

Peanut Allergen Powder-dnfp: A Novel Oral Immunotherapy to Mitigate Peanut Allergy

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Abstract

Objective: To review data on efficacy and safety of peanut allergen powder-dnfp (PAP; Palforzia), a novel oral immunotherapy for peanut allergy, a common food allergy. **Data Sources:** A PubMed/CINAHL search in English was performed from inception to June 30, 2020, using the search words *peanut allergy*, *desensitization*, *ARA101*, and *peanut oral immunotherapy*. **Study Selection and Data Extraction Quantification:** Published phase 2 and 3 clinical trials, documents presented to the Food and Drug Administration, and supplemental study documentation were reviewed. Articles evaluated PAP's pharmacology, pharmacokinetics, mechanism of action, efficacy, and safety. **Data Synthesis:** PAP was efficacious and safe for treatment of peanut allergy in mostly Caucasian children, 4 to 17 years old. A key phase III clinical trial showed a statistically significant difference (primary end point) between PAP 600 mg and placebo groups (67.2% vs 4%; $P < 0.001$). During initial dose escalation and up dosing phases, gastrointestinal and respiratory tract allergic reactions (ARs) were more common in the PAP group. More epinephrine rescue was used in the PAP group. **Relevance to Patient Care and Clinical Practice:** Oral immunotherapy for desensitization of peanut allergy was shown to reduce the severity of reactions if accidental allergen exposure occurs. Risk evaluation and mitigation strategy certification is required for pharmacies, health care providers, and clinics. More data in real-world populations will enhance its effectiveness. **Conclusions:** In patients 4 to 17 years old, PAP mitigated ARs, including anaphylaxis, that may occur with accidental peanut exposure. Although there are risks, it was efficacious in more than two-thirds of participants in phase 2 and phase 3 efficacy trials.

Keywords

adverse drug reactions, allergy, drug trials, hypersensitivity, immunology

Introduction

Peanut (*Arachis hypogaea*) allergen powder-dnfp (PAP), Palforzia, the first oral biological immunotherapy, was approved by the Food and Drug Administration (FDA) on January 31, 2020.¹ It is indicated for initial dose escalation in patients 4 to 17 years old for mitigation of allergic reactions (ARs), including anaphylaxis, that may occur with accidental peanut exposure.² The drug was known as AR101 during clinical studies.³ Because of the unmet need in the market, the drug received both fast track status and then, subsequently, breakthrough therapy designation from the FDA as clinical trials were being completed.³

Peanut allergy, the most common food allergy, can be a serious condition, causing severe, unpredictable hypersensitivity reactions, including life-threatening (LT) anaphylaxis.⁴ Peanut allergy affects 2.2% of children in the United States. Children who have this allergy have the highest risk of a serious reaction of any food allergy.^{4,5} Parlaman et al⁶

reviewed emergency visits between 2007 and 2012 and showed that anaphylaxis caused by peanuts was responsible for 37% of food allergy incidents.⁶ Data suggest that the prevalence of peanut allergy has increased over the past 3 decades.^{6,7} In addition, approximately 80% of children who are allergic to peanuts do not outgrow their peanut allergy as they become adults.^{8,9} Children who have atopic dermatitis, asthma, and allergic rhinitis have an increased risk of having a peanut allergy.⁸

The economic, psychosocial impact, and effect on the quality of life (QOL) of food allergies is significant for children and their parents.^{10–12} The stress and anxiety of accidentally ingesting a peanut negatively affects psychosocial

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health and overall QOL, including QOL surrounding school.^{12,13} Gupta et al¹¹ estimated the direct medical costs (hospitalizations, emergency department, and pediatrician visits) of food allergies at \$4.3 billion annually. For years, strict avoidance of peanuts and use of epinephrine to treat accidental peanut exposures have been the only methods for patients and families to manage the condition.^{7,13}

This article provides a review of the immunology surrounding peanut allergens and the role of oral immunotherapy. The clinical pharmacology, clinical trials including efficacy and safety data, importance of manufacturer and standardization, dosing and significant adverse events (AEs), warnings, and precautions were evaluated for PAP.

Data Sources

A search of PubMed and CINAHL databases from inception through June 30, 2020, was conducted using the following search terms: *peanut allergy*, *desensitization*, *ARA101*, and *peanut oral immunotherapy*. Clinical trials investigating PAP were obtained from the manufacturer's website, the FDA website, and from the literature search. Controlled trials (1 phase 2 study¹⁴ and 2 phase 3 pivotal studies^{3,15,16}) will be the focus of this review. These studies provided the foundation of PAP's efficacy and safety data that led to its FDA approval (Table 1). There is a controlled study completed in Europe and noncontrolled studies that have been completed and some in various stages of completion.³ Much of these data have not been published.³

