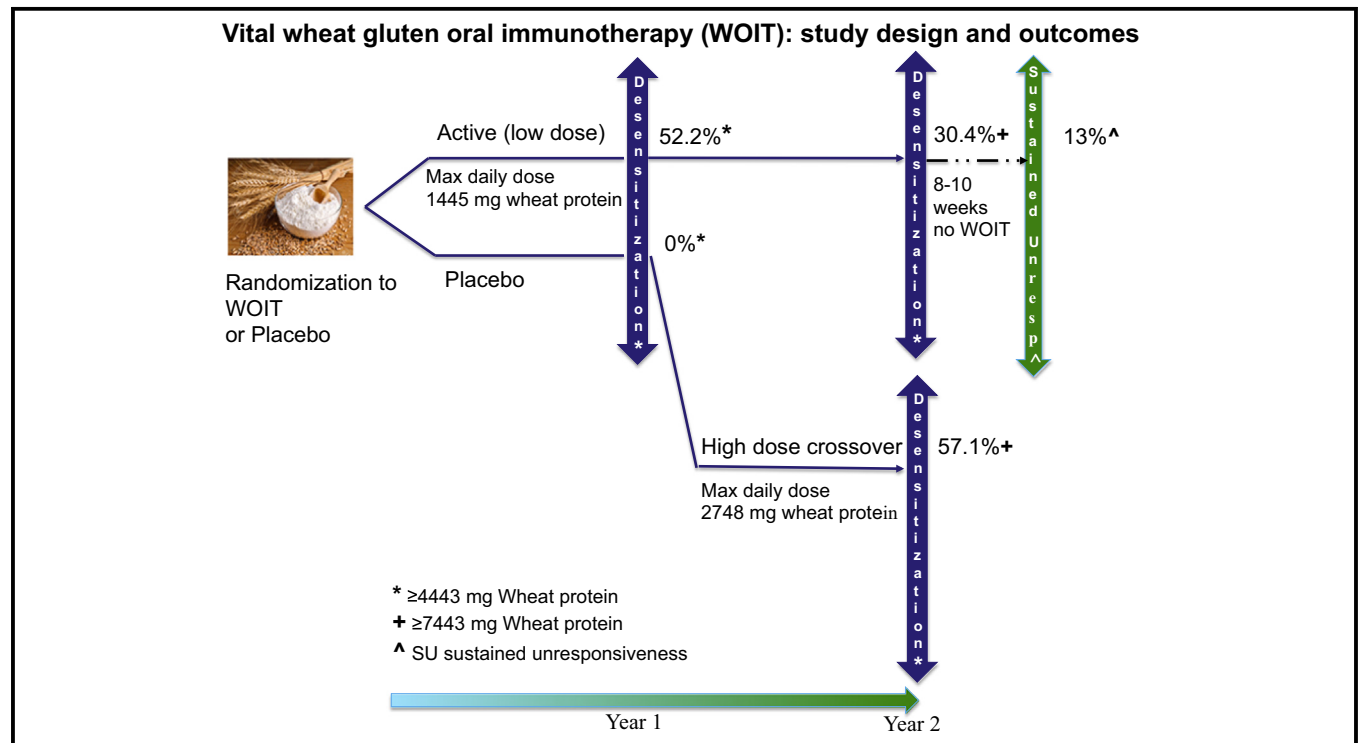


Multicenter, randomized, double-blind, placebo-controlled clinical trial of vital wheat gluten oral immunotherapy

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GRAPHICAL ABSTRACT



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Background: Wheat is a common food allergen that can cause anaphylaxis.

Objective: We sought to determine the efficacy and safety of vital wheat gluten (VWG) oral immunotherapy (OIT).

Methods: After baseline double-blind, placebo-controlled food challenge (DBPCFC), 46 patients with wheat allergy (median age, 8.7 years; range, 4.2–22.3 years) were randomized 1:1 to low-dose VWG OIT or placebo, with biweekly escalation to 1445 mg of wheat protein (WP). After a year 1 DBPCFC, active subjects continued low-dose VWG OIT for another year and underwent a year 2 DBPCFC and, if passed, a subsequent off-therapy DBPCFC. Placebo-treated subjects crossed over to high-dose VWG OIT (maximum, 2748 mg of WP).

Results: The median baseline successfully consumed dose (SCD) was 43 mg of WP in both groups. At year 1, 12 (52.2%) of 23 low-dose VWG OIT-treated and 0 (0%) of 23 placebo-treated subjects achieved the primary end point of an SCD of 4443 mg of WP or greater ($P < .0001$); median SCDs were 4443 and 143 mg, respectively. At year 2, 7 (30.4%) of 23 low-dose VWG OIT-treated subjects were desensitized to an SCD of 7443 mg of WP; 3 (13%) achieved sustained unresponsiveness 8 to 10 weeks off therapy. Among placebo-treated subjects who crossed over to high-dose VWG OIT, 12 (57.1%) of 21 were desensitized after 1 year (median SCD, 7443 mg of WP; nonsignificant vs low-dose VWG OIT). At year 1, skin prick test responses and wheat- and omega-5 gliadin-specific IgE levels did not differ between groups; the low-dose VWG OIT median specific IgG₄ level was greater than placebo (wheat, $P = .0005$; omega-5 gliadin, $P = .0001$). Year 1 SCDs correlated with wheat-specific ($\rho = 0.55$, $P = .0003$) and omega-5 gliadin-specific ($\rho = 0.51$, $P = .001$) IgG₄ levels in all subjects. Among 7822 low-dose VWG OIT doses in year 1, 15.4% were associated with adverse reactions: 0.04% were severe, and 0.08% subjects received epinephrine. Among 7921 placebo doses, 5.8% were associated with adverse reactions; none were severe.

Conclusions: Low- and high-dose VWG OIT induced desensitization in about one half of the subjects after 1 year of treatment. Two years of low-dose VWG OIT resulted in 30% desensitization, and 13% had sustained unresponsiveness. (J Allergy Clin Immunol 2018;■■■:■■■–■■■.)

Key words: Wheat allergy, food allergy, oral immunotherapy, sustained unresponsiveness, desensitization, oral tolerance, gluten

Worldwide, wheat is the most important source of vegetable protein in the human food supply, having higher protein content than other major cereals, such as corn or rice. Wheat is one of the most common childhood food allergens capable of inducing anaphylaxis as well as eczematous rash in patients with atopic dermatitis, eosinophilic esophagitis (EoE), food protein–induced enterocolitis syndrome, and celiac disease.¹ Management of wheat allergy is challenging because of the ubiquitous presence of wheat in the diet. The prognosis of IgE-mediated wheat allergy in children is generally favorable, with the majority becoming tolerant by school age, although those with lifetime peak wheat IgE levels greater than 50 kilounits of antigen (kU_A)/L or gluten IgE levels greater than 25 kU_A/L are likely to retain wheat allergy until adolescence or adulthood.² Clinical trials of oral immunotherapy (OIT) for foods, such as cow's milk, egg, and peanut, reported promising results, including a high rate (70% to 80%) of

Abbreviations used

DBPCFC:	Double-blind, placebo-controlled food challenge
EoE:	Eosinophilic esophagitis
kU _A :	Kilounits of antigen
mg _A :	Milligrams of antigen
OIT:	Oral immunotherapy
pHC:	Partially hydrolyzed wheat-based cereal
SCD:	Successfully consumed dose
sIgE:	Specific IgE
sIgG ₄ :	Specific IgG ₄
SPT:	Skin prick test
SU:	Sustained unresponsiveness
VWG:	Vital wheat gluten
WP:	Wheat protein

subjects reaching desensitization with an acceptable safety profile.^{3–5} To date, 5 small pilot studies explored OIT for wheat allergy in children and reported variable success with desensitization.^{6–10}

Wheat flour contains relatively low amounts of protein compared with protein content in peanut or milk, necessitating ingestion of high doses of wheat flour for OIT and potentially negatively affecting adherence to OIT.¹¹ With that in mind, we designed a randomized, placebo-controlled, multicenter clinical trial of high-protein-content vital wheat gluten (VWG) OIT to determine its safety and efficacy in subjects with IgE-mediated wheat allergy.

METHODS

This was a multicenter, randomized, double-blind, placebo-controlled trial through the first year stratified by initial wheat-specific IgE (sIgE) concentration to investigate the efficacy, safety, and immunologic effects of VWG OIT in subjects with wheat allergy. The primary end point was assessed after the double-blind, placebo-controlled portion of the trial at 1 year. The initial active treatment group continued low-dose VWG OIT for an additional year and was tested for sustained unresponsiveness (SU). After completing the double-blind phase, the placebo group received open-label treatment with a higher dose of VWG OIT for 1 year (ie, the high-dose crossover VWG OIT group).

Subjects with wheat allergy documented by a baseline double-blind, placebo-controlled food challenge (DBPCFC) were randomized 1:1 to active low-dose VWG OIT or placebo. Dose escalation was performed every 2 weeks for up to 44 weeks to a maximum dose of 1445 mg of wheat protein (WP), followed by daily home maintenance dosing. After 52 weeks of treatment (minimum of 8 weeks of maintenance dosing), DBPCFCs were performed up to a cumulative dose of 7443 mg of WP to evaluate for desensitization (roughly equivalent to 2–3 slices of bread). Subjects were subsequently unblinded. Those who received low-dose VWG OIT and had escalated to a maximum of 1445 mg of WP continued maintenance therapy for up to 1 more year. Those who had not escalated to 1443 mg of WP in year 1 continued to escalate in year 2, following the same escalation time table used in the initial escalation phase. Those who received placebo crossed over to a maximum of 2748 mg of WP (ie, the high-dose crossover VWG OIT group), up dosing for 44 weeks, followed by at least 8 weeks of maintenance therapy.

