Supplementary Online Content

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eTable 1. Double-Blind, Placebo-Controlled Food Challenge: Efficacy Outcome Scoring With Standardized Challenge Matrix

eTable 2. Summary and Analysis of Treatment Responders at Month 12 by Treatment Group According to the Treatment Actually Received (Per-Protocol Population)

eTable 3. Summary and Analysis of Treatment Responders at Month 12 Using Worst-Case Imputation and Multiple Imputation by Treatment Group (Intention-to-Treat Population)

eTable 4. Summary and Analysis of Cumulative Reactive Dose at Month 12 Using Last-Observation-Carried-Forward Imputation by Treatment Group and Age Groups (Intention-to-Treat Population)

eTable 5. Actual Values, Change From Baseline, and Improvement in Severity Based on the Oral Food Challenge Score Sheet Using Last-Observation-Carried-Forward Imputation by Treatment Group (Intention-to-Treat Population)

eTable 6. Analysis of Immunological Markers (Log-Transformed) at Month 12 Excluding Missing Data by Treatment Group (Intention-to-Treat Population)

eTable 7. Primary End Point (Last-Observation-Carried-Forward Imputation, Phase 2b Trial Only) per Year and Age Groups

eFigure 1. Study Design

eFigure 2. Baseline Eliciting Dose

eFigure 3. Peanut Skin Prick Test Median (Interquartile Range) Wheal Diameters Over the 12-Month Phase 2b Trial at 3 Dilutions (Undiluted, 1/10 and 1/100) by Treatment Group

eAppendix. Study Methodology

eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Double-Blind, Placebo-Controlled Food Challenge: Efficacy Outcome Scoring With Standardized Challenge Matrix[1]

Category	Objective Symptoms	Grade				Subjective Symptoms
I. Skin	A. Erythematous rash: % area involved					
	B. Pruritus	0	1	2	3	
	C. Urticaria/Angioedema	0	1	2	3	
	D. Rash	0	1	2	3	
II. Upper Respiratory	A. Sneezing/Itching	0	1	2	3	
	B. Nasal congestion	0	1	2	3	
	C. Rhinorrhea	0	1	2	3	
	D. Laryngeal	0	1	2	3	
III. Lower Respiratory	A. Wheezing	0	1	2	3	
IV. Gastrointestinal						**A. Subjective Complaints**
		0	1	2	3	Itchy mouth
		0	1	2	3	Itchy throat
		0	1	2	3	Nausea
		0	1	2	3	Abdominal pain
	B. Objective Complaints					
	Diarrhea	0	1	2	3	
	Vomiting	0	1	2	3	
V. Cardiovascular	Normal heart rate to bradycardia	0	1	2	3	

In red, challenge was stopped in case of objective symptoms likely to indicate a true reaction. In yellow, symptoms likely to indicate a true allergic reaction if 2 or more categories concerned. In green, challenge was to be continued.
Standardized challenge matrix[1]: chocolate dessert base formula.
Standardized semi-logarithmic increase of peanut protein doses every 30 min: per Practall Guidelines (PRACTALL)[2].
Allergic symptoms graded from a standardized published protocol[3] (see score sheet below). Stopping rules are also noted below.

Oral Food Challenge Symptom Score Sheet[4]

Possible reactions

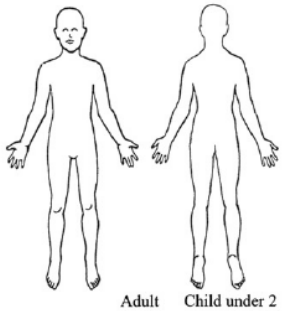
I. Skin

A. Erythematous rash: % area involved (see body surface area diagram)

B. Pruritus
- 0 = Absent
- 1 = Mild, occasional scratching
- 2 = Moderate: scratching continuously for > 2 minutes at a time
- 3 = Severe: hard continuous scratching

C. Urticaria / angioedema
- 0 = Absent
- 1 = Mild: less than 3 hives
- 2 = Moderate: more than 3 and less than 10 hives
- 3 = Severe: generalized involvement

D. Rash
- 0 = Absent
- 1 = Mild: few areas of faint erythema
- 2 = Moderate: areas of erythema, macular and raised rash
- 3 = Severe: generalized marked erythema (>50%), extensive raised lesion (>25%), vesiculation and / or piloerection



	Adult	Child under 2
Head	4.5%	8.5%
Neck	1%	
Anterior trunk	18%	18%
Posterior trunk	18%	18%
Leg	18%	14%
Arm	9%	9%

II. Upper respiratory

A. Sneezing/ Itching
- 0 = Absent
- 1 = Mild: rare bursts
- 2 = Moderate: bursts<10, intermittent rubbing of nose / eyes / external ear canals
- 3 = Severe: continuous rubbing of nose / eyes, periocular swelling and / or long bursts of sneezing

B. Nasal Congestion
- 0 = Absent
- 1 = Mild: some hindrance to breathing
- 2 = Moderate: nostrils feel blocked, breathing through mouth most of the time
- 3 = Severe: nostrils occluded

C. Rhinorrhea
- 0 = Absent
- 1 = Mild: occasional sniffling
- 2 = Moderate: frequent sniffling, requires tissues
- 3 = Severe: nose runs freely despite sniffling and tissues

D. Laryngeal
- 0 = Absent
- 1 = Mild: throat clearing, occasional cough
- 2 = Moderate: hoarseness, frequent dry cough
- 3 = Severe: inspiratory stridor

III. Lower respiratory

A. Wheezing
- 0 = Absent
- 1 = Mild: expiratory wheezing to auscultation
- 2 = Moderate: dyspnea, inspiratory and expiratory wheezing
- 3 = Severe: dyspnea, use of accessory muscles, audible wheezing

IV. Gastrointestinal

A. Subjective Complaints
- 0 = Absent
- 1 = Mild: itchy mouth, nausea, abdominal pain, no change in activity
- 2 = Moderate: frequent complaints of nausea or pain, decreased activity
- 3 = Severe: patient in bed; crying, notably distressed