Immunology Regarding Peanuts

A peanut, approximately 25% protein, contains at least 17 specific allergens (Ara h 1 to Ara h 17).⁸ The 4 major allergens are Ara h 1, Ara h 2, Ara h 3, and Ara h 6. Ara h 2 is reported to be associated with severe reactions, especially respiratory symptoms.^{8,17,18} Protein allergens cause an immunoglobulin E (IgE)-mediated type I hypersensitivity reaction. Generally, the epithelial barrier in the gastrointestinal (GI) tract prevents antigens from freely passing into the systemic circulation.¹⁹ The loss of integrity of the epithelial barrier and intolerance toward these food antigens sensitizes the immune system.¹⁹ Sensitization is the process of mistaking the antigen as a pathogen.¹⁹ The stimulation of T cells and B cells and the subsequent production of IgE toward the peanut allergens provide the opportunity for generation of inflammatory mediators to be released from mast cells, eosinophils, and basophils.^{19,20} The mediators involved include histamine, tryptase, platelet-activating factor, prostaglandins, and leukotrienes.¹⁹

The release of these mediators can trigger patient symptoms in many organs, including the cardiovascular (tachycardia, decrease in blood pressure), GI (itching of mouth or

throat, nausea, abdominal pain, vomiting, diarrhea), and neurological system (dizziness, weakness); respiratory tract (RT; rhinorrhea, nasal congestion, wheezing, stridor); and the skin (erythema, urticaria, angioedema, hives, pruritis).¹⁸ The consortium of food allergy research criteria grades ARs from 1 to 5: grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, life-threatening; and grade 5, death.³ Systemic ARs are also graded based on severity.³ Anaphylaxis generally has a rapid onset and can be a potentially fatal reaction. It commonly involves multiple organ systems.^{3,18} Common symptoms include hives, swelling of the face, nausea, itchy/watery eyes, and difficulty in breathing.¹⁸

Oral Immunotherapy

Peanut oral immunotherapy (POIT) involves exposing a patient to increasing amounts of peanut allergens in order to desensitize the patient.^{19,21} This approach has been increasingly studied over the past 10 years demonstrating proof of the process of desensitization.²² The phases of POIT include the initial dose escalation phase (IDE), updosing phase (UDP), and maintenance phase (MP). The UDP provides increasing amount of allergen until the targeted maintenance dose is reached.²¹ During IDE and UDP of POIT, IgE-mediated ARs are more common.²¹ The threshold for IgE reactivity increases during the UDP, reducing the severity of reactions as the targeted MP is reached.²¹ POIT increases IgG4, decreasing the amount of allergen that binds to antigen-specific IgE, which causes less mast cell activation.^{20,21} The gradual administration of the allergen during POIT causes controlled release of inflammatory mediators from mast cells and basophils, which leads to desensitization.²¹

A complication of POIT is eosinophilic esophagitis (EoE). EoE is a chronic, antigen-mediated inflammatory condition of the esophagus that has been documented as a complication of 3% to 4% of patients undergoing POIT.^{23,24} EoE patients may have a variety of symptoms, including reflux, abdominal pain, dysphagia, and food impaction.²³ Patients are diagnosed by clinical symptoms and histological exam through esophagogastroduodenoscopy biopsy (15 eosinophils/high power field). Discontinuation of the POIT and elimination of the offending food allows EoE to regress.²³

Clinical Pharmacology

Pharmacokinetics and Pharmacodynamics

Because PAP is derived from a food source and is a biologic, it was not evaluated and characterized pharmacokinetically.³ Studies of PAP showed statistically significant increases in IgG4 levels from baseline to exit visit ($P < 0.0001$). In

addition, the ratio of the geometric means of peanut-specific IgE to IgG4 rose in the placebo group (approximately 105 to 125 from baseline to exit visit), whereas in the PAP group, the ratio decreased (approximately 100 to 5 from baseline to exit visit).³

Mechanism of Action

The mechanism of action of how PAP facilitates desensitization through POIT has not been fully elucidated.³ The following has been observed in PAP clinical studies.¹⁵ Immunological changes seen during therapy include increases in IgG4 and regulatory T-cell populations and elimination of antigen-specific T-helper 2A (T_H2A) cells.^{3,15,25} By eliminating T_H2A cells, the production of IgE is decreased because T_H2A cells aid in this process.^{15,25} Additionally, IgG4 is thought to compete with IgE for binding to peanut allergens or by inhibiting activation at the cellular level.²⁰ As noted above, PAP affects the ratio of IgE to IgG4.³ It is this change in ratio between IgE and IgG4 that has been found to provide tolerance in patients who are desensitized to peanuts during POIT.²⁰ Specifically, IgG4 levels have been shown to increase significantly during POIT (during the UDP and MP), with IgE levels not changing significantly. As the ratio of IgE/IgG4 decreases, clinical reactions to peanuts decrease. This decrease in reactions has been shown specifically with increased IgG4 directed against Ara h 2, a potent allergen for basophil and mast cell degranulation and clinical symptoms.²⁰

Manufacturing and Characterization

PAP is a powder made from roasted and defatted peanuts. It is free of microbial contamination.¹⁵ To ensure standardization of product contents and safeguard appropriate manufacturing, labeling, and packaging, PAP is prepared using the FDA's current good manufacturing practices. A consistent profile of the following proteins is found in PAP: Ara h 1 to Ara h 3, Ara h 6, Ara h 7 to Ara h 11, and Ara h 13 to Ara h 15.¹⁵ Testing is done to ensure that the active and inactive ingredients of the drug are consistent. PAP is assessed for total protein and content uniformity using the Dumas method. The Dumas method uses combustion to determine the protein content and content uniformity by measuring the resulting elemental nitrogen contained in the PAP.²⁶ The protein integrity (consistent profile of allergens) is assessed by high-performance liquid chromatography, and the potency of allergens is assessed by using enzyme-linked immunosorbent assay.¹⁵