At study year 2, both low-dose (maximum maintenance dose, 1445 mg of WP) and high-dose crossover (maximum maintenance dose, 2748 mg of WP) VWG OIT participants underwent DBPCFCs to a cumulative dose of 7443 mg of WP. The subjects in the original active group receiving low-dose VWG OIT who did not have dose-limiting symptoms to 7443 mg of WP at the year 2 desensitization DBPCFC stopped treatment and continued strict wheat avoidance for 8 to 10 weeks. They underwent an SU DBPCFC with 7443 mg of WP, followed by an open challenge (Fig 1).

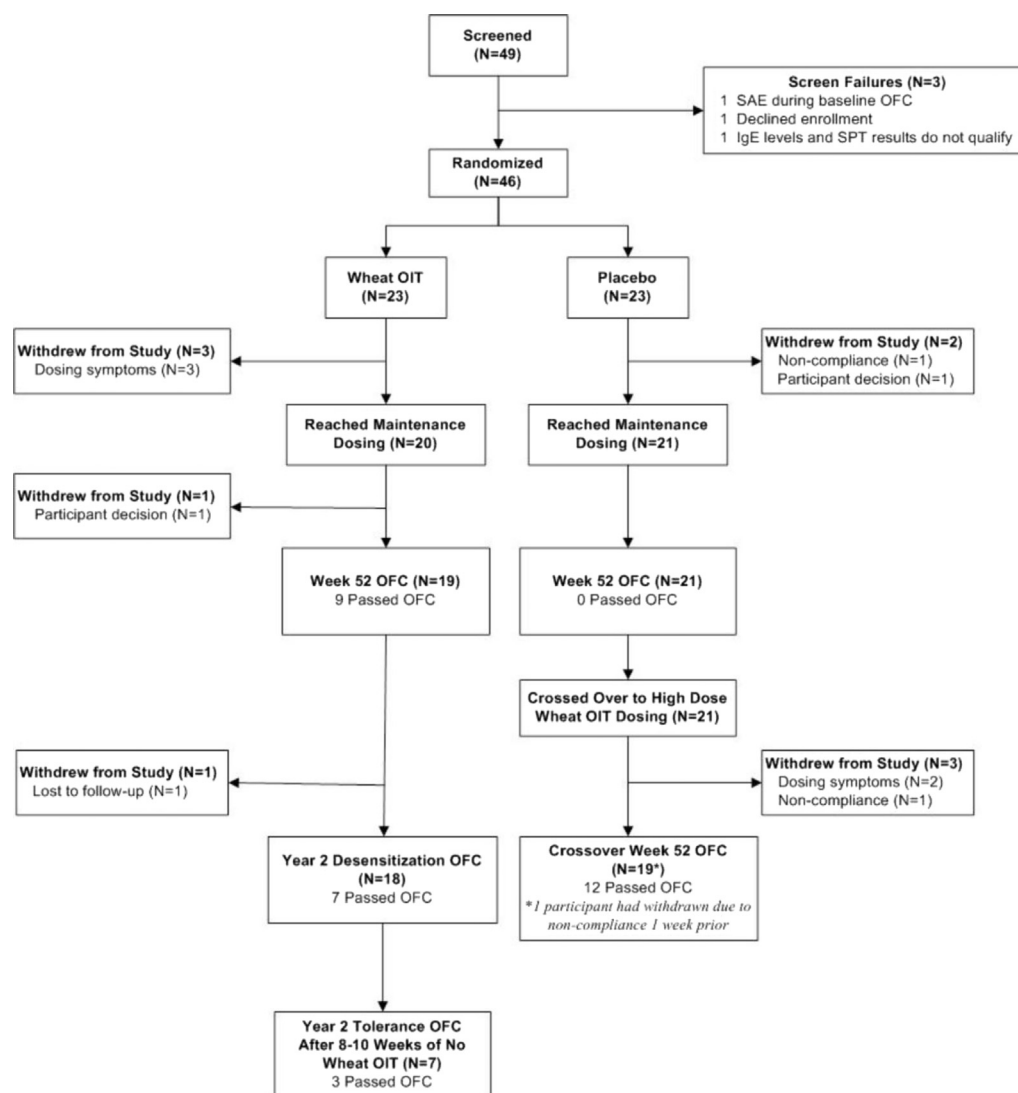


FIG 1. CONSORT diagram of the VWG OIT study. OFC, Oral food challenge.

Dosing was suspended temporarily for intercurrent illnesses, and doses were adjusted based on the duration of the dosing suspension. (see [Box E1](#) in this article's Online Repository at www.jacionline.org). Throughout the study, the participants strictly eliminated wheat from their diet, with the exception of the VWG OIT doses.

The primary end point of the study was to determine whether 1 year of daily oral administration of VWG relative to placebo escalated to a maximum of 1445 mg of WP increased desensitization, as measured by consuming (without dose-limiting symptoms) 4443 mg of WP. Secondary end points included the following: (1) the percentage of subjects in the low-dose VWG OIT group who successfully consumed 7443 mg of WP during an SU-DBPCFC at the 2-year time point; (2) the percentage of subjects who achieved the targeted maintenance dose of low-dose VWG OIT during the desensitization phase of the study; (3) the percentage of subjects who achieved desensitization in the placebo crossover group after 1 year of dosing at the 2-year study time point; (4) immunologic changes associated with OIT; and (5) incidence of all dosing reactions and serious adverse events during the study.

Inclusion criteria

Any subject 4 to 30 years of age with suspected wheat allergy, a positive skin prick test (SPT) response to wheat of 3 mm or greater compared with control and/or a wheat sIgE level of greater than 0.35 kU_A/L, and a positive

baseline challenge result to wheat (successfully consumed dose [SCD], <1443 mg of WP) was eligible for enrollment.

Exclusion criteria

Subjects were ineligible for any of the following reasons: (1) conditions considered to increase risk for anaphylaxis or interfere with treatment of anaphylaxis, such as a history of food-induced anaphylaxis resulting in hypotension, neurological compromise or mechanical ventilation, and uncontrolled asthma; (2) recent immunomodulatory treatments; and (3) eosinophilic gastrointestinal disease in the past 2 years. The detailed specific exclusion criteria can be found in [Box E2](#) in this article's Online Repository at www.jacionline.org.

Study drug

Study drug (commercially available VWG, which was gamma-irradiated to improve sterility) and placebo (commercially available cornstarch) were centrally packaged, stored, and distributed by EMINENT Services (Frederick, Md). VWG contains approximately 70% protein; 1 ounce provides 7 g of WP compared with wheat flour, which provides 1.6 g of WP.¹¹ The study drug was initially provided as premeasured capsules and packets. Once the 525-mg dose of VWG flour (containing 373 mg of WP) was reached, study drug was

dispensed in bulk and measured by the participants at home with the use of special color-coded scoops.

Study centers

The study was conducted at 4 centers in the United States: the Icahn School of Medicine at Mount Sinai, New York, NY; Johns Hopkins University Children's Medical Center, Baltimore, Maryland; Stanford University Medical School, San Francisco, California; and Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University School of Medicine, Chicago, Illinois. The study was approved by each institutional review board; informed consent was obtained from all participants or their parents. The study was registered at clinicaltrials.gov (NCT01980992).

Study procedures

SPTs were performed according to the standard protocol using commercial wheat extract (Greer Laboratories, Lenoir, NC), and results were read at 15 minutes.¹² The SPT score was calculated by subtracting the value in millimeters of the saline wheal diameter from the wheat wheal diameter, and therefore it was possible to have a negative value. Serum levels of sIgE and specific IgG₄ (sIgG₄) antibodies directed against wheat, omega-5 gliadin (Tri a 19), and lipid transfer protein (Tri a 14) were measured with ImmunoCAP (Thermo Fisher, Portage, Mich). DBPCFCs were performed according to the PRACALL protocol.¹³ The DBPCFC dosing schedule is shown in [Table E1](#) in this article's Online Repository at www.jacionline.org.

Study visits

All screening and baseline procedures were performed within 90 days before the first low-dose VWG OIT dose. An initial escalation day (visit 01) was carried out in the research center, followed by dose escalation every 2 weeks in the research center or monitored clinic setting. During the week after each dose escalation, telephone calls were made to assess symptoms and adherence for home VWG OIT dosing. The OIT dosing schedule is shown in [Table E2](#) in this article's Online Repository at www.jacionline.org.

A targeted history and physical examination were performed at each visit. A detailed medical history, wheat allergy history, physical examination, and blood draw before study product administration occurred at 6 months (visit 03), 1 year (visit 04), 18 months (visit 05), 2 years (visit 06), and after the desensitization DBPCFC (visit 07). Subjects were assessed for exacerbation of atopic dermatitis and asthma (as determined by active wheezing) before each medically supervised VWG OIT dosing.

Adherence to the protocol was enforced during the study visits and follow-up telephone calls. Nonadherence with the home VWG OIT dosing protocol (excessive missed days; ie, > 3 consecutive days missed on 3 occasions) was considered a safety issue warranting discontinuation from dosing.

