Oral Immunotherapy and Viaskin® Peanut for Peanut Allergy: Effectiveness and Value

Draft Evidence Report

April 9, 2019

Prepared for

ICER Staff and Consultants	University of Washington School of Pharmacy Modeling Group
Jeffrey A. Tice, MD Associate Professor of Medicine University of California, San Francisco **Serina Herron-Smith, BA** Research Assistant Institute for Clinical and Economic Review **Emily Tsiao, PharmD** (Former) Visiting Resident Institute for Clinical and Economic Review **Rick Chapman, PhD, MS** Director of Health Economics Institute for Clinical and Economic Review **Remziye Zaim, MSc, MS** Research Fellow Institute for Clinical and Economic Review **Celia Segel, MPP** Director of Comparative Effectiveness Research Policy Development Institute for Clinical and Economic Review **David Rind, MD, MSc** Chief Medical Officer Institute for Clinical and Economic Review **Steven D. Pearson, MD, MSc** President Institute for Clinical and Economic Review	**Greg Guzauskas, MSPH, PhD** Research Scientist University of Washington School of Pharmacy **Ryan N. Hansen, PhD, PharmD** Assistant Professor, Department of Pharmacy Adjunct Research Assistant Professor, Department of Health Services University of Washington School of Pharmacy *The role of the University of Washington School of Pharmacy modeling group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of the University of Washington.

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Jeffrey A. Tice served as the lead author for the report, led the systematic review and authorship of the comparative clinical effectiveness section, and wrote the background, other benefits, and contextual considerations sections of the report. Greg Guzauskas and Ryan Hansen developed the cost-effectiveness model and authored the corresponding sections of the report. Rick Chapman and Remziye Zaim were responsible for oversight of the cost-effectiveness analyses and developed the budget impact model. Emily Tsiao authored the section on coverage policies and clinical guidelines. David Rind and Steve Pearson provided methodologic guidance on the clinical and economic evaluations. Celia Segel managed the timeline and public process, and performed quality controls. We would also like to thank Laura Cianciolo for her contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer-review.org/.

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The California Technology Assessment Forum (CTAF) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. CTAF seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

Expert Review

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/peanut-allergy-stakeholder-list/.

Expert Reviewers

Ruchi S. Gupta, MD, MPH
Professor of Pediatrics & Medicine
Ann & Lurie Children's Hospital of Chicago
Northwestern Feinberg School of Medicine

Disclosure: *Dr. Ruchi Gupta has received grants from Aimmune Therapeutics and has served as a medical consultant for DBV Technologies and Aimmune Therapeutics.*

Nurry Hong
Chief of Strategy and Innovation
Food Allergy Research & Education (FARE)

Disclosure: *Nurry Hong is a cofounder of a start-up biotech company that is in its research stages of development. The company is in the pre-financing stage of formation and Nurry Hong does not receive any salary or compensation from the company at this time.*

FARE is a 501(c)(3) public charity and receives financial support from multiple sources, including individuals, other charitable entities, and for-profit companies. Currently or in the past, FARE has received general support grants or corporate sponsorship from each of DBV Technologies and Aimmune Therapeutics. These general support grants/sponsorships are charitable in nature and do not require FARE to perform any service for or on behalf of either DBV or Aimmune. At one time FARE was a shareholder of Aimmune, but those shares were sold in their entirety in 2016.

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List of Acronyms Used in this Report

AAAAI	American Academy of Allergy, Asthma & Immunology
AHRQ	Agency for Healthcare Research and Quality
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
BSACI	British Society for Allergy and Clinical Immunology
BSCA	Blue Shield of California
CADTH	Canadian Agency for Drugs and Technologies in Health
CC	Complications and comorbidities
CDC	Center for Disease Control
CI	Confidence Interval
CMS	Centers for Medicare and Medicaid Services
DBPCFC	Double blind placebo-controlled food challenge
DHCF	California Department of Health Care Services
DRG	Diagnosis Related Group
EAACI	European Academy of Allergy and Clinical Immunology
EFC	Exit Food challenge
EoE	Eosinophilic esophagitis
ER	Emergency Room
FDA	Food and Drug Administration
GDP	Gross domestic product
GMFM	Gross Motor Function Measure
IgE	Immunoglobin G
LCD	Local Coverage Determination
LEAP	Learning Early about Peanut Allergy
LY	Life year
MCC	Major complications and comorbidities
NCD	National Coverage Determination
NIAID	National Institute of Allergy and Infectious Diseases
NICE	National Institute for Health and Care Excellence
NR	Not reported
OFC	Oral food challenge
OIT	Oral Immunotherapy
PSA	Probabilistic sensitivity analysis
PICOTS	Population, Interventions, Comparisons, Outcomes, Timing, Setting, and Study Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
SAE	Serious adverse event
UHC	United Healthcare
USPSTF	United States Preventive Services Task Force
WAC	Wholesale acquisition cost
WHO	World Health Organization
WTP	Willingness-to-pay

