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Original Article

Improvements in Quality of Life in Children Following Epicutaneous Immunotherapy (EPIT) for Peanut Allergy in the PEPITES and PEOPLE Studies

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What is already known about this topic? Food allergy quality of life has been consistently shown to be impaired in children with peanut allergy and their caregivers due to the burden of constant vigilance, including the fear of reactions due to accidental exposure.

What does this article add to our knowledge? Epicutaneous immunotherapy with DBV712 250 μg led to significant improvements in food allergy quality of life in peanut-allergic children after 24 months of treatment, largely driven by patients experiencing any improvement in eliciting dose. This was noted in all Food Allergy Quality of Life Questionnaire-Parent Form and 2 of 4 Food Allergy Quality of Life Questionnaire-Child Form domains.

How does this study impact current management guidelines? These findings suggest that improvements in total and domain-specific food allergy quality of life as a result of increased eliciting doses after DBV712 250 μg treatment represent important patient-centered outcomes as part of the overall clinical benefits of therapy.

BACKGROUND: Food allergy quality of life (FAQL) is impaired in children with peanut allergy. Food Allergy Quality of Life Questionnaires (FAQLQs) provide disease-specific insight into the burden of peanut allergy and potential FAQL changes after peanut immunotherapy.

OBJECTIVE: To examine FAQL changes in children after treatment with epicutaneous immunotherapy for peanut allergy (250 μg, daily epicutaneous peanut protein; DBV712 250 μg).

METHODS: FAQL was prospectively measured using the FAQLQ parent proxy form (Food Allergy Quality of Life

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Abbreviations used
CF- Child form
DBPCFC- Double-blind placebo-controlled food challenge
ED- Eliciting dose
EPIT- Epicutaneous immunotherapy
FAIM- Food Allergy Independent Measure
FAQL- Food allergy quality of life
FAQLQ- Food Allergy Quality of Life Questionnaire
FAQLQ-CF- Food Allergy Quality of Life Questionnaire-Child Form
FAQLQ-PF- Food Allergy Quality of Life Questionnaire-Parent Proxy Form
IT- immunotherapy
LS- Least squares
MCID- Minimal clinically important difference
OFC- Oral food challenge
OIT- Oral immunotherapy
PA- Peanut allergy
PEPITES- Peanut EPIT Efficacy and Safety Study
PF- Parent proxy form
PEOPLE- PEPITES Open Label Extension Study

Questionnaire-Parent Proxy Form [FAQLQ-PF], for children aged ≤12 years) and child form (Food Allergy Quality of Life Questionnaire-Child Form [FAQLQ-CF], child rated if aged ≥8 years) during the 12-month double-blind, randomized, controlled Peanut EPIT Efficacy and Safety Study (PEPITES) trial and the initial 12 months of the open-label PEPITES Open Label Extension Study (PEOPLE) follow-up study. Data were analyzed for between-group differences after treatment unblinding.

RESULTS: FAQLQs from placebo participants (FAQLQ-PF: 96; FAQLQ-CF: 47) and treatment group participants (FAQLQ-PF: 209; FAQLQ-CF: 105) were analyzed. Twenty-four−month global FAQL scores (FAQLQ-PF/FAQLQ-CF) were significantly improved in the treatment group versus the placebo group (least squares mean, 0.34, $P = .008$, and 0.46, $P = .023$, respectively). At 24 months, there was significant FAQLQ-PF score improvement in participants initially randomized to treatment who met the efficacy primary end point (n = 74; least squares mean, 0.55; $P < .001$) and in participants with any eliciting dose increase (n = 127; least squares mean, 0.66; $P < .001$). FAQLQ-PF improvements were observed in social dietary limitations ($P = .002$), food-related anxiety ($P = .029$), and emotional impact ($P = .048$) domains. FAQLQ-CF improvements were observed in risk of accidental exposure ($P = .002$) and allergen avoidance ($P = .04$) domains. Nearly all outcomes met a nontreatment context minimal clinically important difference previously cited for FAQLQ.

CONCLUSIONS: Epicutaneous immunotherapy treatment was observed to be associated with significant global and domain-specific FAQL improvement (FAQLQ-PF/FAQLQ-CF), largely driven by increases in eliciting dose, in children with peanut allergy. **(J Allergy Clin Immunol Pract 2021;9:216-24)**

Key words: *Peanut; Food allergy; Food allergy quality of life; Epicutaneous immunotherapy; Immunotherapy; FAQLQ; Patient-centered outcomes*

INTRODUCTION

Peanut allergy (PA) is a common and largely persistent food allergy with a growing prevalence, which affects an estimated 2% of children in the United States, the United Kingdom, and Australia.[1-3] PA is a common cause among fatal food allergy reactions in children globally, and peanut has been identified in the United States as a food very commonly associated with severe reactions/anaphylaxis and emergency department visits/hospitalizations.[1,4] The burden of constant vigilance, planning, and the need for avoidance have been previously observed to adversely impact patients of all age groups as well as parents of food-allergic children. As a consequence of these and related factors, food allergy quality of life (FAQL) has been consistently shown to be negatively impacted across multiple domains in children with PA.[5-7]