Clinical Trials

The methods were similar between studies to provide consistency in evaluating PAP's effect. In the Bird et al¹⁴ and

PALISADE Group et al studies, participants were screened using a double-blind, placebo-controlled food challenge (DBPCFC; Figure 1), the gold standard in diagnosing peanut allergies.^{14,16} The benefit of the screening DBPCFC is that the sensitivity of participants to peanut allergens is found in a consistent and reproducible method.³ It was used to verify the peanut allergy along with clinical history and laboratory findings. During the screening DBPCFC, participants were required to experience dose-limiting allergic symptoms to ≤ 100 mg (1/3 of peanut kernel) of PAP.^{3,14-16} This approach finds the most sensitive peanut allergic participants and ensures that the participants are symptomatic to peanuts. After screening, participants entered 3 phases: IDE, UDP, and a MP. The UDP and the MP used a characterized oral sensitization immunotherapy protocol.^{3,14-16} The goal was to minimize severe ARs to the PAP and allow increased tolerance to the allergens. The MP was 2 weeks in the phase 2 study¹⁴ (Bird et al) and a minimum of 24 weeks in the phase 3 study¹⁶ (PALISADE Group et al). The IDE and the first dose of each UDP level was provided in the clinic.^{3,14,16} During the studies, participants were given an epinephrine autoinjector in case of an anaphylactic reaction and counseled about maintaining a peanut-free diet.^{3,14,16} Bird et al¹⁴ and PALISADE Group et al both had an exit DBPCFC to assess the primary end point (intention-to-treat population who were randomized and received 1 dose of study medication).^{3,14-16} The exit DBPCFC provided specific amounts of increasing peanut protein to simulate an accidental peanut exposure and to track the level of desensitization to peanut allergen. In all studies, patients were cautioned against increased activity (exercise) or hot showers around study doses.^{3,14-16} Increased GI absorption of the peanut allergens and the release of mediators that occur during exercise are risk factors for AR, especially anaphylaxis.²⁷ Both exercise and hot showers raise the core body temperature and increase the potential for AR through mast cell activation.²⁷

Bird et al¹⁴ conducted a safety and efficacy study of PAP as compared with placebo (Table 2). A total of 55 participants were enrolled (mostly Caucasian and a majority were male; median age = 7 years). Most of the participants had other comorbid allergic conditions. Exclusions were a history of LT anaphylaxis or uncontrolled asthma (UCA). The primary efficacy end point compared the proportion of patients between treatment groups who were able to tolerate 300 mg of PAP (443 mg cumulative dose) at study exit with no or mild symptoms. At the exit DBPCFC (300-mg PAP dose), there was a statistically significant difference between treatment groups (79% vs placebo 19%; $P < 0.0001$). In addition, at the PAP 600-mg dose, there was a statistically significant difference between treatment groups ($P < 0.0001$). Most of the AEs involved the GI tract (Table 3), and 96% were graded as mild throughout the study.¹⁴ During the exit DBPCFC, 38% ($n = 10$) in the placebo arm

