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The Effectiveness and Value of Oral Immunotherapy and Viaskin Peanut for Peanut Allergy

A Summary from the Institute for Clinical and Economic Review's California Technology Assessment Forum

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Peanut is a common childhood allergen in the United States. According to recent estimates, approximately 1.4%-4.5% of U.S. children suffer from peanut allergy.^{1,2} The economic cost of food allergies in the United States is estimated at \$24.8 billion per year, of which only \$4.3 billion are direct medical costs.³ Nonmedical costs accounted for \$20.5 billion and included out-of-pocket medical costs, the costs of special foods, and lost caregiver productivity.

The primary approach to managing food allergies is to avoid the food. Research has focused on desensitizing patients by exposing them to increasing amounts of the food,⁴ but no therapies were approved by the U.S. Food and Drug Administration (FDA) at the time of the review by the Institute for Clinical and Economic Review (ICER). The goal of desensitization is to decrease the likelihood that patients will react to an accidental exposure to peanut protein. However, desensitization does not imply tolerance—the ability to eat any amount of food containing peanuts without risk of a serious reaction.

This evidence review examines the effectiveness and value of 2 technologies to desensitize patients with peanut allergy that are expected to be approved by the FDA: AR101, a form of oral immunotherapy (OIT), and Viaskin Peanut, as well as noncommercialized OIT for peanut allergy.⁵

AR101 (Palforzia, Aimmune Therapeutics) is peanut flour produced using Good Manufacturing Practices.⁶ The peanut flour is mixed into pudding, applesauce, or other foods. The dose is gradually increased every 2 weeks to a goal dose of 300 mg daily. A health care professional must observe the patient during the initial dose and each subsequent increase in dose (minimum of 12 total visits). Therapy must be continued indefinitely to maintain desensitization.

Viaskin Peanut (DBV Technologies) is a patch applied daily to the upper back (rotating the location) that delivers 250 mcg of peanut antigen for desensitization treatment.⁷ The first patch is placed under the supervision of a medical professional, but subsequent patches can be applied at home. The patch is worn 6 hours a day for 1 week, then 12 hours a day for another week, and then 24 hours a day from then on. Therapy must be continued indefinitely to maintain desensitization.

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ICER conducted a review of AR101, Viaskin Peanut, and OIT. In this article, we summarize the systematic literature review and meta-analysis of the clinical effectiveness of the drugs, the cost-effectiveness analysis, and the policy discussion with key stakeholders regarding the overall value of these therapies held at a public meeting of the California Technology Assessment Forum (CTAF) on June 11, 2019. The detailed report is available on the ICER website at <https://icer-review.org/material/peanut-allergy-final-evidence-report-and-meeting-summary/>.

Summary of Findings

Clinical Effectiveness

We compared the clinical effectiveness of AR101 and Viaskin Peanut to standard of care, which is strict avoidance of peanuts. We also reviewed other forms of OIT, which are offered by some allergists but have not received FDA approval. The primary clinical benefit was desensitization, which was defined differently in each of the trials. The primary harms were system allergic reactions, use of epinephrine, and adverse events leading to discontinuation of therapy.

There were no head-to-head randomized or observational trials comparing the therapies. Table 1 summarizes the pivotal trials of the 2 therapies that were submitted to the FDA.^{6,7} Several important differences should be highlighted. The PALISADE trial of AR101 included older patients (aged 12-17 years) who are less likely to respond to desensitization therapy. The PALISADE trial also enrolled participants with a lower-eliciting dose (≤ 100 mg vs. 300 mg), suggesting that their allergy was more severe. The primary outcome in both phase 3 trials was a double-blind placebo-controlled food challenge to evaluate the effectiveness of immunotherapy. However, despite consensus guidelines to assess desensitization,⁸ the 2 trials used different protocols and doses to define desensitization. The PALISADE trial defined desensitization as tolerating 600 mg or higher of peanut protein. The PEPITES trial defined desensitization as tolerating 100 mg for patients enrolled with reactions at < 100 mg and 300 mg enrolled with reactions at 300 mg. Thus, the PALISADE trial of AR101 enrolled participants who were sensitive to lower doses of peanut protein and had a primary outcome that was more difficult to achieve.

The primary benefit documented in both trials was desensitization. In the PALISADE trial, a greater percentage of

participants randomized to AR101 met the definition of desensitization compared with those randomized to placebo (67.2% vs. 4.0%, $P < 0.001$).⁶ In the PEPITES trial, the primary outcome required that the lower bound of the 95% confidence interval (CI) for the difference between the 2 groups be greater than 15%. In the trial, the observed difference was 21.7% (95% CI=12.4%-29.8%).⁷ Since the lower bound (12.4%) was less than 15%, the trial did not meet its primary outcome.