Currently, PA is managed with strict avoidance of peanut-containing products and the use of an epinephrine autoinjector in the event of anaphylaxis as the standard of care.[8,9] Oral immunotherapy (OIT), sublingual immunotherapy, and epicutaneous immunotherapy (EPIT) are allergen-specific immunotherapies (ITs) being evaluated for the treatment of peanut and other food allergies.[10] In the United States, a proprietary form of peanut OIT was recently approved by the US Food and Drug Administration.[11] Although FAQL is increasingly used as a valued measure of success in clinical trials, it has not been consistently studied in food IT trials to date; however, a small number of studies have demonstrated improvements in FAQL attributable to therapy within EPIT and OIT clinical trials.[12,13]

The Food Allergy Quality of Life Questionnaires (FAQLQs)—Parent Proxy Form (FAQLQ-PF) and Child Form (FAQLQ-CF)—were developed to assess FAQL in children (child form [CF], self-report by children aged ≥8 years; parent proxy form [PF], parent proxy report of a child aged <12 years).[14,15] These measures, which help to provide a window into the patient perspective of the burden of food allergy, have been validated in multiple settings[16-19] and are the most widely used patient-reported outcome measure instruments in food allergy. More recently, they have been incorporated into several pivotal food IT clinical trials as secondary outcome measures.[12,20,21]

The aim of the current study was to examine whether treatment with EPIT for PA resulted in changes in the FAQL of children with PA who completed 12 months of therapy during the phase 3 Peanut EPIT Efficacy and Safety Study (PEPITES) study and the first 12 months of the follow-on open-label extension study PEPITES Open Label Extension Study (PEOPLE), as measured by FAQLQ-PF and FAQLQ-CF assessments.

METHODS

Study design

PEPITES was a phase 3, multicenter (the United States, Europe, Canada, and Australia), randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of the epicutaneous peanut patch (DBV712 250 μg) in 356 children aged 4 to 11 years with physician-diagnosed PA, who reacted to less than or equal to 300 mg peanut protein on entry double-blind placebo-controlled food challenge (DBPCFC).[22] Participants were randomized 2:1 to receive DBV712 250 μg epicutaneous peanut patch or placebo patch daily for 12 months.[22] The primary outcome was defined as reaching a month-12 eliciting dose (ED) of greater than or equal to 300 mg (in patients with an entry baseline ED of ≤10 mg, representing a

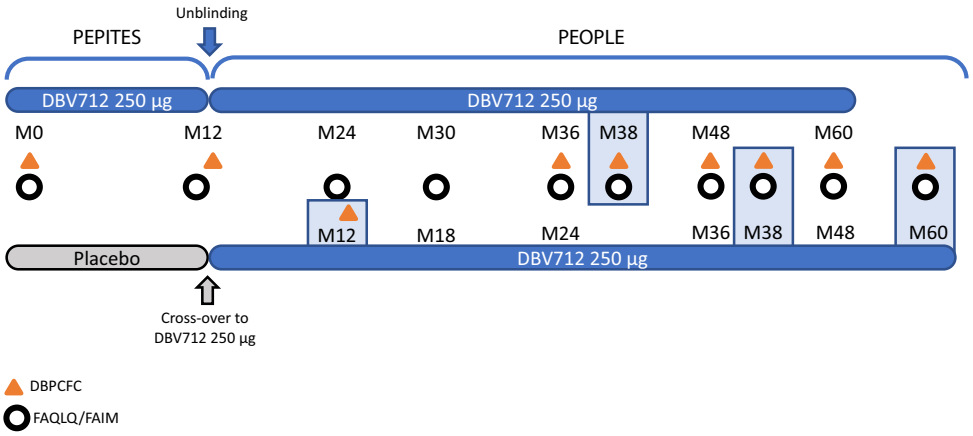

FIGURE 1. Study design. In the phase 3 PEPITES study, children aged 4 to 11 years were randomized 2:1 to receive DBV712 250 µg or placebo patch daily for 12 months. Patients completing PEPITES were eligible to enroll in the ongoing open-label extension PEOPLE trial for a total of up to 5 years of treatment. FAQLQ and FAIM assessments (open circles) were performed throughout the study. Changes in FAQL during the first 24 months of the study are reported here.

≥30-fold increase) or a month-12 ED of greater than or equal to 1000 mg (in patients with an entry baseline ED of >10 mg and ≤300 mg) as assessed by a DBPCFC.[22] These results have been previously published. All participants completing the 12-month PEPITES study were eligible to enroll in PEOPLE, an ongoing open-label extension of the phase 3 PEPITES trial designed to evaluate the long-term safety, tolerability, and efficacy of DBV712 250 µg for a total of up to 5 years of treatment for all enrolled children (ClinicalTrials.gov identifier: NCT03013517).[23] The current report relates to FAQL in children during PEPITES, where children were initially randomized to receive DBV712 250 µg or placebo, and the first 12 months of the open-label extension, where all children received DBV712 250 µg. For the purposes of this report, children initially randomized to active treatment during PEPITES are referred to as the DBV712 250 µg group and those initially randomized to placebo during PEPITES (although they later received active treatment during PEOPLE) are referred to as the placebo group.

