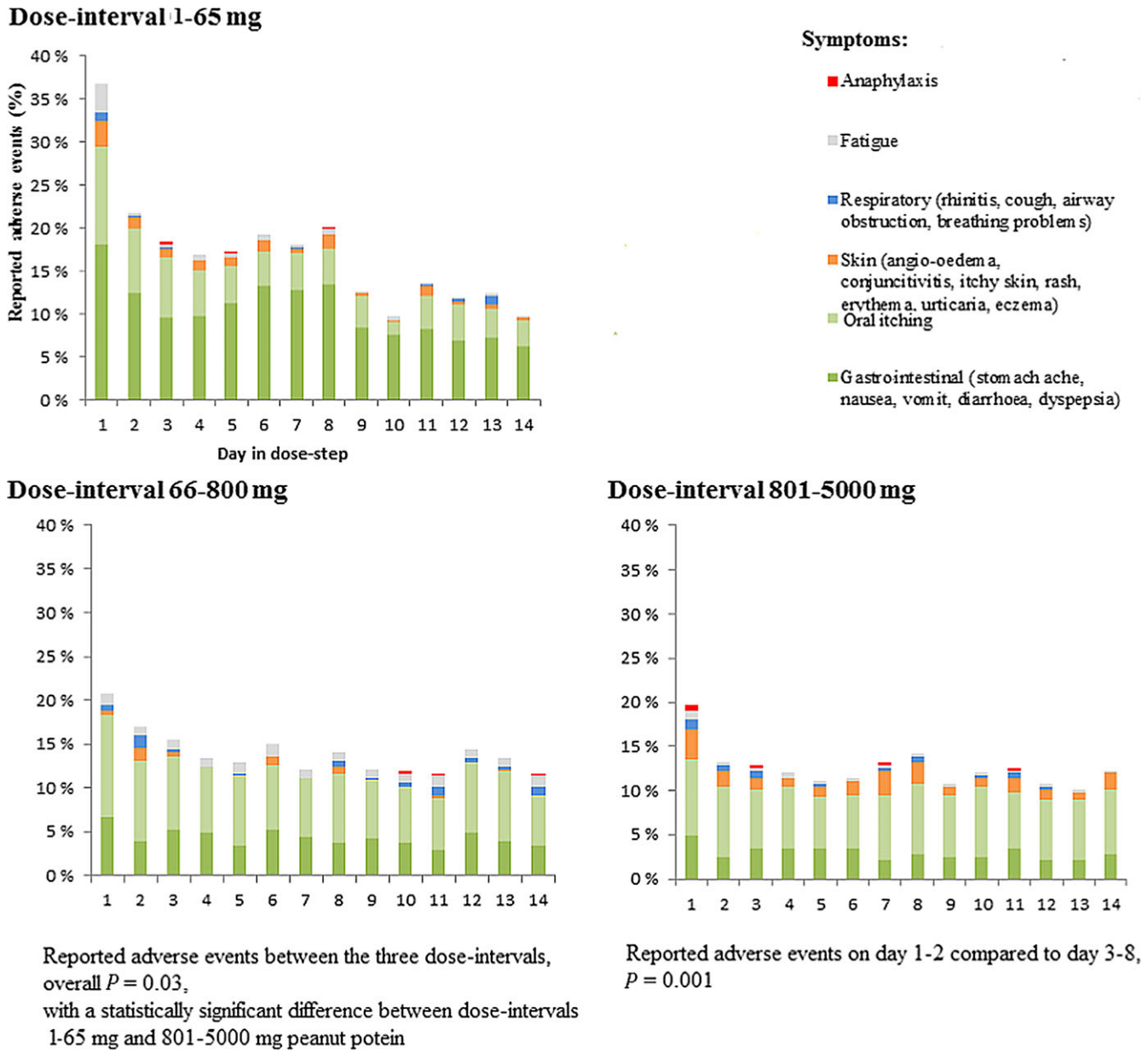

FIGURE 1 Reported doses with adverse events (AEs) per dose day (%) in the three dose intervals of the up-dosing phase. If there were another cycle of 14 days of the same dose step due to AEs or vacations in the same dose interval, this cycle would also be a part of the same dose interval, and the *Y*-axis would still represent reported doses with AEs per dose day (%). One-way ANOVA was applied to determine statistically significant differences between the intervals and the Dunnett's post hoc test to confirm which groups differed.