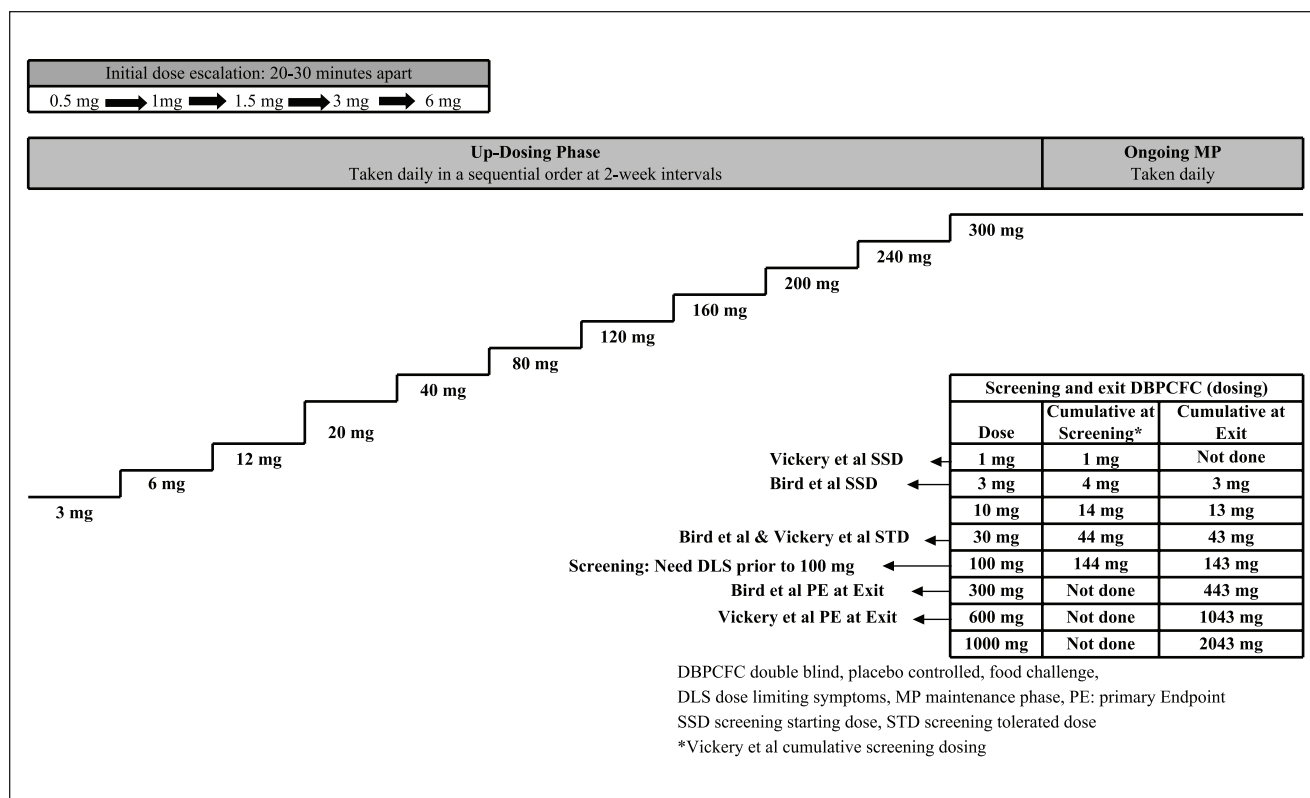


Figure 1. Peanut allergen powder oral immunotherapy dosing algorithm.^{2,3,14-16}

Abbreviations: DBPCFC, double blind, placebo controlled, food challenge; DLS, dose-limiting symptoms; MP, maintenance phase; PE, primary end point; SSD, screening starting dose; STD, screening tolerated dose.

*PALISADE Group et al¹⁶ cumulative screening dosing.

Table 1. List of Acronyms.^{3,15}

Term	Acronym
Adverse events	AE
Allergic reaction	AR
Double-blind, placebo-controlled, food challenge	DBPCFC
Eosinophilic esophagitis	EoE
Food and Drug Administration	FDA
Gastrointestinal	GI
Immunoglobulin E	IgE
Immunoglobulin G4	IgG4
Initial dose escalation	IDE
Life-threatening	LT
Maintenance phase	MP
Oral immunotherapy	OIT
Peanut allergen powder-dnfp	PAP
Peanut oral immunotherapy	POIT
Quality of life	QOL
Respiratory tract	RT
Risk evaluation and mitigation strategy	REMS
Uncontrolled asthma	UCA
Updosing phase	UDP

had severe symptoms compared with no patient in the PAP arm. One patient in the PAP arm was diagnosed with EoE.¹⁴

PALISADE Group et al¹⁶ (Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults [PALISADE]) completed a phase 3 study to measure the efficacy of peanut protein OIT in participants aged 4 to 17 years old. The study originally allowed participants aged 4 to 55 years old to be enrolled. The low enrollment in participants >17 years old provided an impetus to change the age range to 4 to 17 years old. The study enrolled 496 participants, mostly Caucasian and mostly male children (median age 9 years) in a 3:1 ratio (PAP:placebo). Most of the participants had other comorbid allergic conditions.^{3,15,16} Participants who had unstable cardiovascular disease, LT anaphylaxis, and UCA or medications that interfered or masked reactions were excluded. The primary efficacy end point compared the proportion of participants between treatment groups who were able to tolerate 600 mg of PAP (1043 mg cumulative dose) at study exit without dose-limiting symptoms. At the exit DBPCFC (600 mg PAP dose), there was a statistically significant difference in response between treatment groups (PAP 67.2% vs placebo