FAQL assessments

FAQL was assessed at baseline, at month 12 (immediately before the DBPCFC, with treatment allocation blinded), and at month 24 (immediately before the DBPCFC for children initially randomized to placebo during PEPITES, with treatment unblinded). These assessments included the FAQLQ-PF report, the FAQLQ-CF self-report, and the Food Allergy Independent Measure (FAIM) (Figure 1). Details of the instrument precision and validation have been published previously.[14,15,24] Briefly, the FAQLQ-PF is a proxy report (eg, parental impression of the child's FAQL) that was administered to parents of all participants 12 years and younger, whereas the FAQLQ-CF was self-administered by children aged 8 to 12 years at study entry. No measure of parental FAQL related to the child's food allergy was included in the trial. The FAQLQ-PF gives a total score consisting of scores of 3 subscales: emotional impact, food anxiety, and social and dietary limitations. The FAQLQ-CF gives a total score consisting of scores of 4 subscales: allergen avoidance, risk of accidental exposure, emotional impact, and dietary restrictions. Both the FAQLQ-PF and FAQLQ-CF are scored identically using a 7-point Likert scale from 0 to 6. A higher score indicates worse FAQL (ie, a higher impact or burden) for the recall period. The clinical significance of changes in quality-of-life measures is assessed through evaluating a minimal clinically important difference (MCID), the smallest difference in score that patients perceive as beneficial, and would mandate, in absence of troublesome side effects and excessive cost, a change in the patient's management.[25,26] The MCID concept has several benefits. First, it links the magnitude of an observed change to subsequent treatment decisions in clinical practice, and second, it is patient-centered in that it places emphasis on the perspective of the patient living with food allergy. For 7-point Likert scales analyzing quality of life, previous studies have used an approximate measure of 0.5 as an MCID, based on work by Jaeschke et al[26] in cardiac and pulmonary disease, though this level is not specific to any quality-of-life index, and must be established for each index, disease state, and context of use.[26] A 2010 study in 82 parents of children undergoing oral food challenge (OFC) to several types of foods (including 26 with PA) calculated an MCID of 0.45 to 0.5 for the FAQLQ-PF using a distributional-based method involving the standard error of measurement for pre-post OFC change, measured longitudinally at 6-month intervals in the non—allergen-specific total sample.[19,27,28] This did not involve measuring change under the construct of either treatment or prolonged duration of treatment, but represents a plausible target for approximate MCID, which may have applicability for the use of this index for measuring meaningful change in peanut treatment. However, no specifically calculated MCID for allergy treatment using this index exists, and this range remains approximate. No MCID has been calculated for the FAQLQ-CF. The FAIM was initially developed as an anchoring measure for the FAQLQ development validation, testing expectation of outcome, including perception of severity, but is commonly coadministered with the index and has independent validity. The FAIM includes 4 questions, also scored from 0 to 6, with higher scores indicating a worse expectation of adverse outcome if an allergen is accidentally ingested (eg, a severe reaction or death).[24]

Participants' FAQLQ/FAIM data were eligible for inclusion in the analysis if data were available for both time points being compared (ie, data from both baseline and month 24 from the same participant). For FAQLQ assessments where more than 20% of

TABLE I. LS mean change from baseline in FAQLQ and FAIM total scores by treatment group

	DBV712 250 μg + DBV712 250 μg (n = 175)	Placebo + DBV712 250 μg (n = 89)
FAQLQ-PF		
Baseline to month 12		
95% CI	−0.28 (−0.42 to −0.15)	−0.01 (−0.21 to 0.19)
P value	<.001	.896
Baseline to month 24		
95% CI	−0.26 (−0.40 to −0.12)	0.08 (−0.13 to 0.29)
P value	<.001	<.446
FAQLQ-CF		
Baseline to month 12		
95% CI	−0.33 (−0.54 to −0.13)	−0.40 (−0.72 to −0.09)
P value	.002	.012
Baseline to month 24		
95% CI	−0.85 (−1.07 to −0.63)	−0.39 (−0.72 to −0.06)
P value	<0.001	<0.02
FAIM-PF		
Baseline to month 24		
95% CI	−0.44 (−0.56 to −0.31)	−0.26 (−0.44 to −0.09)
P value	<.001	.003
FAIM-CF		
Baseline to month 24		
95% CI	−0.50 (−0.67 to −0.33)	−0.26 (−0.52 to 0.00)
P value	<.001	.048

items in any (sub-) scale were missing, the respective (sub-) score was not included in the analysis. For the purposes of our analysis, FAQL assessments performed at month 24 were used to make the primary comparisons between treatment groups. Month-12 assessments were collected before the DBPCFC at the end of the PEPITES study and at treatment unblinding, and therefore not used as the primary end point for analysis. The rationale for this sequencing was that knowledge of the patient's ED was the most plausible factor related to treatment that could be appreciated by enrolled children and their parents. Because all participants were blinded to treatment allocation up until entry into the PEOPLE study (eg, after the data lock of the PEPITES database) and had not yet completed the month-12 DBPCFC at the time of the month-12 FAQL assessment to know their food challenge outcome, it is likely that these month-12 FAQL assessments reflect gains or changes related to study participation alone, rather than reflecting treatment results. More simply put, detecting FAQL related to EPIT would not be possible before completing the month-12 food challenge and unblinding of the treatment arm, and therefore testing FAQL before this point would only reflect the effect of being in a trial, rather than the effect of the treatment.