Statistical analyses

Data management, statistical analyses, and monitoring were performed by the Emmes Corporation (Rockville, Md). The proportion of primary end point successes, as well as the proportion of successes within the high-dose crossover group at 1 year, were compared by using the Barnard test. Statistical comparisons between treatment groups of the remaining categorical variables were done with the Fisher exact test and of continuous variables, such as immunologic parameters, with the Wilcoxon rank sum test. A signed-rank test was used to see whether change from baseline within a treatment group was significantly different from zero. A Spearman correlation was calculated between the week 52 SCD and immunologic parameters. A significance level of .05 was used, and no adjustments were made for multiple comparisons. Comparisons between the high-dose crossover and low-dose VWG OIT groups were interpreted with caution because of dropout of randomized participants before crossover. SPT scores were calculated by subtracting the diameter of the saline wheal from that of the wheat wheal. Because of the limits of detection of the wheat IgE and wheat component IgE assays being 0.1 to 100 kU_A/L and those for wheat-specific IgG₄ and wheat component–

TABLE I. Baseline demographic and clinical characteristics of the randomized subjects

	Treatment		Total
	Placebo	Wheat	
Total subjects, no. (%)	23 (100)	23 (100)	46 (100)
Sex			
Male	18 (78.3)	18 (78.3)	36 (78.3)
Female	5 (21.7)	5 (21.7)	10 (21.7)
Age (y)			
Median (IQR [25% to 75%])	8.7 (5.4-10.8)	8.6 (6.8-11.3)	8.7 (6.7-10.9)
Minimum-maximum	4.2-22.3	4.6-18.4	4.2-22.3
Race, no. (%)			
White	14 (60.9)	15 (65.2)	29 (63.0)
Black/African American	0 (0.0)	1 (4.4)	1 (2.2)
Asian	7 (30.4)	7 (30.4)	14 (30.4)
Other	2 (8.70)	0 (0.00)	2 (4.4)
Ethnicity, no. (%)			
Non-Hispanic or non-Latino origin	23 (100.0)	23 (100.0)	46 (100.0)
Additional food allergy, no. (%)	23 (100.0)	23 (100.0)	46 (100.0)
Asthma, no. (%)	19 (82.6)	20 (87.0)	39 (84.8)
Asthma severity, no. (%)			
Mild intermittent	15 (65.2)	20 (87.0)	35 (76.1)
Mild persistent	2 (8.7)	0 (0.0)	2 (4.3)
Moderate persistent	2 (8.7)	0 (0.0)	2 (4.3)
Allergic rhinitis, no. (%)	19 (82.6)	19 (82.6)	38 (82.6)
Atopic dermatitis, no. (%)	19 (82.6)	14 (60.9)	33 (71.7)

IQR, Interquartile range.

specific IgG₄ being 0.1 to 30 milligrams of antigen (mg_A)/L, values less than the limit of detection were set to 0.05 kU_A/L or 0.1 mg_A/L for IgE and IgG₄, respectively, and values greater than this were set to 101 kU_A/L for IgE and 31 mg_A/L for IgG₄. IgE and IgG₄ values from the placebo group at week 52 were used as baseline values for the high-dose crossover group. All analyses were completed with SAS software (version 9.3; SAS Institute, Cary, NC), except for the Barnard test of the primary end point, which was calculated by using SAS software (version 9.4).

RESULTS

Forty-six subjects (median age, 8.7 years; range, 4.2-22.3 years) were randomized; 78% were male ([Fig 1](#)). There were no differences between the groups regarding baseline clinical characteristics and immunologic parameters ([Tables I and II](#)).

Study end points

Primary end point. At the baseline DBPCFC, the median SCD was 43 mg of WP in both the low-dose VWG OIT and placebo groups ($P = .88$, [Fig 2](#)). At the 52-week DBPCFC, 12 (52.2%) of 23 VWG OIT-treated and 0 (0%) of 23 placebo-treated subjects achieved the primary end point, which was defined as an SCD of greater than 4443 mg of WP ($P < .0001$). The low-dose VWG OIT group had a significantly higher median SCD (4443 mg of WP) versus the placebo group (median SCD, 143 mg of WP; $P < .0001$; [Fig 2](#)). There was no increase in median SCD at year 2 compared with week 52 in the low-dose VWG OIT group ([Table III](#)). Through week 52, median time to maintenance,

TABLE II. Baseline immunologic parameters and DBPCFC outcomes of the randomized subjects

Result	Treatment group		Total (n = 46)
	Placebo (n = 23)	Low-dose VWG OIT (n = 23)	
Wheat IgE (kU _A /L)			
Median (IQR [25% to 75%])	86.8 (63.7 to 101.0)	94.1 (45.0 to 101.0)	88.4 (51.9 to 101.0)
Minimum-maximum	11.3 to 101	5.2 to 101	5.2 to 101
Omega-5 gliadin IgE (kU _A /L)			
Median (IQR [25% to 75%])	26.1 (12.9 to 85.4)	38.4 (7.6 to 101.0)	32.8 (11.1 to 85.4)
Minimum-maximum	0.9 to 101	1.1 to 101	0.9 to 101
Lipid transfer protein Tri a 14 IgE (kU _A /L)			
Median (IQR [25% to 75%])	2.3 (0.3 to 19.2)	2.9 (0.1 to 13.5)	2.6 (0.1 to 18.7)
Minimum-maximum	0.1 to 50.8	0.1 to 101	0.1 to 101
Wheat IgG ₄ (mg _A /L)			
Median (IQR [25% to 75%])	4.6 (2.5 to 8.6)	3.4 (1.8 to 10.2)	4.3 (2.2 to 9.9)
Minimum-maximum	0.8 to 31.00	0.1 to 31.00	0.1 to 31.00
Omega-5 gliadin IgG ₄ (mg _A /L)			
Median (IQR [25% to 75%])	0.6 (0.3 to 1.7)	0.5 (0.3 to 1.0)	0.5 (0.3 to 1.1)
Minimum-maximum	0.1 to 15.6	0.1 to 4.3	0.1 to 15.6
Lipid transfer protein Tri a 14 IgG ₄ (mg _A /L)			
Median (IQR [25% to 75%])	0.7 (0.1 to 2.5)	0.4 (0.1 to 1.9)	0.4 (0.1 to 2.0)
Minimum-maximum	0.1 to 6.6	0.1 to 12.6	0.1 to 12.6
Wheat SPT score (mm)*			
Median (IQR [25% to 75%])	6.5 (4.5 to 9.0)	4.5 (3.0 to 7.0)	5.8 (3.5 to 9.0)
Minimum-maximum	0.0 to 12.0	−1.0 to 11.5	−1.0 to 12.0
Wheat DBPCFC dose at first symptom (mg of WP)			
Median (IQR [25% to 75%])	13.0 (3.0 to 43.0)	43.0 (13.0 to 143.0)	13.0 (3.0 to 143.0)
Minimum-maximum	3.0 to 1443.0	3.0 to 443.0	3.0 to 1443.0
Maximum initial escalation day dose (mg of WP)			
Median (IQR 25%; to 75%)	12.0 (12.0 to 12.0)	12.0 (12.0 to 12.0)	12.0 (12.0 to 12.0)
Minimum to maximum	3.0 to 12.0	6.0 to 12.0	3.0 to 12.0

None of the baseline immunologic parameters were significantly different between the placebo and low-dose VWG OIT groups.

IQR, Interquartile range.

*SPT scores were calculated by subtracting the average diameter of the saline wheal from the average diameter of the wheat wheal (in millimeters).

time from maintenance to week 52 DBPCFC, and maintenance dose were not statistically different between the placebo and low-dose VWG OIT groups. However, through week 52, the median time to maintenance ($P = .004$) was significantly longer in the high-dose crossover VWG OIT group compared with the low-dose VWG OIT group (see [Table E3](#) in this article's Online Repository at www.jacionline.org).

Secondary end points. At year 2, 7 (30.4%) of 23 low-dose VWG OIT-treated subjects were fully desensitized, which was defined as an SCD of 7443 mg of WP; 3 (13.0%) of 23 achieved SU (SCD, 7443 mg of WP) after discontinuing treatment for 8 to 10 weeks ([Fig 3](#)).

In the first 52 weeks of dosing, 82.6% of the low-dose VWG OIT group achieved the target maintenance dose of 1445 mg of WP (range, 476-1445 mg of WP). In the high-dose crossover group, 57.1% achieved the daily target maintenance dose of 2748 mg of WP (range, 373-2748 mg of WP) during the 52 weeks of OIT dosing.

After 1 year of high-dose crossover VWG OIT, 14 (66.7%) of 21 subjects in the initial placebo group achieved a median SCD of 4443 mg of WP (nonsignificant vs low-dose VWG OIT at week 52). There were 12 (57.1%) of 21 subjects in the high-dose crossover group who were desensitized to the top cumulative reactive dose of 7443 mg of WP at the week 52 crossover oral food challenge ([Fig 1](#)) compared with 9 (39.1%) of 23 of low-dose VWG OIT-treated subjects desensitized to the top dose at week 52 after 1 year of treatment ($P = .37$).

Seven serious adverse events occurred during the study; 5 in the placebo-treated subjects (3 with asthma exacerbations, including 1 status asthmaticus, 1 pneumonia, and 1 gastroenteritis), 1 in the active VWG OIT group (severe anaphylactic reaction to an accidental ingestion of garlic bread 6 months after discontinuation of the study drug that was treated with 2 doses of epinephrine and resulted in an overnight hospitalization), and 1 in a subject who was not randomized (severe anaphylactic reaction during a baseline wheat DBPCFC associated with wheezing, urticaria, and transient hypotension that was treated with 3 doses of epinephrine and resulted in an overnight hospitalization).

Dosing symptoms

Of the total 7822 low-dose VWG OIT doses in year 1, 15.4% were associated with symptoms and 0.04% were severe, and 6 reactions (0.08%) were treated with epinephrine. The frequency of dosing reactions decreased in year 2; of the total 6292 low-dose VWG OIT doses, 3.1% were associated with symptoms, none were severe, and none were treated with epinephrine. Of the total 7921 placebo doses, 5.8% were associated with symptoms, none were severe, and none were treated with epinephrine. Of the total 6932 crossover high-dose VWG OIT doses, 13.4% were associated with symptoms, 0.01% were severe, and 0.07% were treated with epinephrine ([Table IV](#)). Detailed profiles of dosing reactions expressed per subject are shown in [Table E4](#) in this article's Online Repository at www.jacionline.org.