B. Objective Complaints
- 0 = Absent
- 1 = Mild: 1 episode of emesis or diarrhea
- 2 = Moderate: 2-3 episodes of emesis or diarrhea or 1 of each
- 3 = Severe: >3 episodes of emesis or diarrhea or 2 of each

V. Cardiovascular
- 0 = Absent: normal heart rate and / or blood pressure for age or patient's baseline
- 1 = Mild: color change, subjective response (weak, dizzy), mental status change, tachycardia
- 2 = Moderate: drop in blood pressure >20% from baseline
- 3 = Severe: cardiovascular collapse, signs of impaired circulation, unconsciousness, bradycardia

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Stopping Rules

Only **clear-cut, objective, or immediate-type symptoms requiring treatment** were considered appropriate for discontinuing the double-blind, placebo-controlled food challenge and determining the eliciting dose. The main objective symptoms to expect were as follows (the list is not exhaustive):

Generalized pruritus, flushing, local or generalized urticaria, hives, swollen lips, swollen tongue, throat tightness, vomiting, diarrhea, dyspnea, rhinorrhea, repetitive sneezing, wheezing, conjunctivitis, asthma, drop of the peak expiratory flow (PEF), hypoxia, hypotension, hypotonia, decreased level of consciousness associated with collapse and/or incontinence or other life threatening symptoms.

More specifically, the challenge should have been stopped if:

- there was a >1-point rise in any objective symptom from any category in the oral food challenge (OFC) Symptom Score Sheet;
- 2 or more categories in the OFC Symptom score sheet showed at least a 1-point rise in an objective symptom;
- there was a 1-point rise in an objective symptom from any category in the OFC Symptom score sheet with the following exceptions:
  - I.B. Pruritus (0 to 1)
  - I.C. Urticaria (0 to 1)
  - I.D. Rash (0 to 1)
  - II.A Sneeze (0 to 1)
  - II.B. Nasal congestion (0 to 1)
  - II.C. Rhinorrhea (0 to 1)
  - II.D. Laryngeal (0 to 1 if explainable and not persistent)

Further details were provided in the Manual of Procedures for the double-blind, placebo-controlled food challenge.

In case of subjective symptoms, e.g., mouth pruritus, throat pruritus, nausea, abdominal pains, or any other subjective symptoms at a specific dose, the investigator could extend the time between the last dose and the next dose to see how the subject's symptom(s) evolved. The same dose could be repeated to check whether the subjective symptom(s) reappeared and with what intensity, or whether an objective symptom(s) now appeared. If (an) objective symptom(s) appeared, that would be the end of the food challenge. If only (a) subjective symptom(s) still persisted, the next higher dose was then given to the subject, and the challenge would continue until the appearance of a clear objective symptom, at which time the challenge would be stopped.

As a safety precaution, the objective symptom(s) signaling the end of the double-blind, placebo-controlled food challenge was/were treated by administration of the best medications to the subject, per the Investigator's judgment.

The investigator and medical staff used their own clinical judgment for the most effective treatment to give to the subject considering his/her age, the type of the allergic reactions and severity. Also, they referred to recommendations made by Sampson et al. for treating anaphylaxis (Sampson, *J Allergy Clin Immunol*. 2006).[5]

Suggested treatments for the different objective symptoms were detailed in the Manual of Procedures for the double-blind, placebo-controlled food challenge provided to the sites.

eTable 2. Summary and Analysis of Treatment Responders at Month 12 by Treatment Group According to the Treatment Actually Received (Per-Protocol Population)

All Patients	Placebo-patch (N=49)	50µg-patch (N=51)	100µg-patch (N=47)	250µg-patch (N=49)
Treatment Response at Month 12				
Responders, n (%)[a]	13 (26.5)	24 (47.1)	22 (46.8)	26 (53.1)
95% CI[b]	14.9, 41.1	32.9, 61.5	32.1, 61.9	38.3, 67.5
Eliciting dose ≥1,000 mg after 12 months, n (%)	6 (12.2)	14 (27.5)	17 (36.2)	18 (36.7)
≥10-fold increase in the eliciting dose after 12 months, n (%)	10 (20.4)	16 (31.4)	14 (29.8)	21 (42.9)
Non-responders, n (%)	36 (73.5)	27 (52.9)	25 (53.2)	23 (46.9)
P value vs. placebo[c]	—	—[d]	—[d]	0.01
Risk ratio (95% CI)[e]	1.0 [reference]	1.8 (1.0, 3.1)	1.76 (1.0, 3.1)	2.0 (1.2, 3.4)
Risk difference (95% CI)[f]	—	20.5 (2.1, 39.0)	20.3 (1.4, 39.1)	26.5 (7.9, 45.2)

CI=confidence interval; LOCF=last observation carried forward.

The eliciting dose is defined as the last single dose administered in the double-blind, placebo-controlled food challenge prior to the development of objective clinical symptoms.

[a]A patient could meet both sets of criteria and would therefore be categorized in both criteria category counts. Percentages were based on the number of patients in the Per-Protocol population for each treatment group. Note: A treatment responder was defined as a patient with an eliciting dose of ≥1,000 mg peanut protein after 12 months of treatment or a patient with a ≥10-fold increase in the eliciting dose at Month 12 compared to the initial eliciting dose, based on the results of the two double-blind, placebo-controlled food challenges. For patients with missing treatment response at Month 12, LOCF imputation was used (i.e., patients were considered non-responders).

[b]CI using Clopper-Pearson (Exact) method.

[c]*P* value based on two-tailed Fisher's Exact test.

[d]*P* value not presented due to hierarchical stepwise analysis.

[e]Risk ratio and two-sided asymptotic 95% CI of achieving response in active treatment group compared to placebo group.