Statistical analysis

Analyses of FAQLQ and FAIM were prespecified secondary outcomes, according to protocol and statistical analysis plans. Baseline, month-12, and month-24 FAQL (FAQLQ and FAIM) assessments were analyzed by analysis of covariance, according to between-group and in-group differences by longitudinal controlled repeated-measure analysis. All FAQL assessments were analyzed according to the randomized treatment allocation at baseline in the PEPITES trial (DBV712 250 μg or placebo). An exploratory analysis of FAQL change by treatment response was conducted, where response to treatment was defined as (a) those meeting criteria as a primary efficacy responder as per the PEPITES primary outcome assessed at month 12 and (b) any participant experiencing any improvement in ED as assessed at month 12, by treatment group and in the overall study population.

FAQLQ assessments were additionally analyzed post hoc by linear regression analysis using changes in mean and domain-specific FAQLQ-PF and FAQLQ-CF scores from baseline to month 24 as the dependent variable, and treatment group and month-12 FAQLQ assessments as prespecified independent variables. Additional exploratory independent variables that were analyzed included history of anaphylaxis, epinephrine use (ever, outside of the clinical trial OFCs), sex, race, age, peanut IgE, peanut skin prick test, eczema status, asthma status, and number of other food allergies.

Written informed consent was provided by all participants' parents or guardians, and assent from children 7 years of age or older, or per local institutional review board guidelines, was obtained. The study commenced on January 8, 2016.

RESULTS

Participants

A total of 356 children were enrolled in PEPITES, of whom 298 of 320 eligible children subsequently enrolled in the PEOPLE study (93% of those eligible), 83.7% of the intent-to-treat population. FAQLQ/FAIM assessments were available for analysis in a total of 262 (87.9%) children (DBV712 250 μg: n = 175; placebo: n = 87) who had evaluable assessments at both baseline and month 24, including FAQLQ-CF from 130 (94.9%) of 137 children aged 8 years and older who were eligible to complete the FAQLQ-CF (DBV712 250 μg: n = 90; placebo: n = 40). Complete FAIM-PF assessments were available for a total of 244 children (DBV712 250 μg: n = 162; placebo: n = 82) and FAIM-CF assessments for 123 children (DBV712 250 μg: n = 86; placebo: n = 37).