some,[9,13,17,30,31] but younger than in other[10,11] studies, reacted with anaphylaxis during the pre-OIT DBPCFC, which may be explained by most of our children having a history of anaphylaxis to peanut as well as not defining the food challenge positive until the occurrence of two objective symptoms. Some studies[10] define a food challenge positive already by the occurrence of reproducible subjective symptoms as suggested in the PRACTALL guidelines,[25] and one cannot rule out that an anaphylaxis would occur if another dose was given. Calculating the objective LOAEL enables comparison between studies.[22]

Switching ingestion of defatted flour to whole roasted peanuts at a wide range of doses (65-500 mg) may influence the efficacy of the OIT, as whole peanuts are more aromatic and were disliked. A placebo arm could have strengthened the study as distaste was the main reason for not reaching the MMD. However, this was regarded un-ethical based on the unfavourable ratio of treatment burden to expected benefit in the placebo group. A blinded vehicle to our high-dose peanut OIT also seemed unfeasible.

An OFC after up-dosing phase would have been preferable, but was not repeated for ethical reasons.

TABLE 3 Adverse events (AEs) related to oral immunotherapy in children highly allergic to peanut

	Total patients receiving OIT (n = 57) (doses = 18 470)	Patients reaching MMD (n = 12) (doses = 5292)	Patients reaching IMD (n = 31) (doses = 11 536)	Patients discontinuedOIT (n = 14) (doses = 1642)
Total AEs				
Patients, n (%)	56 (98.2)	12 (100.0)	30 (96.8)	14 (100.0)
Events, n (%)	2560 (13.9)	290 (5.5)	1957 (17.0)	313 (19.1)
Mild AEs, total				
Patients, n (%)	56 (98.2)	12 (100.0)	30 (96.8)	14 (100.0)
Events, n (%)	2473 (13.4)	290 (5.5)	1725 (15.0)	515 (31.4)
Moderate AEs				
Patients, n (%)	22 (38.6)	4 (33.3)	14 (45.2)	4 (28.6
Events, n (%)	116 (0.6)	21 (0.4)	81 (0.7)	14 (0.9)
Oral itching				
Patients, n (%)	49 (86.0)	10 (83.3)	28 (90.3)	11 (78.6)
Events, n (%)	1096 (5.9)	173 (3.3)	822 (7.1)	79 (4.8)
GI-related AEs[a]				
Patients, n (%)	48 (84.2)	7 (58.3)	27 (87.1)	13 (92.9)
Events, n (%)	1100 (6.0)	31 (0.6)	959 (8.3)	110 (6.7)
Skin-related AEs				
Patients, n (%)	43 (75.4)	9 (75.0)	27 (87.1)	7 (50.0)
Events, n (%)	140 (0.8)	26 (0.5)	95 (0.8)	71 (4.3)
Respiratory-related AEs				
Patients, n (%)	37 (64.9)	10 (83.3)	19 (61.3)	8 (57.1)
Events, n (%)	59 (0.3)	10 (0.2)	31 (0.3)	18 (1.0)
Anaphylaxis				
Patients, n (%)	11 (19.3)	2 (16.7)	5 (16.1)	4 (28.6)
Events, n (%)	11 (0.06)	2 (0.04)	5 (0.04)	4 (0.24)
Anaphylaxis severity grade: Sampson, median (min, max)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)
Used epinephrine				
Patients, n (%)	6 (10.5)	2 (16.7)	2 (6.5)	2 (14.3)
Events, n (%)	6 (0.03)	2 (0.04)	2 (0.02)	2 (0.12)
Used acute salbutamol[b]				
Patients, n (%)	5 (8.8)	1 (8.3)	2 (6.5)	2 (7.1)
Events, n (%)	5 (0.03)	1 (0.02)	3 (0.03)	2 (0.1)

AEs, adverse events; MMD, subjects who reached the maximum maintenance dose; IMD, subjects who reached the individual maintenance dose.
Percentages were based on the number of patients in each group, stratified by reaching maximum maintenance dose (MMD), a lower individual maintenance dose (IMD) or discontinuing treatment. Patients were counted once per category.
Grading of OIT-related AEs was in line with the modified Bock's criteria by Sampson et al[24,25,43]
[a]Except oral itching.
[b]In relation to OIT AEs.

5 | CONCLUSION

In children highly allergic to peanut and reacting with anaphylaxis at baseline food challenge, reaching a high MMD of 5000 mg peanut protein was feasible for every fifth child. More than half of the children rather stopped at the lower IMD, mainly due to distaste for peanuts. Every fifth child experienced an anaphylactic adverse event, which questions the safety of OIT for these patients.