[f]Risk difference and two-sided asymptotic 95% CI of achieving response in active treatment group compared to placebo group.

eTable 3. Summary and Analysis of Treatment Responders at Month 12 Using Worst-Case Imputation and Multiple Imputation by Treatment Group (Intention-to-Treat Population)

All Patients	Placebo-patch (N=56)	50µg-patch (N=53)	100µg-patch (N=56)	250µg-patch (N=56)
Treatment Response at Month 12				
Responders, n (%)[a]	16 (28.6)	24 (45.3)	23 (41.1)	28 (50.0)
95% CI[b]	17.3, 42.2	31.6, 59.5	28.1, 55.0	36.3, 63.7
Eliciting dose ≥1,000 mg after 12 months, n (%)	7 (12.5)	14 (26.4)	18 (32.1)	18 (32.1)
≥10-fold increase in the eliciting dose after 12 months, n (%)	10 (17.9)	16 (30.2)	14 (25.0)	23 (41.1)
Non-responders, n (%)	40 (71.4)	29 (54.7)	33 (58.9)	28 (50.0)
P value vs. placebo[c] worst case imputation	—	—[d]	—[d]	0.03
P value vs. placebo[e] multiple imputation	—	—[d]	—[d]	0.008
Risk ratio (95% CI)[f] worst case imputation	1.0 [reference]	1.6 (0.9, 2.6)	1.4 (0.9, 2.4)	1.7 (1.1, 2.9)
Risk ratio (95% CI)[f] multiple imputation	1.0 [reference]	1.8 (1.0, 3.1)	1.8 (1.0, 3.0)	2.0 (1.2, 3.5)
Risk difference (95% CI)[g]	—	16.2 (-1.2, 34.6)	12.5 (-5.0, 30.0)	21.4 (3.8, 39.1)

CI=confidence interval.
The eliciting dose is defined as the last single dose administered in the double-blind, placebo-controlled food challenge prior to the development of objective clinical symptoms.
[a]A patient could meet both sets of criteria and would therefore be categorized in both criteria category counts. Percentages were based on the number of patients in the Intention-to-Treat population for each treatment group. Note: A treatment responder was defined as a patient with an eliciting dose of ≥1,000 mg peanut proteins after 12 months of treatment or a patient with a 10-fold increase in the eliciting dose at 12 months compared to the initial eliciting dose, based on the results of the two double-blind, placebo-controlled food challenges. For patients with missing treatment response at Month 12, worst-case imputation was used (i.e., patients from active treatment groups were considered non-responders and patients from the placebo group were considered responders).
[b]CI using Clopper-Pearson (Exact) method.
[c]*P* value based on Fisher's Exact test.
[d]*P* value not presented due to hierarchical stepwise analysis.
[e]Predictive Mean Matching method used for multiple imputations; *P* value computed by pooling logistic regression models post multiple imputations.
[f]Risk ratio and two-sided asymptotic 95% CI of achieving response in active treatment group compared to placebo group.
[g]Risk difference and two-sided asymptotic 95% CI of achieving response in active treatment group compared to placebo group.

eTable 4. Summary and Analysis of Cumulative Reactive Dose at Month 12 Using Last-Observation-Carried-Forward Imputation[a] by Treatment Group and Age Groups (Intention-to-Treat Population)

Cumulative Reactive Dose[a]	Placebo-patch	50µg-patch	100µg-patch	250µg-patch
Patients 6-55 Years of Age				
N	56	53	56	56
Number with missing data (replaced with LOCF)[b]	2	2	6	2
Actual value at Month 12 (mg)				
Mean (95% CI)	469.3 (233.1, 705.5)	730.8 (449.5, 1012.1)	917.0 (579.5, 1254.5)	1117.8 (727.3, 1508.3)
Median (Q1, Q3)	144.0 (44, 444)	244.0 (144, 1444)	444.0 (144, 1444)	444.0 (144, 1444)
LS means difference for treatment vs. placebo (95% CI)[c] at Month 12	—	124.3 (-9.0, 365.2)	173.7 (19.8, 449.8)	336.2 (110.9, 739.7)
P value vs. placebo	—	—[d]	—[d]	<0.001
Change from baseline to Month 12				
Mean (95% CI)	269.5 (40.8, 498.3)	541.0 (275.6, 806.4)	715.9 (395.9, 1035.9)	979.2 (596.3, 1362.1)
Median (Q1, Q3)	0.0 (-1.5, 140.7)	100.0 (0, 970)	35.0 (0, 1300)	385.0 (25, 1300)
LS means difference for treatment vs. placebo (95% CI)[e] at Month 12	—	120.0 (2.3, 321.8)	147.6 (19.7, 365.5)	386.0 (159.7, 771.2)
P value vs. placebo	—	—[d]	—[d]	<0.001
Patients 6-11 Years of Age				
N	31	28	26	28
Number with missing data (replaced with LOCF)[b]	1	0	2	0
Actual value at Month 12 (mg)				
Mean (95% CI)	239.1 (108.3, 369.9)	606.1 (295.6, 916.6)	704.4 (318.0, 1090.8)	1211.9 (588.8, 1835.0)
Median (Q1, Q3)	144.0 (44, 194)	194.0 (44, 1444)	444.0 (69, 1444)	444.0 (144, 1444)
LS means difference for treatment vs. placebo (95% CI)[c] at Month 12	—	111.9 (-4.4, 379.9)	165.0 (17.2, 509.7)	333.7 (92.5, 887.6)
P value vs. placebo	—	—[d]	—[d]	<0.001
Change from baseline to Month 12				
Mean (95% CI)	60.8 (-54.7, 174.7)	471.2 (181.8, 760.6)	570.0 (189.2, 950.8)	1121.0 (494.1, 1747.9)
Median (Q1, Q3)	0.0 (-28, 55)	135.0 (15, 977.5)	114.5 (0, 1225)	400.0 (25, 1407.5)
LS means difference for treatment vs. placebo (95% CI)[e] at Month 12	—	120.5 (9.2, 361.6)	141.1 (17.6, 411.4)	390.4 (133.6, 947.2)
P value vs. placebo	—	—[d]	—[d]	<0.001
Patients 12-55 Years of Age				

eTable 4. Summary and Analysis of Cumulative Reactive Dose at Month 12 Using Last-Observation-Carried-Forward Imputation[a] by Treatment Group and Age Groups (Intention-to-Treat Population)