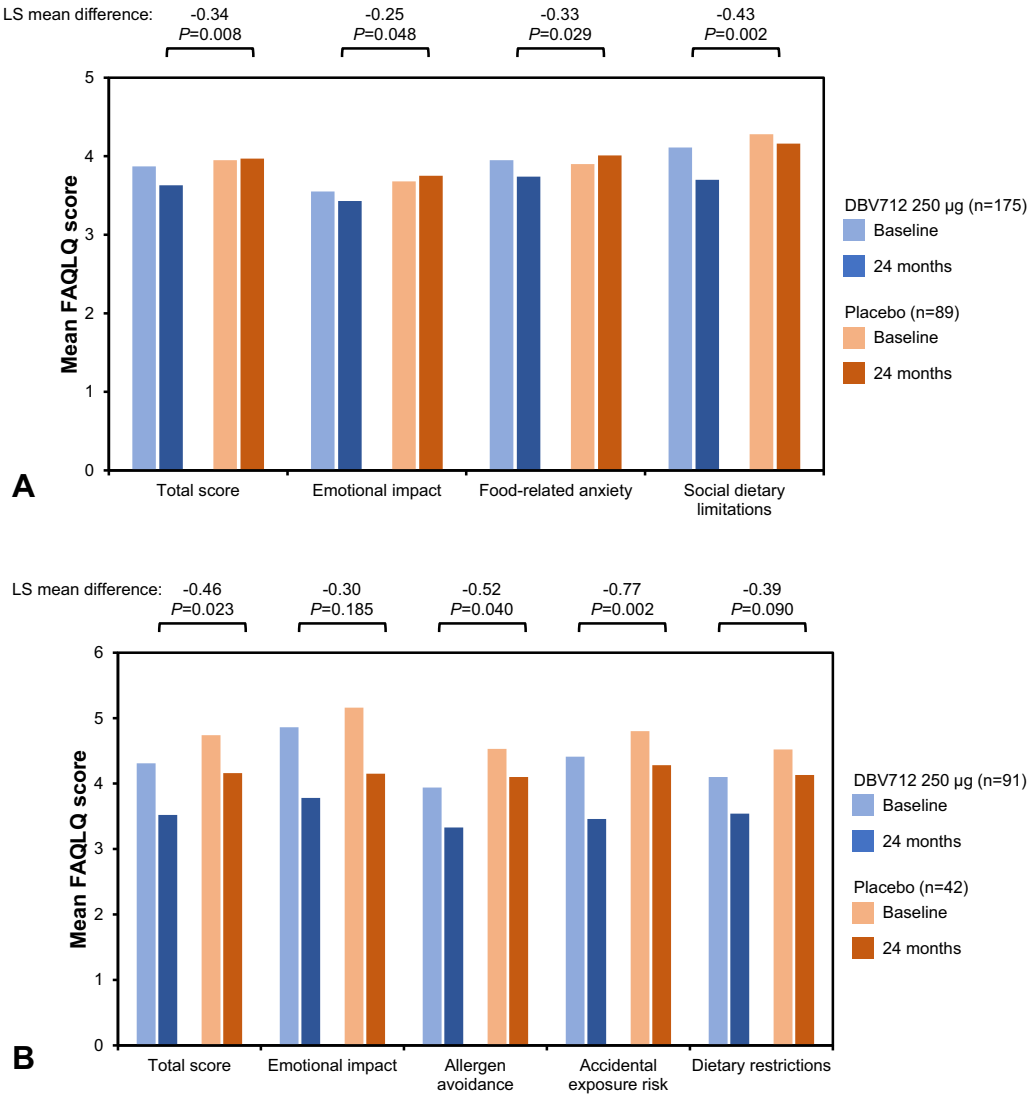

FIGURE 2. FAQLQ total score and subscales at month 24. FAQLQ assessments using the (**A**) parent form and (**B**) child form were analyzed at baseline and month 24 according to treatment group (DBV712 250 µg and placebo). The FAQLQ-PF gives a total score consisting of scores of 3 subscales: emotional impact, food anxiety, and social and dietary limitations. The FAQLQ-CF gives a total score consisting of scores of 4 subscales: emotional impact, allergen avoidance, risk of accidental exposure, and dietary restrictions. Both the FAQLQ-PF and FAQLQ-CF are scored identically using a 7-point Likert scale from 0 to 6. A higher score indicates worse FAQL.

FAQLQ-PF and FAQLQ-CF scores

Total scores on the FAQLQ-PF and FAQLQ-CF generally showed improvement in both the DBV712 250 µg and placebo groups, with least squares (LS) mean changes between baseline and month 24 of −0.26 and 0.08 (FAQLQ-PF) and −0.85 and −0.39 (FAQLQ-CF), respectively (Table I). There was significant further improvement in the FAQLQ-PF total score (ie, mean lower total score) observed in children after treatment with EPIT compared with placebo. The change from baseline to month 24 in FAQLQ-PF mean total scores was significantly larger in the DBV712 250 µg group compared with the placebo group (LS mean difference, −0.34, $P = .008$, where a negative score indicates FAQL improvement) (Figure 2, *A*). Significant mean score changes were also observed between treatment groups in the subscales of emotional impact ($P = .048$), food-related anxiety ($P = .029$), and social dietary limitations ($P = .002$). Similar improvement was also noted for the FAQLQ-CF after EPIT (measuring the child's own assessment of FAQL in the age-eligible population). The change from baseline to month 24 in FAQLQ-CF total scores was significantly greater in the DBV712 250 µg group compared with that in the placebo group (LS mean difference, −0.46; $P = .023$) (Figure 2, *B*), with significant changes also observed in the allergen avoidance ($P = .04$) and accidental exposure risk subscales ($P = .002$), though not in the emotional impact or dietary restrictions subscales.

FAQL among children receiving 24 months of active treatment

A total of 184 patients were randomized to the DBV712 250 µg group in the PEPITES study and then received an additional