Table 2. Clinical Trials Evaluating PAP.^{3,14-16}

Author/design/ location	Key patient demographic (age, sex, race, comorbidities, other FA)	Inclusion/exclusion	End points/duration	Intervention/ control/ITT, n	End point results	Conclusion	Comments
Bird et al ¹⁴ (2015)/P, R, DB, PC, MCI/United States (8 sites)	PAP • Age (median): 7 y • Range: 4-21 y • Sex: male, n = 20 (~69%) • Race: White, n = 26 (90%) • Other allergic conditions o Asthma: n = 12 (41%) o AD: n = 19 (66%) o AR: n = 18 (62%) o Other FA: n = 24 (83%) Placebo • Age (median): 8 y • Range: 4-14 y • Sex: male, n = 16 (~62%) • Race: White, n = 20 (77%) • Other allergic conditions o Asthma: n = 11 (41%) o AD: n = 11 (41%) o AR: n = 18 (67%) o Other FA: n = 20 (74%)	Inclusion • Ages 4-26 y • CHx of PA • PS IgE ≥0.35 kU/L and/or PSPT wheal ≥3 mm larger than negative control with previous 12 months • Experience dose-limiting symptoms ≤100 mg PAP on screening DBPCFC Exclusion • Severe or LTA • Eosinophilic GID • Severe or UCA	• Primary: proportion of patients in each arm tolerating PAP dose of ≥ 300 mg (Cum dose ≥ 443 mg) at exit DBPCFC without DL Sx • Secondary: proportion of patients in each arm tolerating PAP dose of ≥ 600 mg (Cum dose ≥ 1043 mg) at exit DBPCFC without DL Sx 6 months	• PAP: IDE 2-3 days 0.5-6 mg, UDP (20-24 weeks), MP 3 to 300 mg daily (q 2 weeks); n = 29 (79% CT) • Placebo: IDE, UDP, MP with placebo; n = 26 (100% CT)	• Primary (tolerating 300 mg (Cum dose ≥ 443 mg) of PAP during exit DBPCFC) o PAP: 79% (n = 23) o Placebo: 19% (n = 5) o (P < 0.0001) • Secondary (tolerating 600 mg of PAP (1043 mg PAP Cum dose) during exit DBPCFC) o PAP: 62% (n = 18) o Placebo: 0% (n = 0) (P < 0.0001)	PAP significantly reduced symptoms and demonstrated desensitization at the 300- and 600- mg dose levels	PAP increased the amount of peanut protein tolerated by 18-fold from screening to exit. Patients who could not reach the 300-mg/d dose were not eligible for the EFC
PALISADE Group et al (2018)/P, R, DB, PC, MCI/ International (North American 51 sites, 402 patients ~81%; European 15 sites, 94 patients, ~19%)	PAP • Age (median): 9 y • Range: 4-11 y, n = 238 (64%); 12-17 y, n = 134 (36%) • Sex: male, n = 208 (~56%) • Race: White, n = 292 (79%) • Other allergic conditions o Asthma: n = 197 (53%) o AD: n = 236 (63%) o AR: n = 266 (~72%) o Other food allergy: n = 245 (~66%) Placebo • Age: (median) 9 y • Range: 4-11 y, n = 89 (~72%); 12-17 y, n = 35 (~28%) • Sex: male, n = 76 (~61%) • Race: White, n = 97 (~78%) • Other allergic conditions o Asthma: n = 65 (~52%) o AD: n = 72 (~58%) o AR: n = 90 (~73%) o Other food allergy: n = 80 (~65%)	Inclusion • Ages 4-55 y • CHx of PA • PS IgE ≥0.35 kU/L or PSPT wheal ≥3 mm than control • Experience dose-limiting symptoms ≤100 mg PAP on screening DBPCFC Exclusion • Severe or LTA <60 days before screening DBPCFC • Hx of CVD or UC Htn • Eosinophilic GID or Hx of GERD • UC or severe asthma • Corticosteroid use • AH use • Omalizumab use • BB, ACE inhibitor, ARB CCB use • Dose-limiting symptoms to placebo during screening DBPCFC	• Primary: proportion of patients tolerating a PAP dose of 600 mg (Cum dose ≥1043 mg) at exit DBPCFC without DL Sx (4-17 y) • Secondary: proportion of patients in each arm tolerating PAP dose of ≥ 1000 mg (Cum dose ≥2043 mg) at exit DBPCFC without DL Sx 12 months	• PAP: IDE 2 days 0.5-6 mg, UDP (20-40 weeks), MP 3-300 mg daily (24-28 weeks) of 300 mg PAP daily; n = 372 (79% CT) • Placebo: IDE 2 days, UDP (20-40 weeks), MP (24-28 weeks) of placebo; n = 124 (93% CT)	• Primary: tolerating 600 mg of PAP (Cum dose ≥ 1043 mg) during exit DBPCFC o PAP: 67.2% (n = 250) o Placebo: 4.0% (n = 5) (P < 0.001) • Secondary: tolerating 1000 mg of PAP (2043 mg PAP Cum dose) during exit DBPCFC o PAP: 50.3% (n = 187) o Placebo: 2.4% (n = 3) (P < 0.001)	PAP significantly reduced symptoms and demonstrated desensitization in patients aged 4-17 y at 600 and 1000 mg	Patients who could not reach the 300-mg/d dose were not eligible for the EFC

Table 2. (continued)

Author/design/ location	Key patient demographic (age, sex, race, comorbidities, other FA)	Inclusion/exclusion	End points/duration	Intervention/ control/ITT, n	End point results	Conclusion	Comments
RAMSES (2018)/P, R, DB, PC, MCI/ North American, 59 sites; Canadian, 5 sites	PAP - Age (median): NR - Range: 4-11 y, n = 226 - CHx of PA (~67%); 12-17 y, n = 111 (33%) - Sex: male, n = 218 (~65%) - Race: White, n = 245 (~73%) - Other allergic conditions - Asthma: n = 176 (~52%) - AD^a: NR - AR: NR - Other food allergy^a: n = NR	Inclusion - Ages 4-17 y - CHx of PA - SPT for peanut $\geq$ 8 mm compared with negative saline control and elevated PS IgE 14 kUA/L Exclusion - Severe or LTA <60 days before screening DBPCFC - Hx of CVD or UC Htn - Hx of EoE, eosinophilic GID or Hx of GERD - UC or severe asthma - Corticosteroid use - AH use - Omaliuzumab use - BB, ACE inhibitor, ARB CCB use	Safety: frequency of TEAEs, including SAEs/6 months	- PAP: IDE 2 days 0.5-6 mg, UDP (20-48 wk), 3-300 mg daily; n = 337 (NR CT) - Placebo: IE, UDP (20-48 wk); n = 168 (NR CT)	- TEAEs - PAP: 99.1% (n = 334) - Placebo: 94.6% (n = 159) - SAEs - PAP: 2 cases of SAEs; both not related to PAP - Placebo: 2 cases of SAEs; both not related to placebo	AE (severity) mostly mild to moderate, decreased in severity over time	I Patient Dx with EoE from PAP arm. PALISADE Group et al and RAMSES safety analysis combined to exceed FDA requirement of 600 patients