Cumulative Reactive Dose[a] (continued)	**Placebo-patch** (continued)	**50µg-patch** (continued)	**100µg-patch** (continued)	**250µg-patch** (continued)
N	25	25	30	28
Number with missing data (replaced with LOCF)[a]	1	2	4	2
Actual value at Month 12 (mg)				
Mean (95% CI)	754.8 (254.2, 1255.4)	870.4 (365.3, 1375.5)	1101.3 (554.1, 1648.5)	1023.6 (513.4, 1533.8)
Median (Q1, Q3)	174.0 (144, 1444)	444.0 (144, 744)	394.0 (144, 1444)	444.0 (144, 1444)
LS means difference for treatment vs. placebo (95% CI)[c] at Month 12	—	38.6 (-102.2, 418.0)	-1.4 (-116.1, 303.0)	213.3 (-37.1, 886.3)
P value vs. placebo	—	—[d]	—[d]	0.13
Change from baseline to Month 12				
Mean (95% CI)	528.4 (35.8, 1021.0)	619.2 (136.2, 1102.2)	842.3 (326.7, 1357.9)	837.4 (361.0, 1313.8)
Median (Q1, Q3)	10.0 (0, 300)	0.0 (0, 600)	30.0 (0, 1225)	335.0 (77.5, 1071.7)
LS means difference for treatment vs. placebo (95% CI)[e] at Month 12	—	36.3 (-122.3, 374.6)	80.3 (-96.4, 445.3)	247.5 (-18.0, 801.9)
P value vs. placebo	—	—[d]	—[d]	0.08

ANCOVA=analysis of covariance; CI=confidence interval; LOCF=last observation carried forward; LS=least squares.
The cumulative reactive dose is the sum of all doses received in the double-blind, placebo-controlled food challenge prior to the development of objective clinical symptoms.
[a]For the purpose of this ANCOVA analysis, to differentiate patients who reacted to the highest dose of the double-blind, placebo-controlled food challenge and patients who passed the highest dose of this food challenge without an objective allergic reaction, a cumulative reactive dose value imputed to 4,444 mg was applied to patients who passed the challenge (i.e., by convention, 1,000 mg was added to the maximal cumulative reactive dose value of 3,444 mg).
[b]Missing scores for Month 12 were imputed from baseline values. Handling of missing data was carried out using LOCF method; namely, for each patient, a missing value at Month 12 was replaced by the baseline value.
[c]LS means and *P* value are based on type III sum of squares from an ANCOVA model on log-transformed values for the cumulative reactive dose at Month 12, including treatment group, and country as covariates. Back-transformed results are presented.
[d]*P* value not presented due to hierarchical stepwise analysis.
[e]LS means and *P* value are based on type III sum of squares from an ANCOVA model on log-transformed values for the cumulative reactive dose at Month 12, including treatment group, baseline cumulative reactive dose, and country as covariates. Back-transformed results are presented. The LS means for any given treatment group was the estimated mean peanut protein cumulative reactive dose for a patient in that treatment group with the mean value for all baseline covariates in the analysis population. The back-transformed LS means was a geometric LS means. The effect size for any given active treatment group versus placebo was the magnitude of the difference in mean peanut protein cumulative reactive doses between groups relative to the variability in peanut protein cumulative reactive doses within groups. Effect size was obtained by dividing the difference between LS means between the active treatment dose and placebo by the pooled SD of the peanut protein cumulative reactive doses.

eTable 5. Actual Values, Change From Baseline, and Improvement[a] in Severity Based on the Oral Food Challenge Score Sheet Using Last-Observation-Carried-Forward Imputation by Treatment Group (Intention-to-Treat Population)

Total Score	Placebo-patch	50µg-patch	100µg-patch	250µg-patch
Patients 6-55 Years of Age				
N	56	53	56	56
Baseline, n	56	53	56	56
Mean (95% CI)	7.0 (5.7, 8.2)	7.6 (6.2, 9.0)	6.4 (5.3, 7.5)	5.8 (4.9, 6.7)
Median (Range)	6.0 (1, 21)	6.0 (1, 22)	5.0 (1, 19)	5.0 (2, 19)
Month 12 – actual value, n	56	53	56	56
Mean (95% CI)	5.6 (4.5, 6.6)	5.7 (4.5, 6.9)	5.6 (4.4, 6.8)	6.0 (4.7, 7.3)
Median (Range)	5.0 (0, 19)	4.0 (1, 19)	4.0 (0, 21)	5.0 (0, 20)
Month 12 – change from baseline, n	56	53	56	56
Mean (95% CI)	-1.4 (-2.6, -0.2)	-1.9 (-3.2, -0.6)	-0.9 (-2.0, 0.2)	0.2 (-1.0, 1.4)
Median (Range)	-0.5 (-12, 8)	-2.0 (-16, 11)	-1.0 (-9, 17)	-0.5 (-7, 17)
Improved after 12 months, n (%)[b]	23 (41.1)	30 (56.6)	24 (42.9)	21 (37.5)
Did not improve after 12 months, n (%)[b]	33 (58.9)	23 (43.4)	32 (57.1)	35 (62.5)

LOCF=last observation carried forward.

[a]An improvement in total score is defined as a subject who has a decrease in total symptom score of two or more at Month 12 from baseline. The severity score is determined by adding all symptom scores recorded throughout the oral food challenge, not just the symptom score recorded at the final eliciting dose (the last single food challenge dose administered prior to the development of objective clinical symptoms). The total symptom score for each subject is then calculated (excluding erythematous rash and subjective complaints).