For both AR101 and Viaskin Peanut, patients randomized to active therapy experienced more systemic allergic reactions and used epinephrine more often than patients in the placebo group, which are the outcomes that desensitization should prevent. Short-term increases in these key outcomes are expected, but desensitization should reduce these events over the long term. Reductions in systemic reactions and epinephrine use were not observed during these 1-year trials or in open-label extension studies. There is no evidence demonstrating a reduction in these events with longer therapy.

A systematic review and meta-analysis of 12 randomized trials of OIT reported that a higher proportion of patients achieved desensitization (odds ratio [OR]=12.4, 95% CI=6.8-22.6).⁹ However, there were significant increases in the risk for anaphylaxis (OR=3.1, 95% CI=1.8-5.6); epinephrine use (OR=2.2, 95% CI=1.3-3.8); and serious adverse events (OR=1.9, 95% CI=1.0-3.7). These findings were consistent during the buildup and maintenance phases through a maximum follow-up of 5.8 years, although median follow-up was only 1.0 years. Among the 3 studies that assessed quality of life, there were no significant differences between the OIT and placebo groups. The systematic review concluded that high certainty evidence demonstrates that OIT considerably increases allergic and anaphylactic reactions for at least the first year despite effective desensitization without evidence of long-term benefits.

Limitations of the Clinical Evidence for Long-Term Benefit

Given the potential need for lifelong treatment and the relatively short duration of the trials of AR101 and Viaskin Peanut (1 year), there remains considerable uncertainty about the long-term outcomes for AR101 and Viaskin Peanut. There is hope that the rates of systemic allergic reactions, epinephrine use, and reactions to accidental exposure will decrease with continued therapy, but this has not been demonstrated. The need for long-term therapy also raises concerns about adherence to treatment, particularly during adolescence and young adulthood, which could increase the incidence of severe reactions.

Long-Term Cost-Effectiveness

We estimated the lifetime cost-effectiveness of the 2 peanut allergy immunotherapies from a U.S. health care sector perspective using a Markov model. The cost-effectiveness model included 2 separate comparisons: (1) AR101 oral immunotherapy plus avoidance compared with avoidance alone, and

TABLE 1 Comparison of the Phase 3 PALISADE and PEPITES Trials

	AR101	Viaskin Peanut
Key study	PALISADE	PEPITES
Age	4-17 years	4-11 years
Peanut sensitivity	ED ≤ 100 mg	ED ≤ 300 mg
Median baseline ED	10 mg	30 mg
Primary outcome in DBPCFC	Tolerate 600 mg peanut protein at 1 year	ED 300 mg if baseline ED ≤ 10 mg; ED 1,000 mg if baseline ED ≥ 30 mg at 1 year
Dose escalation	3 mg to 300 mg daily with increases every 2 weeks for 24 weeks	250 mcg patch worn for 3 hours day 1, 6 hours week 1, 12 hours week 2, and 24 hours thereafter
Maintenance dose	300 mg orally every day	250 mcg by patch every day
Clinic visits	Every dose escalation	Day 1 only
Met primary outcome, active vs. placebo	67.2% vs. 4.0%, $P < 0.001$	Not met
Quality of life	NR	NR
Overall withdrawal rate, active vs. placebo	21.0% vs. 7.3%, $P = \text{NR}$	10.5% vs. 9.3%, $P = \text{NR}$
Systemic allergic reactions vs. placebo	14.2% vs. 3.4%, $P = \text{NR}$	3.8% related to Viaskin Peanut vs. 0%, $P = \text{NR}$
Use of epinephrine vs. placebo	14% vs. 6.5%, $P = \text{NR}$	9.2% vs. 3.4%, $P = \text{NR}$
Severe or serious AE vs. placebo	5.6% vs. 1.6%, $P = \text{NR}$	4.7% vs. 0.8%, $P = \text{NR}$

AE = adverse event; DBPCFC = double-blind, placebo-controlled food challenge; ED = eliciting dose; NR = not reported.

(2) Viaskin Peanut plus avoidance compared with avoidance alone. Survival, quality-adjusted survival, serious adverse events (anaphylaxis), and health care costs were summarized over a lifetime time horizon for each treatment option. Full details on ICER's cost-effectiveness analysis and model are available on ICER's website at <https://icer-review.org/material/peanut-allergy-final-evidence-report-and-meeting-summary/>.

The costs of immunotherapy with AR101 and Viaskin Peanut were unknown at the time of the public meeting. Based on analyst estimates, we assumed placeholder costs of \$4,200 per year for AR101 and \$6,500 per year for Viaskin Peanut.¹⁰

Trial-reported quality of life outcomes have not yet been published. Health state utilities were derived from the only study in the food allergy literature that included a preference-weighted measure. The estimates of utility were derived using parent-reported (for children) and adolescent-reported EuroQol-5-Dimension responses.¹¹ We assumed that participants in the peanut desensitized health state had an improvement in utility that was 60% of the difference between utilities for the untreated with peanut sensitivity and peanut-tolerant health states. This assumed that benefit is the source of all of the QALY gains in the model.