Abbreviations: ACE, angiotensin-converting enzyme; AD, atopic dermatitis; AE, adverse event; AH, antihistamine; AR, allergic rhinitis; ARB, angiotensin-receptor blocker; BB, β -blocker; CCB, calcium channel blockers; CHx, clinical history; CT, completed trial; Cum, cumulative; CVD, cardiovascular disease; DB, double blind; DBPCFC, double-blind, placebo-controlled, food challenge; DL, dose limiting; DS, desensitization; Dx, diagnosis; EFC, exit food challenge; EoE, eosinophilic esophagitis; FA, food allergy; FC, food challenge; FDA, Food and Drug Administration; GERD, gastroesophageal reflux disease; GID, gastrointestinal disease; Htn, hypertension; Hx, history; IDE, initial dose escalation; Ig, immunoglobulin; LTA, life-threatening anaphylaxis; MC, multicenter; MP, maintenance phase; NR, not reported; P, prospective; PA, peanut allergy; PAP, peanut (*Arachis hypogaea*) allergen powder-dnfp (ARA101); PC, placebo controlled; PS, peanut specific; PSPT, peanut skin prick test; R, randomized; SAE, serious adverse event; Sx, symptoms; TEAE, treatment-emergent adverse event; UC, uncontrolled; UCA, uncontrolled asthma; UDP, up dosing phase.

^aRAMSES did not report specific data for comorbidities for each group; overall percentage for both groups: other FA, 65%; AD, ~58%.

Table 3. Common Adverse Effects From Phase 2 and Phase 3 Trials.^{3,14-16}

	Bird et al, ^{1,4a} overall		PALISADE Group et al, ^b overall/maintenance phase		PALISADE Group et al/RAMSES, IDE/Up-dosing phase	
	PAP, n (%)	Placebo, n (%)	PAP, n (%); n = 372/310	Placebo, n (%); n = 124/118	PAP, n (%); n = 709	Placebo, n (%); n = 292
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gastrointestinal	19 (66)	7 (27)	319 (85.8)/160 (51.6)	86 (69.4)/43 (36.4)	604 (85.2)	172 (58.9)
Abdominal pain	6 (21)	2 (8)	194 (52.2)/46 (14.8)	30 (24.2)/7 (5.9)	363 (51.2)	62 (21.2)
Abdominal pain upper	6 (21)	2 (8)	152 (40.9)/41 (13.2)	26 (21)/9 (7.6)	214 (30.2)	43 (14.7)
Vomiting	7 (24)	1 (4)	154 (41.4)/50 (16.1)	30 (24.2)/14 (11.9)	262 (37.0)	49 (16.8)
Nausea	6 (21)	1 (4)	146 (39.2)/45 (14.5)	29 (23.4)/8 (6.8)	248 (35.0)	42 (14.4)
Oral pruritus	3 (10)	1 (4)	151 (40.6)/39 (12.6)	20 (16.1)/5 (4.2)	190 (26.8)	24 (8.2)
Throat irritation	NR	NR	152 (40.9)/43 (13.9)	34 (27.4)/11 (9.3)	296 (41.7)	56 (19.2)
Respiratory, thoracic, and mediastinal disorders	14 (48)	3 (12)	302 (81.2)/162 (51.6)	89 (71.8)/49 (41.5)	541 (76.3)	178 (61)
Cough	4 (14)	1 (4)	152 (40.9)/61 (19.7)	42 (33.9)/22 (18.6)	229 (32.3)	68 (23.3)
Rhinorrhea	2 (7)	2 (8)	113 (30.4)/46 (14.8)	28 (22.6)/9 (7.6)	NR	NR
Sneezing	2 (7)	2 (8)	98 (26.3)/33 (10.6)	18 (14.5)/5 (4.2)	151 (21.3)	37 (12.7)
Throat tightness	NR	NR	86 (23.1)/20 (6.5)	8 (6.5)/0 (0)	109 (15.4%)	10 (3.4)
Throat irritation	4 (14)	0 (0)	152 (40.9)/43 (13.9)	34 (27.4)/11 (9.3)	296 (41.7)	56 (19.2)
Dyspnea	NR	NR	44 (11.8)/17 (5.5)	5 (4)/1 (0.8)	54 (7.6)	6 (2.1)
Wheezing	2 (7)	0 (0)	NR/19 (6.1)	NR/10 (8.5)	87 (12.3)	21 (7.2)
Skin and subcutaneous tissue disorders	4 (14)	5 (19)	249 (66.9)/118 (38.1)	69 (55.6)/40 (33.9)	419 (59.1)	139 (47.6)
Urticaria	3 (10)	3 (12)	143 (38.4)/63 (20.3)	30 (24.2)/17 (14.4)	206 (29.1)	59 (20.2)
Pruritis	2 (7)	0 (0)	153 (41.1)/45 (14.5)	34 (27.4)/14 (11.9)	252 (35.5)	68 (23.3)
Rash	1 (3)	1 (4)	81 (21.8)/24 (7.7)	18 (14.5)/7 (5.9)	NR	NR
General disorders	3 (10)	0 (0)	139 (37.4)/58 (18.7)	39 (31.5)/13 (11)	215 (30.3)	70 (24)
Chest discomfort	2 (7)	0 (0)	24 (6.5)/8 (2.6)	1 (0.8)/0 (0)	41 (5.8)	2 (0.7)
Ear disorders	1 (3)	1 (4)	48 (12.9)/17 (5.5)	3 (2.4)/0 (0)	NR	NR
Ear pruritus	1 (3)	1 (4)	25 (6.7)/7 (2.3)	0 (0.0)/0 (0)	43 (6.1)	3 (1.0)