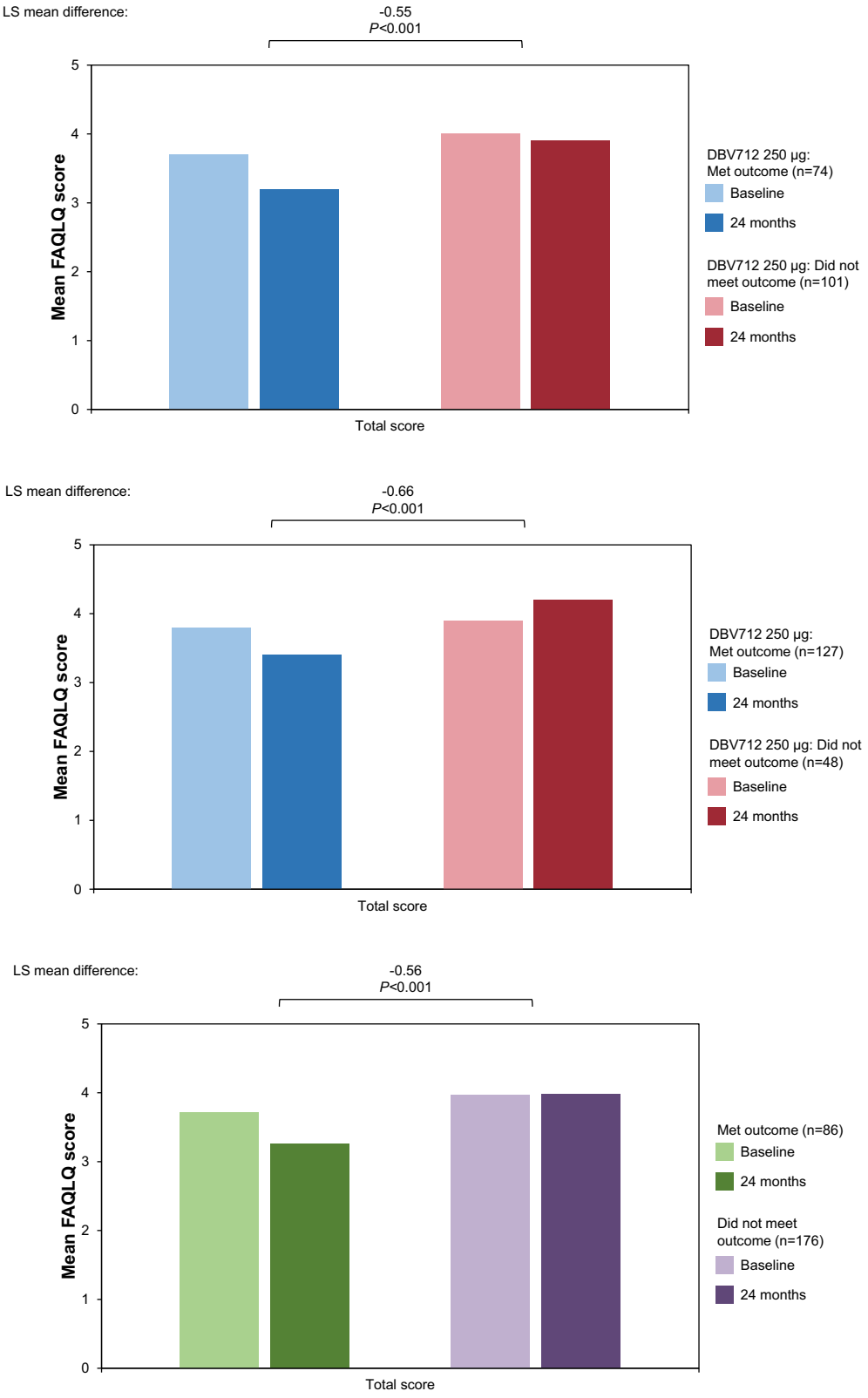

FIGURE 3. FAQLQ-PF total score at month 24 by treatment response at month 12. Exploratory analyses of FAQLQ-PF total scores at month 24 compared changes in FAQL according to treatment response: (**A**) patients in the DBV712 250 µg treatment group who met the primary end point* at month 12 of PEPITES compared with those who did not meet the primary end point, (B) patients in the DBV712 250 µg treatment group who experienced any increase in ED compared with those who did not, and (C) patients who met the primary end point at month 12 irrespective of treatment group. A higher score indicates worse FAQL. *The primary end point of PEPITES was defined as reaching a month-12 ED of greater than or equal to 300 mg (in patients with an entry baseline ED of $\leq$10 mg) or a month-12 ED of greater than or equal to 1000 mg (in patients with an entry baseline ED of $>$10 mg and $\leq$300 mg) as assessed by a DBPCFC.

12 months of DBV712 250 μg treatment in the first year of the open-label extension PEOPLE study. The relationship between response to EPIT treatment and FAQL was explored in this subgroup. Patients who met the predefined primary outcome (criteria described above) at the end of the PEPITES study had significant improvement in FAQLQ-PF score over the 24-month period compared with those who did not meet the primary outcome measure in the PEPITES study (LS mean difference, −0.55; $P < .001$) (Figure 3, *A*). Similarly, among the group that received DBV712 250 μg treatment for the entire 24 months, the FAQLQ-PF total score change from baseline was significantly greater among PEPITES patients experiencing any improvement in ED at month 12 compared with PEPITES patients without any ED change (LS mean difference, −0.66; $P < .001$) (Figure 3, *B*). No significant changes in FAQL were noted for treatment response based on either the primary outcome or on any increase in ED using the FAQLQ-CF.

Total month-24 FAQL change irrespective of initial treatment allocation in PEPITES

When the entire PEOPLE cohort was examined for relationship between response to therapy and changes in ED, irrespective of the participants' initial treatment group allocation (DBV712 250 μg or placebo in PEPITES), the month-24 change in FAQLQ-PF total scores was significantly greater in participants meeting the primary efficacy end point at month 12 compared with participants not meeting the end point (LS mean difference, −0.56; $P < .001$) (Figure 3, *C*).

Linear regression analysis

Linear regression analysis was performed to identify covariates impacting changes in FAQL, where the dependent variable was change in mean FAQL (month-24 baseline), with independent variables as described in the Methods section. Treatment group and patient age were jointly predictive of changes in FAQL from baseline to month 24 according to the FAQLQ-PF (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). According to the FAQLQ-CF, treatment group, FAQLQ total score at month 12, ethnicity, and history of asthma were jointly prognostic of FAQL change from baseline to month 24 (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

Food Allergy Independent Measure

Total scores on the FAIM-CF showed improvement in both DBV712 250 μg and placebo groups between baseline and month 24, with LS mean changes of −0.50 and −0.26, respectively (Table I). Similarly, parent score for expectation of outcome if an accidental ingestion occurred (FAIM-PF) showed improvement in both DBV712 250 μg and placebo groups between baseline and month 24, with LS mean changes of −0.44 (DBV712 250 μg) and −0.22 (placebo). In addition, changes from baseline to month 24 in FAIM total scores were greater in the DBV712 250 μg group compared with the placebo group for both PF and CF, although these comparisons between treatment groups did not reach statistical significance (LS mean difference, −0.17, $P = .12$, and −0.24, $P = .13$, respectively).

DISCUSSION

Use of food allergy–specific quality-of-life measures is a valuable addition in determining the clinical impact of treatments on daily life from the patient perspective, consistent with a "patient-centered care" approach. Although FAQL is not currently accepted as a primary efficacy end point by the Food and Drug Administration, nonetheless it allows for the inclusion of the patient perspective, which is important in the evaluation of treatment impact and acceptability and for clinical decision making. In previous research on FAQL, both qualitative and quantitative, significant adverse impact has been observed, principally related to the persistent fear of an allergic reaction, a central theme captured by the FAQLQ measures. However, despite this being consistently documented, to date the field has lacked an intervention or treatment that can directly improve this fear and concomitant restrictive impacts on diet and social activities.