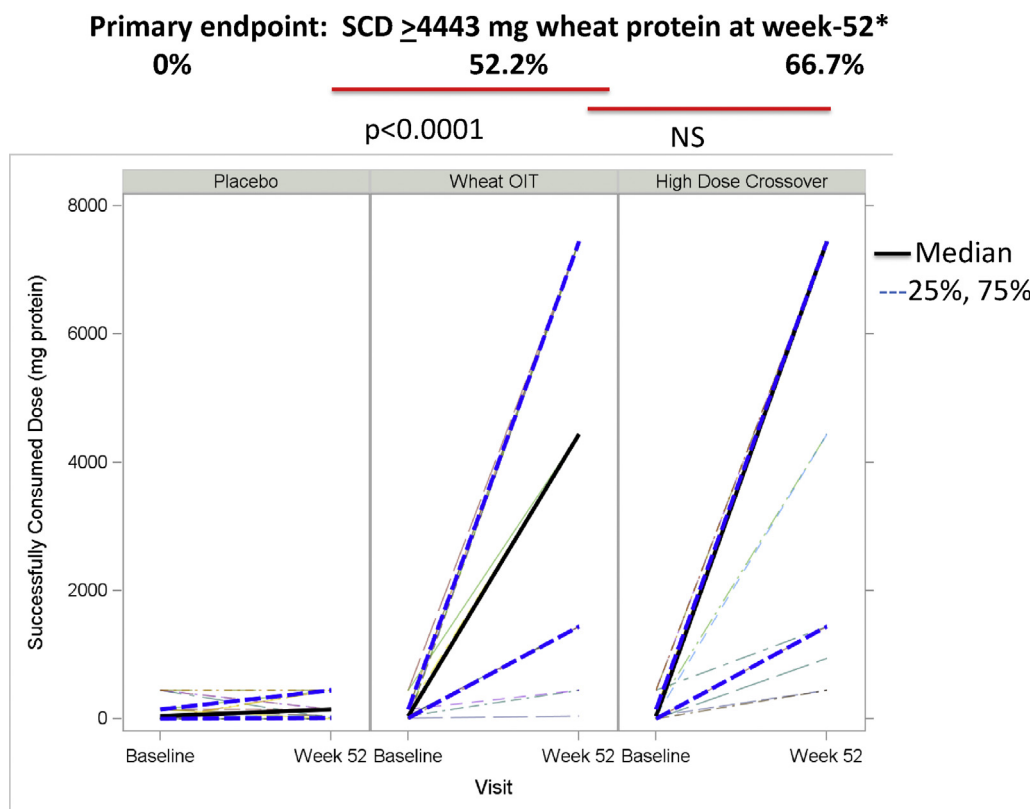


FIG 2. SCDs through week 52 oral food challenge/crossover week 52 oral food challenge by treatment group. SCDs are expressed as milligrams of WP. Thin dashed lines represent individual subjects, the solid black line represents the median, and dashed blue lines represent 25% and 75% values. *Two placebo-treated and 4 low-dose VWG OIT-treated subjects did not complete week 52 and were counted as treatment failures. NS, Not significant.

Immunologic parameters

There were no significant differences in SPT scores between the study groups at any time point, as shown in [Fig E1](#) in this article's Online Repository at www.jacionline.org. However, within treatment groups, change from baseline to 2 years for low-dose VWG OIT (median, -2.25 mm; $P = .002$) and change from baseline to crossover week 52 for high-dose VWG OIT (median, -3.50 mm; $P = .007$) decreased significantly. [Fig 4](#) shows serum levels of the sIgE and sIgG₄ antibodies for wheat, Tri a 19 (omega-5 gliadin), and Tri a 14 by treatment group. There were no significant differences in wheat sIgE levels between the low-dose VWG OIT-treated and placebo-treated subjects at any study visit, but median wheat sIgG₄ levels were significantly greater in the low-dose VWG OIT-treated subjects at week 12 ($P = .04$), week 26 ($P = .002$), and week 52 ($P = .0005$). There were no significant differences for wheat sIgE or sIgG₄ levels between subjects receiving low-dose and high-dose crossover VWG OIT at any time point. Similarly, there were no significant differences in Tri a 19 sIgE, Tri a 14 sIgE, and Tri a 14 sIgG₄ levels among the study groups at any time point. However, Tri a 19 sIgG₄ levels were significantly greater in the low-dose VWG OIT group compared with the placebo group ($P = .0001$) at week 52. Tri a 19 sIgG₄ levels did not differ between the low-dose and high-dose crossover VWG OIT groups at week 52. Among all subjects

at week 52, the SCD showed moderate correlation with wheat sIgG₄ levels ($\rho = 0.55$, $P = .0003$) and Tri a 19 sIgG₄ levels ($\rho = 0.51$, $P = .001$).

Study discontinuations

Eleven (24%) subjects discontinued the study; 1 subject in the low-dose VWG OIT group discontinued after completing the year 2 oral food challenge. Six subjects discontinued the study before week 52 and were counted as failures for the primary end point; 4 in the active VWG OIT arm (3 because of dosing-related symptoms and 1 because of participant's decision) and 2 in the placebo arm (1 because of participant's decision and 1 because of nonadherence). In addition, in the high-dose crossover group 2 subjects discontinued participation because of dosing symptoms (1 was given a diagnosis of both ulcerative colitis and EoE) and 1 because of nonadherence. The subject given a diagnosis of ulcerative colitis and EoE while receiving the study drug had a long history of chronic abdominal pain, intermittent diarrhea, and weight loss that was not disclosed to the study team at the time of enrollment. [Box E3](#) in this article's Online Repository at www.jacionline.org contains specific reasons for discontinuations caused by dosing symptoms.

TABLE III. SCDs during wheat DBPCFCs

SCD (mg of WP)	Treatment group		Total
	Placebo	Low-dose VWG OIT	
Baseline			
No.	23	23	46
Median (IQR [25% to 75%])	43.0 (3.0 to 143.0)	43.0 (13.0 to 143.0)	43.0 (3.0 to 143.0)
Minimum-maximum	0.0 to 443.0	3.0 to 443.0	0.0 to 443.0
Week 52			
No.	21	19	40
Median (IQR [25% to 75%])	143.0 (13 to 143.0)	4443.0 (1443.0 to 7443.0)	443.0 (93.0 to 4443.0)
Minimum-maximum	0.0 to 443.0	43.0 to 7443.0	0.0 to 7443.0
Week 52 change in SCD			
No.	21	19	40
Median (IQR [25% to 75%])	0.0 (−3.0 to 100.0)	4440.0 (1400.0 to 7400.0)	300.0 (0.0 to 4370.0)
Minimum-maximum	−430.0 to 443.0	30.0 to 7440	−430.0 to 7440
Crossover week 52			
No.	19	0	19
Median (IQR [25% to 75%])	7443.0 (1443.0 to 7443.0)	NA	7443.0 (1443.0 to 7443.0)
Minimum-maximum	443.0 to 7443.0	NA	443.0 to 7443.0
Crossover week 52 change in SCD			
No.	19	0	19
Median (IQR [25% to 75%])	7000.0 (1440.0 to 7300.0)	NA	7000.0 (1440 to 7300.0)
Minimum-maximum	400.0 to 7443.0	NA	400.0 to 7443.0
Year 2 desensitization			
No.	0	18	18
Median (IQR [25% to 75%])	NA	4443.0 (1443.0 to 7443.0)	4443.0 (1443.0 to 7443.0)
Minimum-maximum	NA	143.0 to 7443.0	143.0 to 7443.0
Year 2 desensitization change in SCD			
No.	0	18	18
Median (IQR [25% to 75%])	NA	4415.0 (1449 to 7300.0)	4415.0 (1440.0 to 7300.0)
Minimum-maximum	NA	100.0 to 7430.0	100.0 to 7430.0
Year 2 SU SCD			
No.	0	7	7
Median (IQR [25% to 75%])	NA	4443.0 (1443.0 to 7443.0)	4443.0 (1443.0 to 7443.0)
Minimum-maximum	NA	443.0 to 7443.0	443.0 to 7443.0
Year 2 change in SU SCD			
No.	0	7	7
Median (IQR [25% to 75%])	NA	4430.0 (1300.0 to 7300.0)	4430.0 (1300.0 to 7300.0)
Minimum-maximum	NA	300.0 to 7400.0	300.0 to 7400.0
			P value
Baseline SCD (mg of WP): placebo vs low-dose VWG OIT			.88
Week 52 SCD (mg of WP): placebo vs low-dose VWG OIT			<.0001
Week 52 change in SCD (mg of WP): placebo vs low-dose VWG OIT			<.0001
Week 52 SCD (mg of WP): high-dose crossover vs low-dose VWG OIT			.39
Week 52 change in SCD (mg of WP): high-dose crossover vs low-dose VWG OIT			.68

Wilcoxon *P* values for wheat DBPCFC SCDs by treatment group are shown.

IQR, Interquartile range; NA, not applicable.