[b]Percentages are based on the number of subjects in the Intention-to-Treat Population for each treatment group.

eTable 6. Analysis of Immunological Markers (Log-Transformed) at Month 12 Excluding Missing Data by Treatment Group (Intention-to-Treat Population)

Parameter (units) Comparison	LS Means[a]		Difference in LS Means	
	Active-patch (95% CI)	Placebo-patch (95% CI)	Active-patch – Placebo-patch (95% CI)[a]	Active-patch – Placebo-patch *P* Value[a]
Peanut-specific IgE (kU_A/L)				
50µg-patch vs. placebo-patch	71.0 (57.7, 87.5)	52.0 (42.8, 63.3)	19.0 (3.1, 39.5)	—[b]
100µg-patch vs. placebo-patch	75.5 (61.8, 92.2)	52.0 (42.8, 63.3)	23.4 (6.8, 44.7)	—[b]
250µg-patch vs. placebo-patch	73.6 (60.8, 89.2)	52.0 (42.8, 63.3)	21.6 (5.7, 41.8)	0.005
Peanut-specific IgG4 (mg_A/L)				
50µg-patch vs. placebo-patch	1.9 (1.5, 2.5)	0.6 (0.5, 0.8)	1.3 (0.7, 2.0)	—[b]
100µg-patch vs. placebo-patch	2.0 (1.5, 2.5)	0.6 (0.5, 0.8)	1.3 (0.8, 2.1)	—[b]
250µg-patch vs. placebo-patch	2.8 (2.2, 3.5)	0.6 (0.5, 0.8)	2.2 (1.4, 3.2)	<0.001

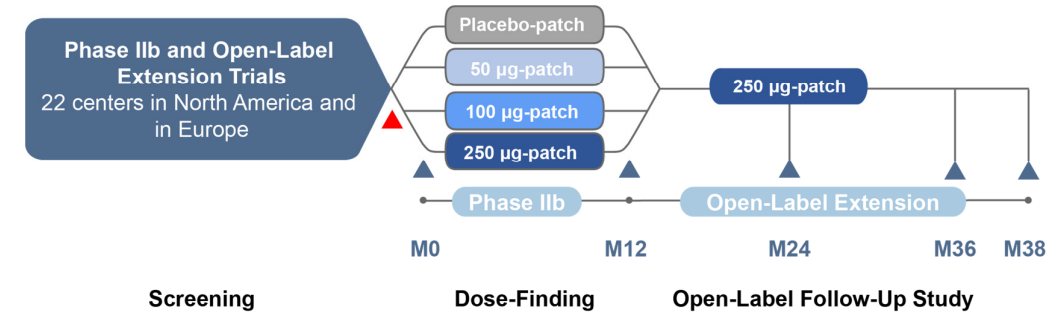
ANCOVA=analysis of covariance; CI=confidence interval; IgE=Immunoglobulin E; IgG4=Immunoglobulin G4; LS=least squares.
[a]LS means and *P* values were based on type III sum of squares from an ANCOVA model on log-transformed value for the Immunological Markers at Month 12, including treatment group, baseline marker, age stratum, and country as covariates.
Back-transformed results are presented. The LS means for any given treatment group was the estimated mean immunological marker for a patient in that treatment group with the mean value for all baseline covariates in the analysis population. The effect size for any given active treatment dose group vs. placebo is the magnitude of the difference in mean Immunological marker between groups relative to the variability in immunological marker within groups.
[b]*P* value not presented due to hierarchical stepwise analysis.

eTable 7. Primary End Point (Last-Observation-Carried-Forward Imputation, Phase 2b Trial Only) per Year and Age Groups

	Phase IIb Trial	Open-Label Extension Trial		
	Month 12	Month 12 (baseline)	Month 24	Month 36
Patients 6-55 Years of Age				
Treatment Response	N=221	N=171	N=149	N=124
Responders, n[a] (%)	89 (40.3)	74 (43.3)	89 (59.7)	80 (64.5)
95% CI[b]	33.8, 47.1	35.7, 51.1	51.4, 67.7	55.4, 72.9
Eliciting dose ≥1,000 mg, n (%)	57 (25.8)	—	63 (42.3)	51 (41.1)
≥10-fold increase in eliciting dose, n (%)	63 (28.5)	—	68 (45.6)	63 (50.8)
Non-responders, n (%)	132 (59.7)	—	60 (40.3)	44 (35.5)
Patients 6-55 years of age on 250µg-patch				
Treatment Response	N=56	N=38	N=33	N=25
Responders, n[a] (%)	28 (50.0)	21(55.3)	23 (69.7)	19 (76.0)
95% CI[b]	36.3, 63.7	39.5, 71.1	51.3, 84.4	54.9, 90.6
Eliciting dose ≥1,000 mg, n (%)	18 (32.1)	—	17 (51.5)	15 (60.0)
≥10-fold increase in eliciting dose, n (%)	23 (41.1)	—	20 (60.6)	17 (68.0)
Non-responders, n (%)	28 (50.0)	—	10 (30.3)	6 (24.0)
Patients 6-11 Years of Age				
Treatment Response	N=113	N=97	N=90	N=79
Responders, n[a] (%)	49 (43.4)	43 (44.3)	57 (63.3)	54 (68.4)
95% CI[b]	34.1, 53.0	34.24, 54.8	52.5, 73.2	56.9, 78.4
Eliciting dose ≥1,000 mg, n (%)	27 (23.9)	—	37 (41.1)	31 (39.2)
≥10-fold increase in eliciting dose, n (%)	43 (38.1)	—	53 (58.9)	49 (62.0)
Non-responders, n (%)	64 (56.6)	—	33 (36.7)	25 (31.6)
Patients 6-11 years of age on 250µg-patch				
Treatment Response	N=28	N=21	N=20	N=18
Responders, n[a] (%)	15 (53.6)	12 (57.1)	16 (80.0)	15 (83.3)
95% CI[b]	33.9, 72.5	36.0, 78.3	56.3, 94.3	58.6, 96.4
Eliciting dose ≥1,000 mg, n (%)	9 (32.1)	—	12 (60.0)	11 (61.1)
≥10-fold increase in eliciting dose, n (%)	15 (53.6)	—	16 (80.0)	15 (83.3)
Non-responders, n (%)	13 (46.4)	—	4 (20.0)	3 (16.7)
Patients 12-55 Years of Age				
Treatment Response	N=108	N=74	N=59	N=45
Responders, n (%)	40 (37.0)	31 (41.9)	32 (54.2)	26 (57.8)
95% CI[b]	27.9, 46.9	30.5, 53.9	40.8, 67.3	42.2, 72.3
Eliciting dose ≥1,000 mg, n (%)	30 (27.8)	—	26 (44.1)	20 (44.4)
≥10-fold increase in eliciting dose, n (%)	20 (18.5)	—	15 (25.4)	14 (31.1)
Non-responders, n (%)	68 (63.0)	—	27 (45.8)	19 (42.2)
Patients 12-55 years of age on 250µg-patch				
Treatment Response	N=28	N=17	N=13	N=7
Responders, n (%)	13 (46.4)	9 (52.9)	7 (53.8)	4 (57.1)
95% CI[b]	27.5, 66.1	29.2, 76.7	25.1, 80.8	18.4, 90.1
Eliciting dose ≥1,000 mg, n (%)	9 (32.1)	—	5 (38.5)	4 (57.1)
≥10-fold increase in eliciting dose, n (%)	8 (28.6)	—	4 (30.8)	2 (28.6)
Non-responders, n (%)	15 (53.6)	—	6 (46.2)	3 (42.9)