Abbreviations: IDE, initial dose escalation; NR, not reported; PAP, peanut (*Arachis hypogaea*) allergen powder-dmfp (ARA101).

^aTreatment-related hypersensitivity, treatment emergent reported by > 1 participant.

^bAdverse events in the peanut allergen powder-dmfp group with at least 5% higher incidence over placebo.

Table 4. Severe and Critical Adverse Events and Epinephrine Use (Per Patient).^{3,14-16}

	PALISADE Group et al, overall/maintenance phase		PALISADE Group et al/ RAMSES, IDE/updosing phase	
	PAP, n (%); n = 372/310	Placebo, n (%); n = 124/118	PAP, n (%); n = 709	Placebo, n (%); n = 292
Severity of adverse event/(patients with ≥ 1 adverse event)				
Mild	129 (34.7)/161 (51.9)	62 (50)/57 (48.3)	325 (45.8)	180 (61.6)
Moderate	222 (59.7)/101 (32.6)	55 (44.4)/37 (31.4)	348 (49.1)	84 (28.8)
Severe	16 (4.3)/8 (2.6)	1 (0.8)/0 (0)	20 (3.8)	4 (1.4)
Critical AEs				
Systemic allergic reactions	53 (14.2)/27 (8.7)	4 (3.2)/2 (1.7)	67 (9.4)	11 (3.8)
Anaphylaxis	1 (0.3)/1 (0.3)	0 (0)/0 (0)	4 (0.6)	0 (0)
SAE	8 (2.2)/4 (1.3)	1 (0.8)/1 (0.8)	6 (0.8)	2 (0.7)
SAE related to study drug	4 (0.6)/1 (0.3)	0 (0)/0 (0)	3 (0.4)	0 (0)
EoE	1 (0.3)/0 (0)	0 (0)/0 (0)	3 (0.4)	0 (0)
Withdrawal from study				
AEs leading to withdrawal from study	43 (11.6)/4 (1.3)	3 (2.4)/0 (0)	80 (11.3)	7 (2.4)
Discontinuation not caused by AEs	37 (9.9)/27 (8.7)	7 (5.6)/2 (1.7)	78 (11)	13 (4.5)
Epinephrine use (during study)				
Throughout study (except DBPCFCs)	52 (14)/24 (7.7)	8 (6.5)/4 (3.4)	74 (10.4)	14 (4.8)
Epinephrine use (during DBPCFC)	PAP, n (%); n = 372	Placebo, n (%); n = 124		
Screening DBPCFC	107 (36.1)	43 (37.1)	NR	NR
Exit DBPCFC	28 (9.5)	62 (53.4)	NR	NR
DBPCFC, maximum severity of symptoms	PAP (%), n = 372	Placebo (%), n = 124		
None	38	2	NR	NR
Mild	32	28	NR	NR
Moderate	25	59	NR	NR
Severe	5	11	NR	NR

Abbreviations: AE, adverse events; DBPCFC, double-blind, placebo-controlled, food challenge; EoE, eosinophilic esophagitis; IDE, initial dose escalation; NR, not reported; PAP, peanut allergen powder-dnfp; SAE, serious adverse event.

4%; $P < 0.001$). In addition, at the PAP 1000-mg dose when compared with placebo, there was a statistically significant difference ($P < 0.001$). The most common AEs involved the GI tract (Table 3), and most were graded as moderate throughout the study.^{3,15,16} There were more hypersensitivity reactions, serious AEs, and AE-related withdrawals in the PAP group. These AEs led to more epinephrine use in the PAP group (Table 4). During the exit DBPCFC, more participants in the placebo arm had moderate and severe symptoms compared with participants in the PAP arm.^{3,15,16} One PAP study participant was diagnosed with EoE.¹⁶

The Real-World AR101 Market-Supporting Experience Study (RAMSES) was a phase 3 safety study that assessed PAP during IDE and a UDP (Table 1).^{3,15} It was completed to test the safety of PAP in a larger number of participants. A total of 506 participants were randomized in a 2:1 ratio (PAP:placebo). The patients in this study had ages, ethnicity, and comorbidities similar to that of the patients from PALISADE Group et al.^{3,15,16} The study omitted the

screening and exit DBPCFC.^{3,15} The participant's clinical history, a more stringent criterion for the skin prick testing, and peanut-specific IgE values were required for entry into the study (Table 2). The primary end point compared the number of PAP treatment-emergent AEs between groups.^{3,15} The safety data from this trial were added to data from PALISADE Group et al.^{3,15,16} Most AEs occurred in the GI and RT during the IDE and UDPs (Table 3 and 4).^{3,15} More participants randomized to the PAP arm of the clinical trials than in the placebo arm discontinued participation in the studies because of AEs or withdrawal of consent.^{3,15}