Food allergy ITs are felt to be one such potential intervention. Indeed, from smaller, early-phase trials of OIT, there has been evidence that FAQL may improve after OIT, as demonstrated by a 1.61 mean decrease in FAQLQ-PF score among treatment responders in the STOP II trial.[21] Because EPIT is a novel and proprietary investigative technology, there have been far fewer EPIT studies performed as compared with OIT. Outside of a very small follow-on pilot study of patients at a single center from the phase 2 OLFUS-VIPES EPIT study (where improvement was noted),[12] no EPIT FAQL data have been described previously.

Herein, we demonstrate evidence that supports that treatment with DBV712 250 μg is associated with significant FAQL improvement in children across multiple domains, as measured by the FAQLQ and reported by the children themselves and by parents on their behalf. The findings suggest that fears and restrictions relating to daily life have been lessened. The longitudinal validity of the FAQL measures has previously been established; however, there is still work to be done on defining the MCID for all age groups. It is difficult also to determine the clinical meaningfulness of these changes because the MCID for a treatment trial may differ from the MCID for a chronic study. However, all but 1 finding exceeds the 0.45 MCID for the FAQLQ-PF established for 6 months pre-post OFC change, a similar food allergy quality-of-life index, which provides indication that the degree of change is likely clinically meaningful as well. Work regarding MCID by Revicki et al[29] has suggested that most index MCIDs fall into a range between 6% and 10% of the total score, which corresponds to effect sizes (LS mean difference in our case) of 0.3 to 0.5 SDs as indicative of meaningful change. Significant improvements were also found in FAIM scores corresponding to reductions in the parents' and children's expectation of the likelihood of a severe reaction and of death occurring on accidental ingestion of peanut. Taken together, these findings suggest that EPIT treatment had a meaningful impact on the lives of children and adolescents. We believe these unique and important findings add value to the field. These are encouraging findings, in particular because the child and proxy measures of improvement appear concordant. Previous reports of FAQL improvement in clinical trials are generally limited to the PF measure alone. Our findings build upon the similar data regarding FAQL reported by Lewis et al[12] in a small sample of phase 2 OLFUS-VIPES patients, including improvement noted after rollover into the open-label extension phase.

Another novel and important aspect of this study is that it provides evidence that FAQL improvement is likely attributable to treatment effect and not to clinical trial participation alone. FAQL improvement in our population was largely driven by patients experiencing either response as defined by the prespecified primary outcome of the PEPITES study, or by any improvements in ED, as assessed by the month-12 DBPCFC.

Similar improvement was not seen in those without such a response. We note here that any degree of desensitization (increased ED) was associated with this improvement, and that this improvement was not restricted to those participants who achieved a prespecified "responder" cutoff. The improvement seen among patients experiencing any gain in ED from baseline is also consistent with findings previously reported in a qualitative study of caregivers of phase 3 trial participants, where important treatment goals were achieving a "buffer" of protection, indicating that small increases in dose threshold (eg, including small ED increases) may be important and meaningful to families.[30] The significant findings in the adjusted regression analysis further substantiate that the FAQL changes were most likely attributable to treatment effect. FAQL improvement at month 24 in the treatment group persisted irrespective of sex, age, or history of anaphylaxis, and change was not found to be driven by the degree of FAQL impairment at baseline. These effects were noted in addition to general FAQL improvements that were observed in the placebo arm at month 12, consistent with the notion that study participation irrespective of group allocation may positively (or in some cases negatively) influence FAQL, and should be taken into account during analysis and study design. These will be potentially important findings if EPIT with DBV712 250 μg is incorporated into clinical practice, and will help inform shared decision-making discussions between patients/caregivers and health care providers around topics such as whether some type of limited or "mini" open food challenge may be worth pursuing after some period of time on treatment. These involve assessment of values and treatment goals that are beyond the scope of the current article, however.

A recent meta-analysis of 6 placebo-controlled OIT studies where FAQL was an outcome noted some form of significant improvement in FAQL scores for either a parental, parental burden, or CF rating over treatment, though none showed changes in all 3 measures. Similar FAQL improvement in the FAQLQ-PF score (but not in the FAQLQ-CF score) was noted in a 6-month open-label extension of the peanut OIT PALISADE study, but only within a subset of 110 participants from the larger parent study.[31] Although the FAQL improvement in the PF in the aforementioned STOP II trial was quite large, the gains in both the active and control groups were seen over the course of treatment, which may have reflected study participation and not actual treatment effect. Food allergy IT strategies differ considerably, and therefore the adverse event profiles and dose escalation protocols are very different between OIT and EPIT. It is possible that FAQL is differentially impacted, including a different magnitude of change, by the differences in the protocols and routes of administration. Nonetheless, treatment by either route has the potential to improve poor FAQL.