CI=confidence interval.
The eliciting dose is defined as the last single dose administered in the double-blind, placebo-controlled food challenge prior to the development of objective clinical symptoms.
[a]A patient could meet both sets of criteria and would therefore be categorized in both criteria category counts. Percentages were based on the number of patients in the intention-to-treat population (all randomized patients). Note: A treatment responder was defined as a patient with an eliciting dose of ≥1,000 mg peanut proteins or a patient with a 10-fold increase in the eliciting dose at the respective month compared to the initial eliciting dose, based on the results of the two double-blind, placebo-controlled food challenges.
[b]CI using Clopper-Pearson (Exact) method.

eFigure 1. Study Design



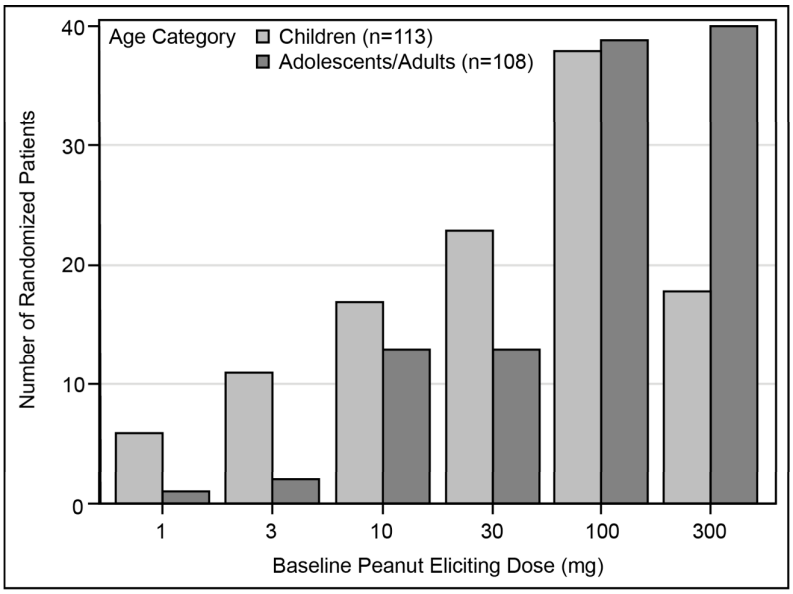
▲ Randomization

▲ Double-Blind, Placebo-Controlled Food Challenge

In the screening period of the Phase IIb study, there were three visits; the third visit corresponded to the second day of the double-blind, placebo-controlled food challenge and had to take place within a week after the first day of the double-blind, placebo-controlled food challenge.

Of 168 patients who received the 250µg-patch in the open-label extension study, 57 switched to the 250µg-patch at Month 6: 22 patients who received the 50µg-patch in the Phase IIb study received the 50µg-patch at open-label extension study entry before switching to the 250µg-patch at Month 6; 20 patients who received the 100µg-patch in the Phase IIb study received the 100µg-patch at open-label extension study entry before switching to the 250µg-patch at Month 6; 7 patients who received the placebo-patch in the Phase IIb study received the 50µg-patch at open-label extension study entry before switching to the 250µg-patch at Month 6; 8 patients who received the placebo-patch in the Phase IIb study received the 100µg-patch at open-label extension study entry before switching to the 250µg-patch at Month 6.