DISCUSSION

We report the results of the first multicenter, randomized, double-blind, placebo-controlled trial of VWG OIT. The study met its primary end point and demonstrated that low-dose VWG OIT induced desensitization to a minimum cumulative dose of 4443 mg of WP (equivalent to approximately 1 to 2 slices of bread) after 52 weeks of treatment in half of treated subjects (52.2%) compared with 0% of subjects in the placebo group ($P < .0001$). At year 2, 7 (30.4%) of 23 low-dose VWG OIT-treated subjects were fully desensitized (defined as SCD = 7443 mg of WP), which is equivalent to a typical serving of a wheat product (eg, 2-4 slices of bread or ½-cup of cooked pasta), but only 3 (13.0%) of 23 achieved SU after discontinuing treatment for 8 to 10 weeks. For direct comparison, in a

multicenter clinical trial of egg OIT with a daily maintenance dose of 1500 mg of egg white protein for 22 months, 55% were desensitized to 3.75 g at month 10, 75% were desensitized to 6 g at month 22, and 28% achieved SU at month 24 (8 weeks off egg OIT).¹⁴

Our results suggest that wheat allergy might be less responsive to OIT, thus requiring higher maintenance doses and likely a longer course of OIT. Data from the high-dose crossover group treated with a maximum maintenance dose highlight such a possibility because although statistically nonsignificant, there appears to be a trend for better efficacy with a higher maintenance dose of WP. In the egg OIT trial SU increased from 28% to 50% after an additional 2 years (total of 4 years) of egg OIT, suggesting that longer duration of OIT translates to better efficacy.¹⁵

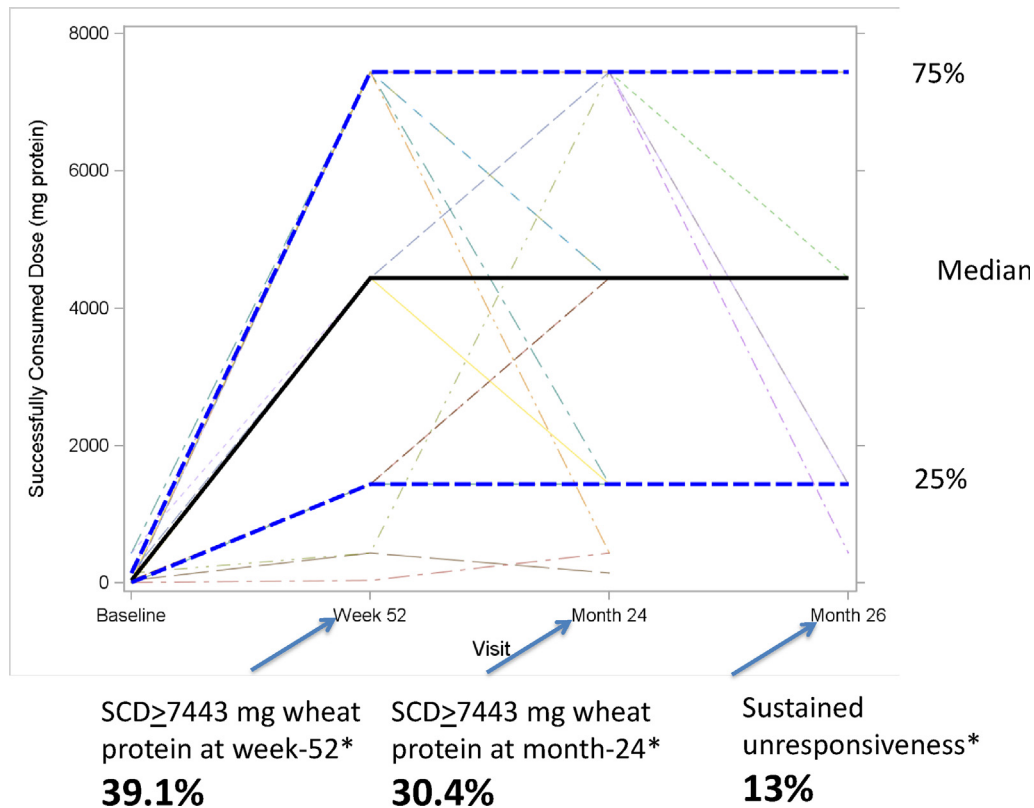


FIG 3. Primary (desensitization at week 52) and secondary (SU at month 26) end points in the lower-dose active VWG OIT group. *Thin dashed lines* represent individual subjects, the *solid black line* represents the median, and *dashed blue lines* represent 25% and 75% values. *Subjects who did not complete oral food challenges at week 52 (n = 4) and at month 24 (n = 5) were counted as treatment failures.

TABLE IV. Dosing symptoms by dose

Visit type	No. of doses	Symptoms																									
		Any symptom		Any symptom excluding oral/pharyngeal		Oral/pharyngeal		Skin		Respiratory tract		Gastrointestinal		Other		Symptoms >0.5 h		Treated		Treated with epinephrine		Mild symptoms		Moderate symptoms		Severe symptoms	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Before week 52																											
Placebo-treated subjects																											
First-day clinic dose	180	19	10.6	18	10.0	9	5.0	12	6.7	6	3.3	3	1.7	1	0.6	0	0.0	0	0.0	0	0.00	18	10.0	0	0.00	0	0.00
Clinic dose	386	42	10.9	37	9.6	12	3.1	26	6.7	12	3.1	3	0.8	7	1.8	4	1.0	5	1.3	0	0.00	35	9.1	2	0.52	0	0.00
Home dose	7355	399	5.4	390	5.3	36	0.5	289	3.9	43	0.6	22	0.3	48	0.7	15	0.2	39	0.5	0	0.00	365	5.0	25	0.34	0	0.00
All	7921	460	5.8	445	5.6	57	0.7	327	4.1	61	0.8	28	0.4	56	0.7	19	0.2	44	0.6	0	0.00	418	5.3	27	0.34	0	0.00
Wheat OIT-treated subjects																											
First-day clinic dose	183	15	8.2	13	7.1	8	4.4	5	2.7	9	4.9	2	1.1	0	0.0	2	1.1	4	2.2	0	0.00	13	7.1	0	0.00	0	0.00
Clinic dose	411	86	20.9	75	18.2	32	7.8	29	7.1	34	8.3	24	5.8	2	0.5	11	2.7	13	3.2	1	0.24	73	17.8	2	0.49	0	0.00
Home dose	7228	1100	15.2	1059	14.7	132	1.8	159	2.2	527	7.3	477	6.6	206	2.9	205	2.8	223	3.1	5	0.07	1000	13.8	56	0.77	3	0.04
All	7822	1201	15.4	1147	14.7	172	2.2	193	2.5	570	7.3	503	6.4	208	2.7	218	2.8	240	3.1	6	0.08	1086	13.9	58	0.74	3	0.04
High-dose crossover subjects																											
First-day clinic dose	162	12	7.4	10	6.2	3	1.9	6	3.7	3	1.9	6	3.7	0	0.0	1	0.6	0	0.0	0	0.00	10	6.2	0	0.00	0	0.00
Clinic dose	399	86	21.6	71	17.8	28	7.0	25	6.3	43	10.8	13	3.3	3	0.8	8	2.0	19	4.8	1	0.25	70	17.5	1	0.25	0	0.00
Home dose	6371	831	13.0	757	11.9	122	1.9	363	5.7	280	4.4	143	2.2	69	1.1	93	1.5	246	3.9	4	0.06	675	10.6	81	1.27	1	0.02
All	6932	929	13.4	838	12.1	153	2.2	394	5.7	326	4.7	162	2.3	72	1.0	102	1.5	265	3.8	5	0.07	755	10.9	82	1.18	1	0.01
After week 52																											
Wheat OIT-treated subjects																											
Clinic dose	49	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.00	0	0.0	0	0.00	0	0.00
Home dose	6243	198	3.2	188	3.0	14	0.2	23	0.4	73	1.2	78	1.2	36	0.6	16	0.3	63	1.0	0	0.00	165	2.6	23	0.37	0	0.00
All	6292	198	3.1	188	3.0	14	0.2	23	0.4	73	1.2	78	1.2	36	0.6	16	0.3	63	1.0	0	0.00	165	2.6	23	0.37	0	0.00