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TABLE 4 Possible factors that could explain the feasibility of reaching maintenance dose using bivariate logistic regression analyses

	Reached MMD or IMD (n = 43)	*P*-value	Reached MMD (n = 12)	*P*-value
Parent education (graded 1 (low)-5 (high))	1.25 (0.95, 1.66)	0.12	0.95 (0.70, 1.30)	0.77
Siblings	1.04 (0.43, 2.53)	0.94	0.83 (0.32, 2.12)	0.69
Male sex	2.55 (0.72, 9.10)	0.15	0.80 (0.23, 2.82)	0.73
Current asthma	1.89 (0.56, 6.41)	0.31	2.44 (0.66, 8.97)	0.18
Allergic rhinitis	2.14 (0.46, 10.03)	0.33	2.55 (0.67, 9.63)	0.17
Peanut SPT (mm)	0.95 (0.86, 1.05)	0.31	0.94 (0.82, 1.08)	0.40
sIgE (kUA/L)				
Peanut	1.00 (1.00, 1.00)	0.07	1.00 (1.00, 1.00)	0.42
Ara h 2	1.00 (0.99, 1.00)	0.07	1.00 (0.99, 1.00)	0.57
Peanut sIgE/total IgE (kUA/L)	0.10 (0.01, 1.08)	0.06	0.44 (0.03, 5.87)	0.53
Peanut sIgG$_4$/sIgE (ng/mL)	1.01 (0.99, 1.03)	0.45	1.02 (1.00, 1.04)	**0.02**
BAT (%CD63$^+$)[a]	0.99 (0.96, 1.03)	0.98	0.99 (0.96, 1.03)	0.66
CAPT positive (dilution)	1.36 (0.76, 2.40)	0.30	1.55 (0.83, 2.89)	0.17
Anaphylaxis severity				
Modified EAACI	1.35 (0.38, 4.74)	0.64	0.36 (0.10, 1.32)	0.12
LOAEL (mg)	1.00 (1.00, 1.00)	0.99	1.00 (1.00, 1.01)	0.08
During up-dosing				
AEs[a] (days/period/child)	0.80 (0.64, 1.01)	0.06	0.69 (0.39, 1.20)	0.18
Anaphylaxis (days/period/child)	1.83 (0.42, 79.71)	0.75	1.86 (0.25, 136.35)	0.78
Asthma medication (yes/no)	1.89 (0.56, 6.41)	0.31	2.44 (0.66, 8.97)	0.18
Postponements (total)	1.46 (0.88, 2.42)	0.14	0.87 (0.55, 1.38)	0.55
Dose reductions (total)	3.00 (0.34, 26.60)	0.32	1.40 (0.17, 11.24)	0.75

SPT, skin prick test; IgE/G/G$_4$, immunoglobulin E/G/G$_4$; BA, basophil activation; CAPT, conjunctival allergen provocation test; OIT, oral immunotherapy; DBPCFC, double-blind placebo-controlled food challenge; LOAEL, lowest observed adverse effect level; AEs, adverse events.
Associations are given as odds ratio (OR) (95% CI).
Bold values are statistically significant ($P < 0.05$).
Parent education: 1 – primary school; 2 – secondary school; 3 – high school; 4 – college/university ≤ 3 years; 5 – college/university > 3 years N = 57 children randomized to active peanut OIT in the TAKE-AWAY trial.
The right column presents reaching any maintenance dose (MMD (5000 mg peanut protein) + IMD (<5000 mg)) compared with children who discontinued OIT. The left column presents reaching the MMD compared with children not reaching MMD (eq. IMD + discontinued).
[a]N = 50. The BAT was not performed in five children due to technical causes (n = 5), and nonresponders were excluded from the analyses (n = 2).

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CONFLICT OF INTEREST

Magnus P. Borres is employed by Thermo Fisher Scientific. The other authors declare no conflict of interest for the present study.

AUTHOR CONTRIBUTIONS

G. Håland, K. C. Lødrup Carlsen, and K-H. Carlsen designed the project. M. M. Michelsen, G. Håland and T. Reier-Nilsen included patients, collected data and carried out the up-dosing protocol. U. Nygaard, E. Namork and M. P. Borres were responsible for the immunological tests. The analytic approaches were designed by G. Håland, K. C. Lødrup Carlsen, K-H. Carlsen, P. Mowinckel and T. Reier-Nilsen, while the main statistical analyses were performed by T. Reier-Nilsen in collaboration with the statistician P. Mowinckel. T. Reier-Nilsen is the lead author with significant contribution from all authors who read and approved the submitted manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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