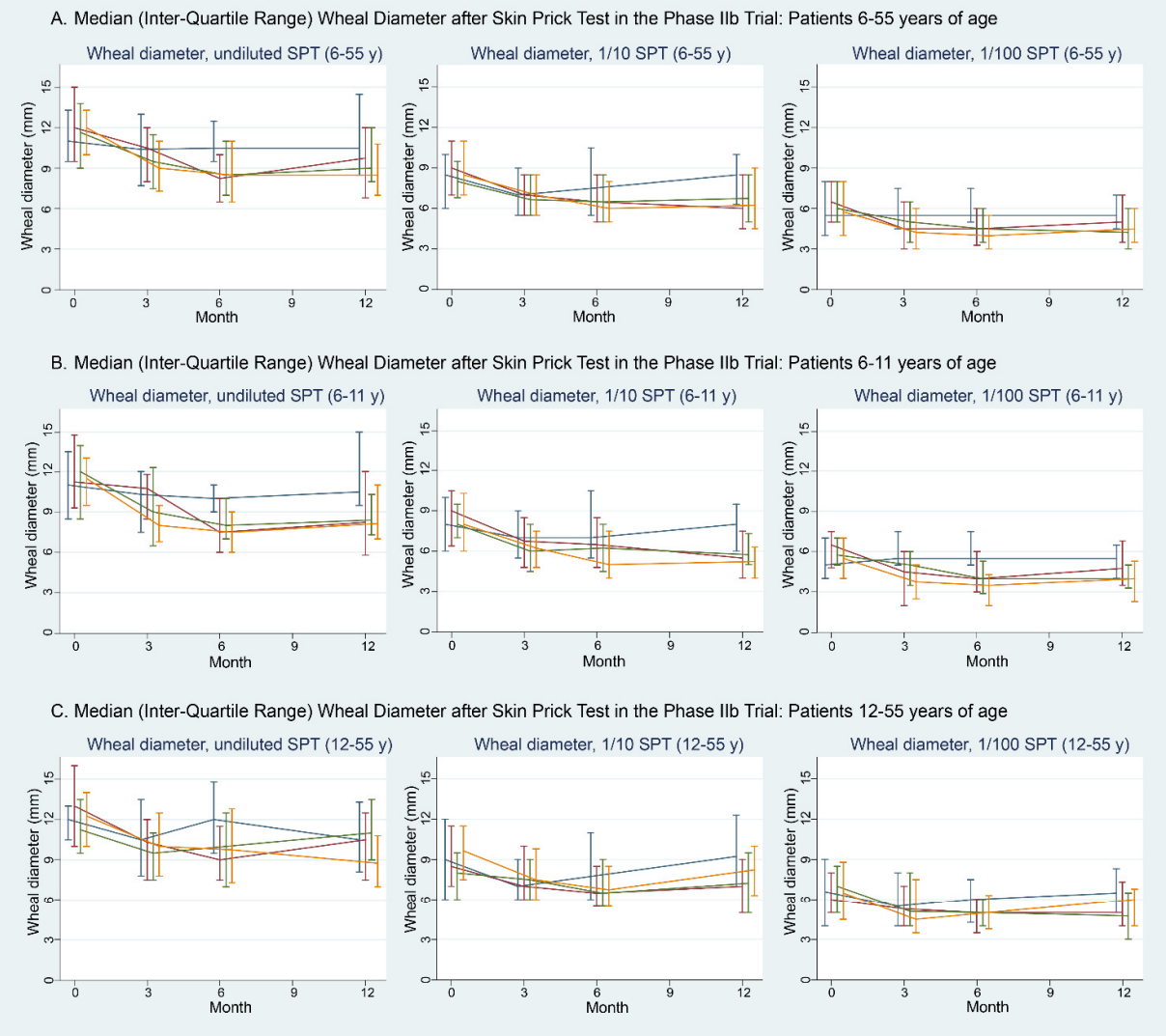
eFigure 2. Baseline Eliciting Dose



	Eliciting Dose (mg)					
	1	**3**	**10**	**30**	**100**	**300**
Children (6-11 y), n	6	11	17	23	38	18
Adolescents /adults (12-55 y), n	1	2	13	13	39	40

The eliciting dose is defined as the last single dose administered in the double-blind, placebo-controlled food challenge prior to the development of objective clinical symptoms.
Median eliciting dose for children (6-11 years of age) was 30 mg peanut protein; it was 100 mg for adolescents/adults (12-55 years of age).

eFigure 3. Peanut Skin Prick Test Median (Interquartile Range) Wheal Diameters Over the 12-Month Phase 2b Trial at 3 Dilutions (Undiluted, 1/10 and 1/100) by Treatment Group



		Month 0	Month 3	Month 6	Month 12
All ages (6-55 y), N	**Placebo-patch**	56	56	53	55
	50 µg-patch	53	53	52	52
	100 µg-patch	56	54	53	54
	250 µg-patch	56	56	55	56
Children (6-11 y), N	**Placebo-patch**	31	31	29	31
	50 µg-patch	28	28	27	28
	100 µg-patch	26	24	24	24
	250 µg-patch	28	28	27	28
Adolescents/ Adults (12-55 y), N	**Placebo-patch**	25	25	24	24
	50 µg-patch	25	25	25	24
	100 µg-patch	30	30	29	30
	250 µg-patch	28	28	28	28

Peanut skin prick test median wheal diameters over the 12-month trial at 3 dilutions (undiluted, 1/10 and 1/100) in (A) patients 6–55 years of age, (B) patients 6–11 years of age, and (C) patients 12–55 years of age.

eAppendix. Study Methodology

Clinical Assessments

Skin prick tests: Limiting dilution skin prick tests were performed with five 10-fold dilutions (from undiluted up to 1:10,000) of peanut extract (ALK-Abelló; Horsholm, Denmark) at baseline and at Months 3, 6, and 12 of the Phase IIb trial and at Months 6, 12, 18, 24, and 26 of the Open-Label Extension trial. The average wheal diameter for skin prick tests was defined as the average length of the longest diameter and the longest perpendicular diameter.

Serum peanut-specific IgE and peanut-specific IgG4 levels: Peanut-specific IgE and peanut-specific IgG4 (ImmunoCAP; Thermo Fisher, Waltham, MA, USA) levels were obtained at baseline and at Months 3, 6, and 12 of the Phase IIb trial and at Months 6, 12, 18, 24, and 26 of the Open-Label Extension trial. Assays were performed as specified by the manufacturer.

Pre-specified secondary endpoints:

- The mean eliciting doses of peanut proteins at Month 12 in the 50µg, 100µg, and 250µg groups versus the placebo group.
- The mean cumulative reactive dose of peanut proteins at Month 12 in the 50µg, 100µg, and 250µg groups versus the placebo group.
- The change in the severity of symptoms elicited during the peanut (double-blind, placebo-controlled food challenges from baseline to Month 12 for each treatment group. Symptoms graded according to the Oral Food Challenge Symptom Score Sheet (Appendix 3 of the protocol) described by the Work Group Report on Oral Food Challenge testing.
- Time of appearance of the very first objective symptom during the double-blind, placebo-controlled food challenge at Month 12 in the 50µg, 100µg, and 250µg groups versus the placebo group.
- The change in peanut end point titration by skin prick testing from baseline to Months 3, 6, and 12 for each subject in the 50µg, 100µg, and 250µg groups and in the placebo group.
- The change in peanut-specific IgE and IgG4 from baseline to Months 3, 6, and 12 for each subject in the 50µg, 100µg, and 250µg groups and in the placebo group.
- The correlation between the presence of peanut protein component(s) and response to Viaskin® Peanut immunotherapy.
- The basophil activation test change from baseline in % CD203c basophils and in the ratio of CD203c expression (MFI)/negative CD203c expression (MFI), assessed by flow cytometry, at Months 3, 6, and 12 for each subject in the 50µg, 100µg, and 250µg groups and in the placebo group. These results correlated with the primary efficacy criterion.
- Primary efficacy endpoint in each age group.
- Secondary efficacy endpoints in each age group for the mean eliciting dose in each treatment group, time of appearance of the first objective symptom, change in peanut-specific IgE and in IgG4, and the basophil activation change from baseline in % CD203c basophils and in the ratio of CD203c expression/negative CD203c expression.