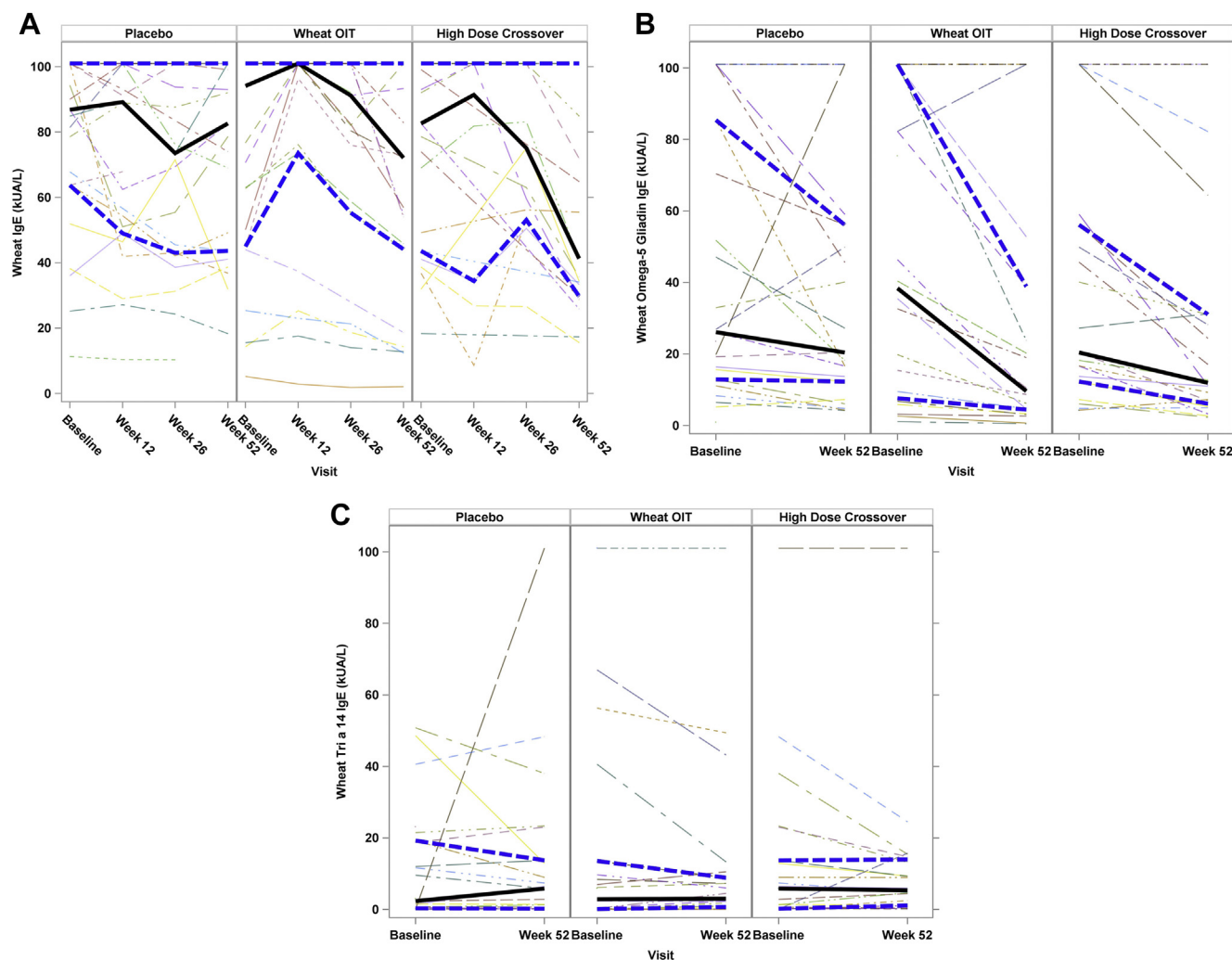


FIG 4. Serum levels of sIgE (A-C) and sIgG₄ (D-F) to wheat, omega-5 gliadin (Tri a 19), and wheat lipid transfer protein (Tri a 14) through week 52/crossover week 52 by treatment group. *Thin dashed lines* represent individual subjects, the *solid black line* represents the median, and *dashed blue lines* represent 25% and 75% values. Because of the limits of detection of wheat IgE and wheat component IgE assays being 0.1 to 100 kU_A/L and those for wheat IgG₄ and wheat component IgG₄ being 0.1 to 30 mg_A/L, values of less than the limit of detection were set to 0.05 kU_A/L or 0.1 mg_A/L for IgE and IgG₄, respectively, and values greater than the limit of detection were set to 101 kU_A/L for IgE and 31 mg_A/L for IgG₄.

In general, the profile of treatment-emergent dosing reactions in this study was comparable with the previously published studies of food OIT.⁵ The most common dosing symptoms during the first 52 weeks of low-dose VWG OIT were respiratory and gastrointestinal, with 0.04% classified as severe. In year 2 reaction frequency was lower; respiratory and gastrointestinal symptoms were 1.2% each, none of which were severe. The high-dose crossover subjects had a comparable profile of reactions during 52 weeks of active drug. However, it should be noted that overall 24% of subjects discontinued treatment because of dosing reactions.

The allergenic proteins in wheat are not fully characterized but are believed to be comprised largely of glycoproteins in the water-insoluble gluten fraction, whereas the major allergenic proteins in milk, egg, and peanut are much more water soluble. Given the often more “delayed” onset of symptoms after ingestion/challenge of wheat, it is likely that the responsible proteins undergo some degree of breakdown/denaturation, which results in their allergenic form. We tried to compensate for this by using

VWG, which is enriched in gluten proteins, but it is likely that the nonbroken form is not optimal for activating the appropriate cell populations. Therefore we chose VWG flour that has, on average, twice the amount of WP compared with the other commercially available flours, allowing for greater WP dosing with lower volumes of the study drug and because the gluten fraction of wheat is considered to contain the major allergenic proteins in wheat. The practical aspect of wheat OIT needs to be considered because daily dosing with large volumes of wheat flour can be difficult or uncomfortable for patients and might negatively affect treatment adherence.

We did not detect significant changes in serum wheat sIgE levels and SPT responses from baseline to week 52 and between the low-dose VWG OIT and placebo groups. This might be confounded by the absence of measurements on diluted serum samples to verify whether wheat IgE levels increased in some subjects. Although food sIgE levels have been reported to increase during the first year of food OIT and decrease with the

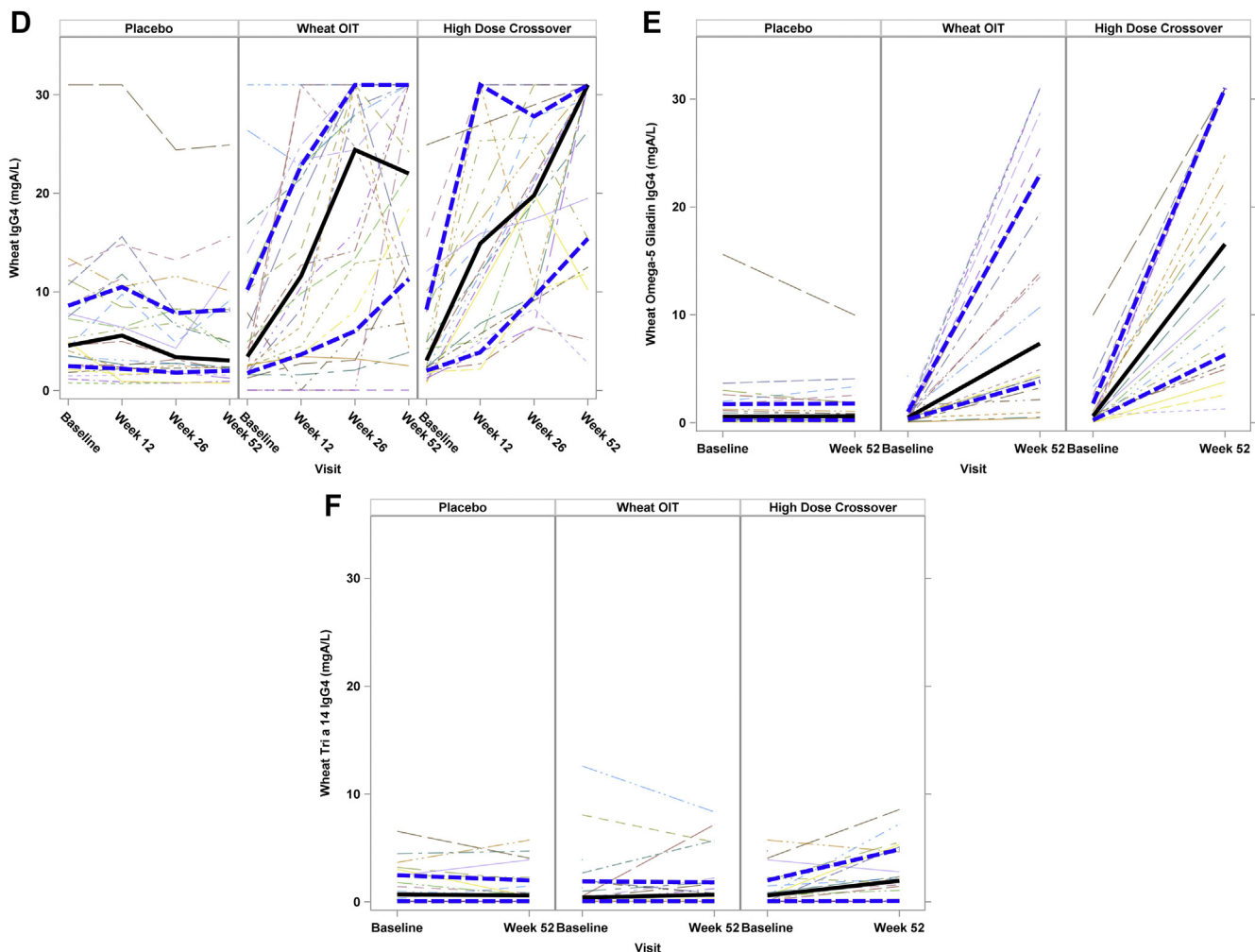


FIG 4. (Continued).

continued course of OIT, the lack of change in SPT responses is somewhat surprising because SPT responses are usually reported to decrease within the first year of OIT. However, it is known that the commercially available wheat SPT extract contains relatively little gluten, thus having limited capacity to accurately reflect the immunologic changes occurring during VWG OIT. Consistent with OIT trials using milk, egg, and peanut, there were significant increases in serum sIgG₄ antibodies against wheat and omega-5 gliadin that positively correlated with the initial year 1 SCDs.^{14,16-19}

There are limited data regarding wheat OIT published to date. In the largest study Sato et al⁷ reported outcomes of wheat OIT for 18 subjects with a mean age of 9 years. Sixteen subjects achieved the target daily maintenance dose (5.2 g of WP) and, after a 2-week period of avoidance, ingested this dose without symptoms during the DBPCFC to wheat. At the 2-year follow-up, 11 (61%) actively treated subjects tolerated 5.2 g of WP during an open challenge compared with 1 (9%) of the 11 historical untreated control subjects. Among a total of OIT 5778 doses, 6.8% resulted in symptoms, with administration of epinephrine on 1 occasion. One open-label, multicenter pilot study used hydrolyzed WP OIT without any advantage regarding safety.¹⁰ Nine children (mean age, 7.2 ± 3.23 years) with IgE-mediated wheat allergy received OIT with partially hydrolyzed wheat-

based cereals (pHCs) at a daily maintenance dose equivalent of 2.2 g of WP.¹⁰ Of the 9 patients enrolled in the trial, 4 discontinued pHC OIT because of mild-to-severe reactions at the initial escalation phase, suggesting that for some patients, pHCs might be more allergenic than the intact WP. The 5 patients who passed the escalation phase consumed pHCs daily for up to 6 months; 4 patients completed the study and passed the open oral wheat challenge with 4.43 g of WP (nonhydrolyzed).