There are several limitations to the data we present. First, because of the age range of the children in the PEPITES/PEOPLE study (ages 4-11 years), not all children were able to self-assess their FAQL via the FAQLQ-CF, though all enrolled children had parents provide proxy assessments of FAQL via the FAQLQ-PF and the FAIM. Nonetheless, the FAQLQ-CF results may not be representative across the whole cohort, and are fewer in number than the proxy assessments. This is an accepted limitation in FAQL research, where the reliability of the child self-report is age-dependent. Because FAQL was a secondary outcome in the PEPITES/PEOPLE trials, no stratified sampling approach was taken to compensate for this. Despite the potential lack of statistical power, significant differences in FAQL were still observed in multiple domains, and future studies of PA IT with changes in FAQL as a primary outcome should be considered. Second, the timing of the month-12 FAQL assessments in the PEPITES study (before the peanut challenge outcome and unblinding) did not allow for assessment of robust treatment-related changes in FAQL. Because the month-12 FAQL assessment occurred before any potential ED change was known, this most likely reflects FAQL related to trial participation. As mentioned in a blinded study where daily management did not change, we would not expect to see differences between active and placebo arms before any treatment benefit has been realized. The use of a 24-month horizon for FAQL assessments allowed for the change in ED and knowledge of the PEPITES treatment assignment to be incorporated into the assessment, as well as for all patients to have received at least 12 months of active treatment in the PEOPLE study. It is possible that measuring FAQL at the 24-month time point has some carryover effect of the unbinding; however, all participants had received 12 months of active therapy by this time point, and therefore it is unlikely that unblinding was a primary driver of the observed differences. In the PALISADE trial,[31] investigators also noted limited FAQL change until after unblinding, which suggests a fixed limitation in current food allergy IT trial design if FAQL or other patient-reported outcomes are measured before the exit DBPCFC and unblinding. Third, not all enrolled caregivers/participants had completed FAQL assessments available for analysis, although most did. This may skew the cohort being assessed to those who would be more likely to positively assess their FAQL, though overall adherence with completing the index was more than 80% over the 2-year period. Likewise, because we were unable to capture data from those subjects who either did not roll over into the PEOPLE study, or who discontiunted either PEPITES or PEOPLE, it is possible that this may have skewed the results to more favorable changes in health-related quality of life, although it is unlikely to have altered the comparisons between those children initially on placebo compared with DBV712 250 μg in PEPITES. Fourth, although all subscales in the FAQLQ-PF demonstrated change, only 2 of the 4 subscales in the FAQLQ-CF noted change. Although the total score is the most crucial parameter in which to demonstrate change, with respect to EPIT it is unclear which subscales would be expected to change, at what point change is likely to occur, and to what degree. This is an evolving area for future study because this is the first such report of any form of IT to show improvement in the FAQLQ-CF. Fifth, use of the FAQLQ indices is limited by lack of a known MCID specific for a treatment and prolonged longitudinal use context, and although most of our findings exceeded an FAQLQ MCID estimate for short-term change after OFC, a few fell just below this level. Therefore, it is difficult to definitively specify the clinical meaningfulness of any of the statistically significant trends in this treatment study, or any other treatment study. Taken together, however, these findings suggest that EPIT treatment had a meaningful impact on the lives of children and adolescents. Finally, as is the case for all clinical intervention studies in food allergy, the DBPCFC as a measure of treatment response, although the best tool currently available, and in line with Food and Drug Administration guidance on the appropriate outcome assessments for evaluation of treatment, remains a surrogate only for real-world reduction in harm.

CONCLUSIONS

This study demonstrates that EPIT treatment of PA, when associated with improvement in ED, was associated with significant improvement in FAQL from baseline to month 24, from both the child's perspective and the parent's proxy impression for the child. Importantly, although change was certainly noted among those meeting the primary efficacy end point for the PEPITES trial, improvement was also noted among those achieving smaller gains in ED, which may be of real-world significance. Furthermore, there was a significant change noted in subscales dealing with social and dietary limitations and with risk of accidental exposure, including expectations of subsequent severe reactions and/or death, domains that align well with the proposed effect of EPIT desensitization, and caregivers' reported goals when seeking therapy.

Longitudinal study of peanut EPIT is ongoing to better understand the clinical relationship between intermediate and long-term ED changes, product safety, and FAQL, as well as how FAQL may evolve among patients who experience changes in their ED. These data contribute to the growing body of literature demonstrating that there may be potential interventions that can help improve FAQL. It will be important to evaluate health-related quality-of-life outcomes in the real-world setting with DBV712 250 μg, if approved, for the treatment of PA.

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TABLE E1. Covariates impacting changes in FAQL according to parent assessment (FAQLQ-PF total scores) based on linear regression

	P values			
Base model + covariate	**Model fit**	**Month-12 FAQL**	**Treatment**	**Covariate**
History of anaphylaxis	.03	.54	.03	.08
Sex	.0009	.48	.03	.001
Age	.002	.15	.05	.002
Peanut IgE	.14	.41	.04	.04

	Parameter estimates	**SE**	***P* value**
Intercept	0.59	0.20	.003
Treatment	−0.37	0.19	.05
Age	−0.60	0.18	.001

SE, Standard error.

TABLE E2. Covariates impacting changes in FAQL according to child assessment (FAQLQ-CF total scores) based on linear regression

	P values			
Base model + covariate	**Model fit**	**Month 12 FAQL**	**Treatment**	**Covariate**
Sex	.04	.10	.28	.03
Race	.01	.04	.10	.01
History of asthma	.02	.12	.20	.02

	Parameter estimates	**SE**	***P* values**
Intercept	−0.62	0.41	.13
Treatment	−0.37	0.22	.09
Month-12 FAQL	0.14	0.07	.04
Sex	−0.36	0.20	.08
Race	−0.62	0.26	.02
History of asthma	0.39	0.20	.05

SE, Standard error.