Study Stopping Rules

Study enrollment suspended pending an expedited safety review by an independent Data and Safety Monitoring Board if any of the following occurred:

1. Any death related to the epicutaneous immunotherapy patch dosing.
2. More than one Stage 3 anaphylaxis (see Section 3 of Study Methodology: Anaphylaxis Staging System) related to the epicutaneous immunotherapy patch application (not occurring during the double-blind, placebo-controlled food challenge).
3. More than three subjects requiring more than one injection of epinephrine in relation to the epicutaneous immunotherapy patch application (not occurring during double-blind, placebo-controlled food challenge).

Upon safety review, one of the following outcomes would be determined:

- Accrual to the study may continue without modification.
- Accrual to the study may continue with modifications as prescribed by the Data and Safety Monitoring Board.
- Accrual to the study should be discontinued.

Anaphylaxis Staging System

Anaphylaxis is a generalized allergic reaction that is rapid in onset and may progress to death (adapted from Sampson, 2006[6]).

Staging System of Severity of Anaphylaxis	
Stage	**Defined by**
1. *Mild* (skin and subcutaneous tissues, gastrointestinal, and/or mild respiratory)	Flushing, urticaria, periorbital or facial angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain and/or emesis
2. *Moderate* (mild symptoms and features suggesting moderate respiratory, cardiovascular or gastrointestinal symptoms)	Marked dysphagia, hoarseness, and/or stridor; shortness of breath; wheezing and retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea; and/or mild dizziness
3. *Severe* (hypoxia, hypotension, or neurological compromise)	Cyanosis or $SpO_2 \leq 92\%$ at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence

Statistical Methodology

Additional Information on Statistical Analysis: Each epicutaneous immunotherapy patch dose was compared to placebo for the percentage of treatment responders at Month 12 using Fisher's exact tests. Overall Type-I error rate for the primary analyses was controlled through a prespecified fixed-sequence (pairwise comparisons between 250µg, 100µg, and 50µg versus placebo, each) testing strategy. Accordingly, testing would cease beyond the first observed p-value ≥0.05. The analysis was performed on the intention-to-treat population (all randomized subjects) using last-observation-carried-forward imputation. The same analysis was repeated in each age stratum. This analysis was then repeated using worst-case imputation and multiple imputations to assess the robustness of the primary efficacy conclusion.

The treatment effects on eliciting dose, cumulative reactive dose, and immunological markers were tested using an analysis of covariance (ANCOVA) model. The comparison was made after adjustment with the baseline value, the age stratum, and the country. Analyses of secondary outcomes were performed using observed data as well as using imputation methods (missing data at Month 12 were imputed with the baseline score [baseline observation carried forward] for endpoints measured at Entry and Month 12 or multiple imputation for endpoints measured at repeated time points).[7,8] The 95% bilateral confidence interval for the difference in least squares means was used to evaluate superiority of epicutaneous immunotherapy patch groups versus placebo. *P*-values of less than 0.05 were considered to indicate statistical significance.

For each series of skin prick test dilutions at each time point, the mean wheal diameter was determined and reported as a change from baseline.

All adverse events reported in subjects who had at least one application of the epicutaneous immunotherapy patch were analyzed descriptively; in addition, symptoms were graded each day by the patient during the first 3 months using the following scales:

ITCHING
0 = no symptom
1 = localized to the epicutaneous immunotherapy patch application area, easily bearable, painless, occasional scratching
2 = localized but intense, and barely bearable, continuous scratching for > 2 minutes
3 = spreading, unbearable, interfering with daily activities, requiring treatment, continuous scratching

REDNESS
0 = no symptom
1 = redness localized to the application area under the epicutaneous immunotherapy patch, painless
2 = intense redness or redness wider than the epicutaneous immunotherapy patch, painless
3 = intense redness + bruises largely spread around the epicutaneous immunotherapy patch

SWELLING
0 = no symptom
1 = localized to the application area under the epicutaneous immunotherapy patch, no pain, no discomfort
2 = large swelling area causing no pain or discomfort
3 = large swelling area, causing pain and/or discomfort

Statistical analyses were performed with SAS 9.2, 9.3, and 9.4 statistical packages (SAS Institute; Cary, NC, USA).

Narrative of the Case of Anaphylaxis "Possibly Related" to Therapy in Phase IIb Trial

One case of non-serious moderate anaphylaxis was reported as possibly related to therapy: a 30-year-old female patient with an ongoing history of untreated asthma and cat allergy, being treated with epicutaneous immunotherapy 50µg-patch experienced symptoms of asthma, cough, ear pruritus, eyelid edema, and 5-6 erythematous papules on her neck, arm, and back after removing the patch on Day 34 of treatment and replacing it with a new patch. She quickly recovered on the same day with self-use of salbutamol inhaler and brief discontinuation of the patch application. After the treatment was restarted, no systemic reactions were reported; the only reported reaction was a moderate local eczema in the area of patch application lasting two months; the patient completed the one-year treatment of the study.

eReferences

1. Cochrane SA, Salt LJ, Wantling E et al. Development of a standardized low-dose double-blind placebo-controlled challenge vehicle for the EuroPrevall project. *Allergy.* 2012;67(1):107-113.
2. Sampson HA, Gerth van WR, Bindslev-Jensen C et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol.* 2012;130(6):1260-1274.
3. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS. Work Group report: oral food challenge testing. *J Allergy Clin Immunol.* 2009;123(6 Suppl):S365-S383.
4. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS; Adverse Reactions to Food Committee of American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2009;123(6 Suppl):S365-83.
5. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-397.
6. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.
7. O'Kelly M, Ratitch B. Combining analysis results from multiply imputed categorical cata. PharmaSUG 2013 - Paper SP03.
8. Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med. 2012;367(14):1355-60.