It is challenging to compare the results of the 5 pilot studies with our results because of significant heterogeneity in the design and reporting of outcomes.⁶⁻¹⁰ The pilot studies used generally higher maintenance daily doses ranging from 4 g of WP to 13 g of WP over the treatment period of 6 to 24 months. The desensitization (defined differently for each study) was achieved by approximately 80% of the subjects in 4 studies, with the exception of an Iranian study that reported 100% desensitization to 50 g of bread (4 g of WP) in 12 children (median age, 2.25 years; range, 2-10 years) treated with a daily maintenance dose of 4 g of WP for 24 months. The median serum wheat sIgE level decreased from 55.9 IU/mL at baseline to 4.68 IU/mL (Astra Biotech, Berlin, Germany) after 24 months of wheat OIT. The median wheat SPT wheal diameter decreased from 10 mm at baseline to 3 mm at month 24. These preliminary results suggest that similar to peanut OIT, the efficacy of wheat OIT might be superior in younger

children with different sensitization profiles to the wheat components.²⁰ In terms of safety, 2 studies reported treatment-emergent adverse events with 6.25% and 6.8% of the doses.^{6,7}

There are several limitations to our trial. In spite of the multicenter design, the sample size is small, and the results might not be representative of the majority of the patients with wheat allergy. We have enrolled highly allergic patients with a very low SCD and severe symptoms treated with epinephrine during the baseline wheat DBPCFC. It is possible that efficacy and safety would be better in patients with a milder phenotype of wheat allergy, as well as in younger children. We have chosen VWG flour as OIT material, whereas other studies administered food products (eg, wheat pasta, bread, or cakes) during the maintenance phase of OIT. Use of wheat food items, although having a risk for less precise dosing, might allow for much higher maintenance doses and possibly improved adherence to OIT in the long term. In our trial VWG flour was mixed with a food vehicle, ensuring accuracy of dosing, but the maintenance doses were lower compared with those in the other studies. In addition, raw VWG has the highest allergenic potential, but it is not the form of wheat that is ingested in the usual diet. There might be a disadvantage to using the most potent form of the allergenic food for OIT because of lower rates of adherence to long-term treatment and higher risk of allergic reactions. This aspect might be of special relevance to wheat OIT in which high maintenance dosing might be necessary for improved efficacy.

In summary, in this first multicenter, randomized, double-blind, placebo-controlled clinical trial, low- and high-dose VWG OIT induced desensitization in the majority of treated subjects after 1 year of treatment. Low- and high-dose VWG OIT were not significantly different regarding SCD and dosing symptoms. After 2 years of low-dose VWG OIT, 30% of subjects achieved an SCD of 7443 mg of WP, and 13% achieved SU at 8 to 10 weeks off therapy. Compared with egg OIT, VWG OIT induced desensitization and SU in a lower percentage of subjects treated for 2 years, suggesting that a higher dose, longer duration, or both might be necessary for subjects with wheat allergy. The profile of dose-related adverse events in subjects with wheat OIT was comparable with OIT to other foods. Our trial provides the first safety and efficacy results for VWG OIT in a large group of patients with wheat allergy and supports further study to establish the optimal maintenance dose and duration of wheat OIT.

We thank the study subjects and their families for participation in the clinical trial. We also thank the research coordinators and dietitians at all study sites for their expert contributions.

Clinical implications: High-protein wheat flour OIT induced desensitization in the majority after 1 year and SU in 13% of subjects after 2 years. Safety of wheat OIT was comparable to OIT with other foods.

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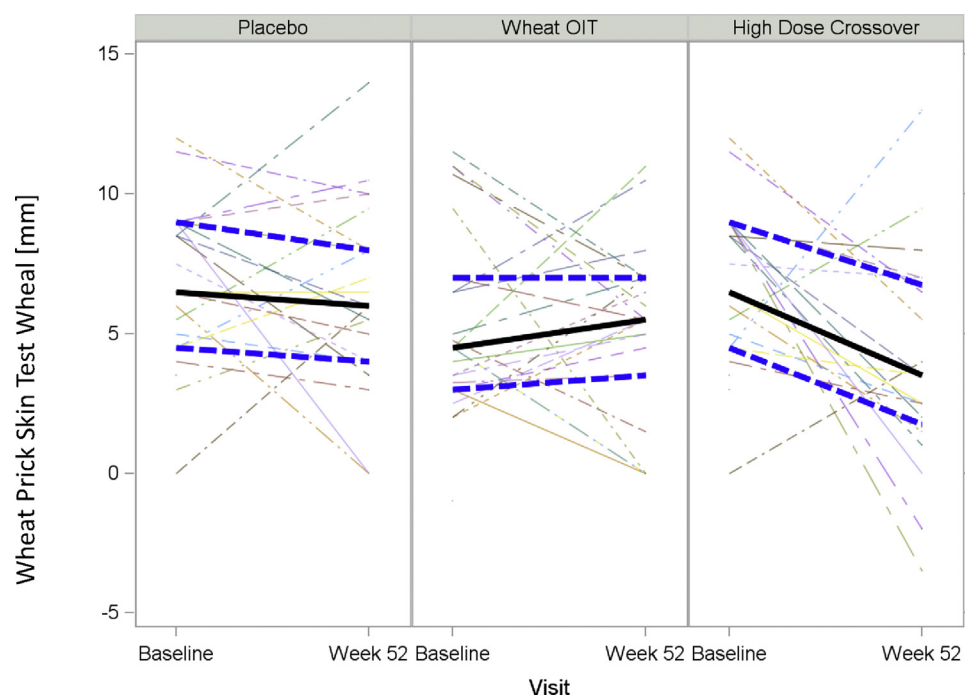


FIG E1. Wheat prick skin test through week 52/crossover week 52 by treatment group.

Box E1. Algorithm for missed consecutive doses

- Miss 1 dose: The next dose would be the current dose and could be given at home.
- Miss 2 doses in a row: The next dose would be the current dose and could be given at home.
- Miss 3 doses in a row: The next dose would be the current dose and would be given under observation (clinical research center [CRC]).
- Miss 4 doses in a row: The next dose would be the current dose and would be given under observation (CRC).
- Miss 5-7 doses in a row: Initiate the next dose at approximately 25% of the last tolerated dose. This would be done under observation (CRC). Dose escalation would occur in the CRC with an escalation no sooner than weekly and no longer than every 4 weeks with dose increases of 1-dose level at each escalation. If symptoms occur, the dosing symptom rules in the build-up phase would apply.

Missing more than 7 consecutive days of therapy (this does not include subjects intentionally removed from therapy to administer a 7443-mg WP oral food challenge [OFC] off therapy) constitutes an individual stopping rule, and the subject would no longer receive active therapy but would be followed longitudinally. Additionally, excessive missed days (ie, >3 consecutive days missed on 3 occasions) constitutes an individual stopping rule, and the subject would no longer take active therapy but would be followed longitudinally.

Box E2. Exclusion criteria

1. History of anaphylaxis to wheat resulting in hypotension, neurological compromise, or mechanical ventilation
2. Known allergy to corn (placebo)
3. Known celiac disease
4. Chronic disease (other than asthma, atopic dermatitis, or rhinitis) requiring therapy (eg, heart disease and diabetes)
5. Active eosinophilic gastrointestinal disease in the past 2 years
6. Participation in any interventional study for treatment of food allergy in the past 6 months
7. Subjects on “build-up phase” of aeroallergen immunotherapy (ie, has not reached maintenance dosing)
8. Severe asthma (2007 National Heart, Lung, and Blood Institute [NHLBI] Criteria Steps 5 or 6)
9. Uncontrolled mild or moderate asthma (2007 NHLBI Criteria Steps 1-4)
10. A burst of oral, intramuscular, or intravenous steroids of more than 2 days for an indication other than asthma in the past 1 month
11. Inability to discontinue antihistamines for initial-day escalation, skin testing, or oral food challenge
12. Use of omalizumab or other nontraditional forms of allergen immunotherapy (eg, oral or sublingual) or immunomodulatory therapy (not including corticosteroids) or biologic therapy within the past year
13. Use of β -blockers (oral), angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, or calcium-channel blockers
14. Use of investigational drug within 90 days or plan to use investigational drug during the study period
15. Pregnancy or lactation

Box E3. Reasons for discontinuations for subjects with symptoms associated with OIT dosing

Wheat OIT

- One participant was having abdominal symptoms. On their dosing symptom log, they reported mild abdominal pain, as well as several minor episodes of vomiting.
- One participant experienced shortness of breath, itchy throat, cough, and diffuse raised rash.
- One participant said they were experiencing symptoms and were stressed with school, but it does not specify what type of symptoms. Looking at their dosing symptom logs, they reported mild abdominal pain most commonly; mild throat discomfort was their next most common symptom, and in the 11 days immediately before discontinuation, they experienced diarrhea.

High-dose crossover

- One participant discontinued because of symptoms from ulcerative colitis and EoE. On the subject's dosing symptom log, he or she reported most commonly oral/pharyngeal symptoms; the second most common was mild throat discomfort, and there were 9 instances of mild abdominal pain.
- One participant experienced intermittent gastrointestinal symptoms despite twice-daily proton pump inhibitors PPI and an H2 antagonist and had fear of possible reactions.