TABLE 2 Health Care Sector Cost-Effectiveness Results for Peanut Desensitization Therapies

	Annual Price, \$ ^a	Cost per QALY (95% CR), \$
AR101	4,200	88,000 (52,000-195,000)
Viaskin Peanut	6,500	216,000 (126,000-491,000)

^aPlaceholder prices based on analyst estimates for ICER public meeting. Aimmune stated that it expects the first 6 months of treatment with AR101 (Palforzia) to cost \$5,000-\$10,000 and \$300-\$400 a month after that. CR = credible range; ICER = Institute for Clinical and Economic Review; QALY = quality-adjusted life-year.

The economic model estimated that the incremental cost-effectiveness ratios for the 2 therapies ranged from \$88,000 (95% credible range [CR] = \$52,000-\$195,000) per quality-adjusted life-year (QALY) for AR101 to \$216,000 (95% CR = \$126,000-\$491,000) per QALY for Viaskin Peanut (Table 2). In one-way sensitivity analyses, the results were most sensitive to the utilities associated with peanut sensitivity and peanut desensitization, the cost of immunotherapy, and results of the exit food challenge.

Limitations of the Cost-Effectiveness Model

Long-term clinical evidence on immunotherapy was not available, and the short-term data suggested greater harm than benefit. The effect of peanut allergy on preference-weighted health-related quality of life is also not well characterized. The economic model used preference-weighted utility estimates from a convenience sample of Swedish children with food allergies compared with children without food allergies, so the effect of immunotherapy on QALYs may be inaccurate. Improvement in health-related quality of life (utility) for the desensitized health state were crucial for estimating the overall benefit of the immunotherapies, but there are no data supporting improvements in utilities using the 2 novel therapies or OIT.

Policy Discussion

The ICER report on immunotherapy for peanut allergy was the subject of a CTAF meeting on June 11, 2019. Following discussion, the CTAF panel members voted that the evidence was not adequate to demonstrate the superiority of AR101 to standard of care (4-12) and that there was not adequate evidence to demonstrate the superiority of Viaskin Peanut to standard of care (4-12). Furthermore, they voted that the evidence was not adequate to distinguish between AR101 and Viaskin Peanut (0-16). Because there was not adequate evidence to demonstrate clinical benefit, no votes were taken on value.

The CTAF panel voted on “other potential benefits” and “contextual considerations” as part of a process to signal to policymakers whether there are important considerations

TABLE 3 Other Benefits or Disadvantages

Does desensitization therapy for children with peanut allergy offer one or more of the following potential other benefits or disadvantages compared with strict avoidance of peanut protein?

Potential Other Benefits	Viaskin Votes	AR101 Votes
This intervention will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.	9/16	7/16
This intervention will significantly reduce caregiver or broader family burden.	10/16	11/16
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	11/16	5/16
This intervention will have a significant effect on improving return to work and/or overall productivity.	9/16	8/16
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	12/16	10/16

when making judgments about long-term value for money not adequately captured in analyses of clinical and/or cost-effectiveness. The results of these votes are shown in Tables 3 and 4. The most important other benefit was the potential to significantly reduce family and caregiver burden. The most important contextual consideration was the considerable uncertainty about the long-term benefits and harms.

The policy roundtable discussion explored how best to translate the evidence and broader perspectives discussed into clinical practice and into pricing and insurance coverage policies. The full set of policy recommendations can be found in the Final Evidence Report on the ICER website: <https://icer-review.org/material/peanut-allergy-final-evidence-report-and-meeting-summary/>. Several key policy recommendations are described below:

- Manufacturers should pursue further evidence development to provide greater certainty about the long-term safety and effectiveness of desensitization therapies. Evidence should not rely on short-term surrogate outcome measures such as desensitization.
- Prescribing peanut desensitization therapies should be restricted to specialists (allergy and immunology specialists), or for those patients with inadequate access to allergists, by primary care physicians only in consultation with a specialist.
- Payers may consider limiting coverage for initiation of desensitization treatment to patients between the ages of 4-17 years who represent the population studied to date.
- Payers should not stop coverage at age 18 for patients who have been on continuous desensitization therapy.

TABLE 4 Contextual Considerations

Are any of the following contextual considerations important in assessing the long-term value for money of desensitization therapy compared with strict avoidance of peanut protein?

Potential Other Contextual Considerations	Viaskin Votes	AR101 Votes
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of effect on length of life and/or quality of life.	9/15	8/15
Compared with strict avoidance, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	13/15	13/15
Compared with strict avoidance, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	13/15	13/15
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	4/15	4/15

Conclusions

Both therapies led to higher rates of desensitization to peanut protein in a double-blind food challenge after 1 year of therapy. However, there were higher rates of serious adverse events, systemic allergic reactions, and greater use of epinephrine in the active treatment arm for both therapies compared with placebo treatment. These outcomes should have decreased with effective therapy but did not during 1 year of treatment. In addition, no improvements in quality of life or reductions in anxiety were reported.

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