Dosage Forms

PAP is available in 5 capsule strengths (0.5, 1, 10, 20, and 100 mg) and a 300-mg sachet (Figure 1).² Each of the capsules has a distinct color to prevent dosing errors. The capsules may be combined to configure the specific dose levels during UDP. When administered, the contents of

each capsule or sachet are to be emptied, mixed thoroughly, and completely ingested with semisolid food (applesauce, yogurt, pudding that is at a temperature no higher than room temperature).² The capsule and sachet are not to be swallowed whole, nor should the powder be inhaled.²

Dosing

Based on Bird et al¹⁴ and PALISADE Group et al, PAP is initiated using the IDE.^{14,16} It consists of 5 dose levels that are administered over 20- to 30-minute intervals under medical supervision (Figure 1).² No dose level should be skipped. Once the last dose is given, the patient is observed for at least 60 minutes. If the 3-mg dose is tolerated, the patient will return to the provider's office the next day and begin the UDP (Figure 1). There are 11 different dose levels in the UDP, and each dose level is given daily for 2 weeks. The first dose of each new level is administered under 60-minute medical observation. If the UDP dosing is tolerated, the patient will continue their maintenance therapy of 300 mg to be taken every day at the same time with a meal.²

Safety

Warnings, Precautions

Warnings for PAP in the package insert emanate from reactions and major AEs that occurred in the clinical studies.² The most common AEs of PAP are related to the GI and RT that occurred during the IDE and UDP.^{2,15} During these phases, there was a higher use of epinephrine. Consequently, the drug has warnings that it may cause anaphylaxis, GI reactions, and EoE and should be used cautiously in asthmatic patients. Based on these risks, PAP has the requirement of a risk evaluation and mitigation strategy (REMS) program with elements to ensure safe use.²⁸ The REMS requirement is largely based on the seriousness of potential AEs that may occur with administration of PAP and seriousness of being allergic to peanuts. Prescribers, health care centers, pharmacies, and patients are required to be certified and enrolled in the program to prescribe, receive, dispense, or administer this drug.^{2,28} Specialty pharmacies are currently the only pharmacies dispensing PAP.²⁸ These pharmacies are required to be certified with the manufacturer, Aimmune Therapeutics Inc, to dispense PAP. A representative from the pharmacy is required to complete the REMS pharmacy enrollment form to become certified. Pharmacists are positioned to provide critical education concerning PAP and oversight during the dispensing of PAP. Before the medication is dispensed, the pharmacist must ensure that (1) the prescriber is certified in the REMS program, (2) the patient is enrolled in the REMS program, and (3) only 1 dose level is dispensed at a time.²⁸ Pharmacists can ensure that patients are prescribed injectable epinephrine and receive instruction and training on appropriate use.^{2,28}

Relevance to Patient Care and Clinical Practice

As noted, peanuts cause unpredictable reactions and have the potential to cause a high burden of morbidity and LT ARs, and economic burden and affect QOL. The findings in these trials will advance the care of patients in the management of peanut allergies. The PAP study program included strict and consistent methods, including the use of the screening DBPCFC and the exit DBPCFC to strengthen the integrity of the results.^{3,14-16} Participants who were selected for the trials were some of the most sensitive to peanuts. Deschildre et al²⁹ showed that the median peanut amount that elicits a reaction is 125 mg. This dose is considerably higher than the dose participants needed to tolerate to be enrolled in PAP clinical trials.^{3,14-16} In addition, PALISADE Group et al showed that more than two-thirds of patients were able to tolerate at least 300 mg of PAP at the exit DBPCFC.¹⁶ Baumert et al³⁰ showed that increasing the threshold from less than 100 mg to 300 mg decreases the risk of accidental reaction by >95%. Patients with UCA, history of EoE, or other eosinophilic GI disease are contraindicated from taking PAP.² In addition, patients who have a history of anaphylaxis, patients with controlled asthma, and patients who are pregnant who have been exposed to PAP should be monitored carefully.² The manufacturer has a pregnancy exposure registry to monitor outcomes in women exposed to PAP during pregnancy.² PAP was shown to be efficacious in primarily Caucasian participants who were mostly male, with common comorbidities, including allergic rhinitis, asthma, atopic dermatitis, and other food allergies. Additional studies with increased sample sizes and in additional countries outside of the United States (including additional races and ethnicities) will improve generalizability. The drug's effectiveness is now being assessed in these real-world studies to understand its value in these populations.^{3,15}

Conclusion

Peanut allergy is a complex condition that affects more than 2% of children in the United States and may cause LT hypersensitivity reactions. It affects economic, psychosocial, and QOL aspects of patients with peanut allergies and their families. PAP provides the opportunity for these patients to have the ability to better manage this condition and improve their QOL. Although there are significant risks and AEs from PAP, it was efficacious in more than two-thirds of participants in phase 2 and phase 3 efficacy trials. Additional PAP studies including effectiveness studies will provide better understanding of peanut allergy and how best to manage this condition.

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