TABLE E1. Challenge protocol

Dose no.	Dose, wheat protein (mg)	Dose, wheat powder (mg)	Cumulative dose, wheat protein (mg)	Cumulative dose, wheat powder (mg)	Comment
1	3	5.4	3	5.4	
2	10	18	13	23.4	
3	30	54	43	77.4	
4	100	180	143	257.4	
5	300	540	443	797.4	
6	1,000	1,800	1,443	2,597.4	Eligibility for the study
7	3,000	5,400	4,443	7,997.4	Year 1 OFC, primary end point success amount
8	3,000	5,400	7,443	13,397.4	Year 2 OFC, success

OFC, Oral food challenge.

TABLE E2. Wheat OIT dosing schedule

Dose no.	Dose (wheat protein mg)	Dose (wheat powder in mg)	Interval	Dose format	Increase (%)
1	0.07	0.1	Day 1	Vial	100
2	0.14	0.2	Day 1	Vial	100
3	0.28	0.4	Day 1	Vial	100
4	0.57	0.8	Day 1	Vial	100
5	1.1	1.5	Day 1	Vial	87.5
6	2.1	3.0	Day 1	Vial	100
7	4.3	6.0	Day 1	Vial	100
8	8.5	12.0	Day 1	Vial	100
9	17.8	25	2 wk	Vial	108
10	35.5	50	2 wk	Vial	100
11	53.3	75	2 wk	Capsule	50
12	71	100	2 wk	Capsule	33
13	111	156	2 wk	Capsule	56
14	160	225	2 wk	Capsule	44
15	213	300	2 wk	Capsule	33
16	284	400	2 wk	Capsule	33
17	373	525	2 wk	Scoop 1*	31
18	476	670	2 wk	Scoop 2	28
19	596	840	2 wk	Scoop 3	25
20	731	1030	2 wk	Scoop 4	23
21	923	1300	2 wk	Scoop 5	26
22	1150	1620	2 wk	Scoop 6	25
23	1445	2035	2 wk	Scoop 7	26
24	1800	2535	2 wk	Scoop 8	25
25	2272	3200	2 wk	Scoop 9	26
26	2748	3870	2 wk	Scoop 10	21

VWG powder contains approximately 71% WP. Dose escalation occurs in a clinical research center. Boldface dose levels represent the following: 8.5 mg of WP is the maximum dose escalation on day 1, 373 mg of WP is the minimum maintenance dose, 1445 mg of WP is the maximum dose escalation for participants initially receiving active treatment, and 2748 mg of WP is the maximum dose escalation for placebo crossover participants.

*All scoops are approximate weights based on scoop size and leveling.

TABLE E3. Wheat OIT: Maintenance dosing through week 52

	Treatment group		
	Placebo	Wheat OIT	High-dose crossover
Days to maintenance			
No.	21	20	19
Mean	232.90	244.20	279.16
Standard	20.37	38.00	21.39
Median	234.00	237.00	280.00
Minimum	197.00	162.00	238.00
P25	218.00	220.00	264.00
P75	250.00	276.50	296.00
Maximum	270.00	317.00	321.00
Days from maintenance to week 52/week 52 crossover DBPCFC			
No.	21	19	19
Mean	132.86	128.74	73.95
Standard	27.59	36.08	21.92
Median	133.00	130.00	73.00
Minimum	77.00	53.00	13.00
P25	112.00	118.00	61.00
P75	154.00	155.00	88.00
Maximum	183.00	196.00	112.00
Maintenance dose (mg WP)			
No.	21	20	19
Mean	1445.00	1394.90	2279.20
Standard	0.00	216.47	783.40
Median	1445.00	1445.00	2744.68
Minimum	1445.00	475.17	372.34
P25	1445.00	1445.00	2269.50
P75	1445.00	1445.00	2744.68
Maximum	1445.00	1445.00	2744.68

TABLE E4. Dosing symptoms by subject

		Any symptom																									
		Any symptom		Any symptom excluding oral/pharyngeal		Oral/pharyngeal		Skin		Respiratory		Gastrointestinal		Other		Symptoms >0.5 h		Treated		Treated with epinephrine		Mild symptoms		Moderate symptoms		Severe symptoms	
Visit type	No. of subjects	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Before week 52																											
Placebo-treated subjects																											
First-day clinic dose	23	10	43.5	10	43.5	5	21.7	6	26.1	6	26.1	1	4.3	1	4.3	0	0.0	0	0.0	0	0.00	10	43.5	0	0.00	0	0.00
Clinic dose	23	10	43.5	9	39.1	5	21.7	8	34.8	7	30.4	2	8.7	3	13.0	3	13.0	3	13.0	0	0.00	9	39.1	1	4.35	0	0.00
Home dose	23	14	60.9	13	56.5	8	34.8	9	39.1	11	47.8	5	21.7	8	34.8	7	30.4	8	34.8	0	0.00	12	52.2	3	13.04	0	0.00
All	23	18	78.3	18	78.3	11	47.8	15	65.2	16	69.6	6	26.1	9	39.1	7	30.4	9	39.1	0	0.00	18	78.3	3	13.04	0	0.00
High-dose crossover																											
First-day clinic dose	21	5	23.8	4	19.0	2	9.5	3	14.3	3	14.3	1	4.8	0	0.0	1	4.8	0	0.0	0	0.00	4	19.0	0	0.00	0	0.00
Clinic dose	21	15	71.4	15	71.4	7	33.3	13	61.9	12	57.1	5	23.8	2	9.5	4	19.0	9	42.9	1	4.76	15	71.4	1	4.76	0	0.00
Home dose	21	20	95.2	20	95.2	12	57.1	15	71.4	17	81.0	14	66.7	11	52.4	14	66.7	15	71.4	3	14.29	20	95.2	9	42.86	1	4.76
All	21	20	95.2	20	95.2	16	76.2	18	85.7	18	85.7	14	66.7	11	52.4	15	71.4	16	76.2	4	19.05	20	95.2	9	42.86	1	4.76
Wheat OIT																											
First-day clinic dose	23	8	34.8	7	30.4	4	17.4	4	17.4	5	21.7	2	8.7	0	0.0	2	8.7	4	17.4	0	0.00	7	30.4	0	0.00	0	0.00
Clinic dose	23	18	78.3	16	69.6	11	47.8	9	39.1	13	56.5	7	30.4	2	8.7	6	26.1	9	39.1	1	4.35	15	65.2	2	8.70	0	0.00
Home dose	23	23	100.0	22	95.7	14	60.9	14	60.9	22	95.7	17	73.9	12	52.2	16	69.6	18	78.3	4	17.39	22	95.7	11	47.83	3	13.04
All	23	23	100.0	22	95.7	17	73.9	15	65.2	22	95.7	17	73.9	12	52.2	16	69.6	19	82.6	5	21.74	22	95.7	13	56.52	3	13.04
After week 52																											
Wheat OIT																											
Clinic dose	14	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.00	0	0.0	0	0.00	0	0.00
Home dose	19	12	63.2	12	63.2	5	26.3	5	26.3	9	47.4	6	31.6	7	36.8	3	15.8	10	52.6	0	0.00	12	63.2	2	10.53	0	0.00
All	19	12	63.2	12	63.2	5	26.3	5	26.3	9	47.4	6	31.6	7	36.8	3	15.8	10	52.6	0	0.00	12	63.2	2	10.53	0	0.00

TABLE E5. Reactions to oral food challenges

	Total OFCs	Any symptoms		Major* symptoms		Minor† symptoms		Other symptoms that stopped OFCs		Treatment given		Epinephrine		Antihistamines		Steroids (intravenous or oral)		Inhaled β-agonist		Intravenous fluids		
		No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	
		No.	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
OFC type																						
Baseline (1443 mg of protein)	47	0.0	100.0	40.4	59.6	2.1	97.9	85.1	14.9	0.0	100.0	44.7	55.3	0.0	100.0	57.4	42.6	74.5	25.5	95.7	4.3	
Week 52 (7443 mg of protein)	40	20.0	80.0	60.0	40.0	30.0	70.0	80.0	20.0	25.0	75.0	70.0	30.0	25.0	75.0	72.5	27.5	85.0	15.0	100.0	0.0	
Year 2 desensitization (7443 mg of protein)	18	38.9	61.1	61.1	38.9	44.4	55.6	77.8	22.2	44.4	55.6	83.3	16.7	44.4	55.6	94.4	5.6	77.8	22.2	100.0	0.0	
Year 2 SU (7443 of mg protein)	7	42.9	57.1	57.1	42.9	57.1	42.9	100.0	0.0	42.9	57.1	71.4	28.6	42.9	57.1	100.0	0.0	85.7	14.3	100.0	0.0	
Week 52 desensitization crossover (7443 mg of protein)	19	57.9	42.1	78.9	21.1	68.4	31.6	84.2	15.8	63.2	36.8	89.5	10.5	63.2	36.8	94.7	5.3	84.2	15.8	100.0	0.0	

OFC, Oral food challenge.

*Major symptoms are defined as confluent erythematous pruritic rash; respiratory signs, such as wheezing, inability to speak, dysphonia, and aphonia; 3 or more urticarial lesions; 1 or more sites of angioedema; 2 or more distinct episodes of vomiting; hypotension for age not associated with vasovagal episode; or evidence of severe abdominal pain that persists for 5 or more minutes.

†Minor symptoms are defined as 1 to 2 urticarial lesions, a single episode of vomiting, diarrhea, notable distressed caused by nausea and/or abdominal pain with decreased activity, dry hacking cough that lasts 3 or more minutes, complaint of throat tightness and/or pruritus plus 3 or more episodes of throat clearing, persistent rubbing of nose or eyes that lasts for 5 or more minutes, persistent rhinorrhea that lasts for 5 or more minutes, continuous hard scratching that lasts for 3 or more minutes, or a distinct change in affect (whining, crying, and/or clinging to parent).