1. Introduction

1.1 Background

Background

Peanut is a common childhood allergen in the United States (US). According to recent estimates approximately 1.4-4.5% of children suffer from peanut allergy.[1-3] In addition, peanut allergy is the leading cause of death from anaphylaxis due to food, particularly in teenagers, though the rate is low.[4] The national food allergy death registry reports less than four deaths per year over the past 10 years in the US.[5] Other sources report that the risk of death from peanut allergy is lower than the risk for accidental death in the general population.[6]

Food allergy reactions can range from mild cutaneous symptoms, to gastrointestinal (GI) symptoms such as abdominal pain, nausea, vomiting, and diarrhea, on to anaphylaxis.[7,8] The allergy usually begins early in life and only a minority of patients outgrow their food allergy.[7] Furthermore, up to 55% of patients with peanut allergy suffer from additional food allergies.[3,9] The economic cost of food allergies in the US is estimated at $24.8 billion per year, of which only $4.3 billion was direct medical costs.[10] Non-medical costs accounted for $20.5 billion and included out-of-pocket medical costs, the costs of special foods, and lost caregiver productivity. There are important economic disparities in the distribution of these costs: patients from lower income households have 2.5 times higher costs for emergency department visits and hospitalizations, but lower costs for visits to specialists and out of pocket costs.[11]

The primary approach to managing food allergies is to avoid the trigger. Notably, avoidance of the trigger is not a treatment for children with food allergies, but rather a strategy to avert a reaction to accidental exposure, which in certain cases potentially can cause life-threatening patient reactions. However, up to 40% of those with peanut allergy may experience an accidental exposure with an annual incidence of 10% to 20%.[2,3,7,12] However, that rate appears to have declined significantly according to recent studies (accidental exposures 4.7% per year, epinephrine use 1.1% per year).[13] Antihistamines are used to manage mild to moderate symptoms and epinephrine is used first line for anaphylaxis, often administered by the patient or family using an autoinjector (e.g., EpiPen®, Auvi-Q®). Research has focused on desensitizing patients by exposing them to increasing amounts of the food, but no therapies are FDA approved. Desensitization means that patients are less likely to react to an accidental exposure to peanut protein with ongoing treatment, but does not imply tolerance – the ability to eat any amount of food containing peanuts without risk of a serious reaction.

This evidence review will examine the effectiveness and value of two technologies to desensitize patients with peanut allergy that are expected to be approved by the FDA – AR101 and Viaskin® Peanut – as well as non-commercialized oral immunotherapy (OIT) for peanut allergy.[14]

AR101 (Aimmune Therapeutics) is defatted, slightly roasted peanut flour produced using Good Manufacturing Practices, which comes in a capsule or sachet form and has a characterized allergen profile. The product is not ingested in capsule form; the peanut flour-containing capsule is pulled apart and the peanut flour mixed into pudding, applesauce, or other foods. The first day of therapy consists of five escalating oral doses separated by 30 minutes. Subsequently, the dose is gradually increased every two weeks to a goal dose of 300 mg daily. The initial dose escalation and each subsequent increase in dose must be observed by a health care professional (minimum of 12 total visits). The dose escalation phase may be extended due to symptoms requiring more than twelve weeks to resolve, illness that requires dose reduction, or missed doses. Given the current state of knowledge, therapy must be continued daily to maintain desensitization. AR101 is being studied primarily in pediatric patients ages four to 17 years.

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. The first patch is placed under the supervision of a medical professional, but subsequent patches can be applied at home. The patch is worn six hours a day for one week, then 12 hours a day for another week, and then 24 hours a day from then on. The dose escalation phase may be extended if patients have significant skin reactions. Given the current state of knowledge, therapy must be continued daily to maintain desensitization. Viaskin Peanut is being studied primarily in pediatric patients ages four to 11 years.

An FDA approval decision for AR101 is expected in January 2020. The timeline for Viaskin Peanut is currently unknown, but is expected to be sometime in 2020.

1.2 Scope of the Assessment

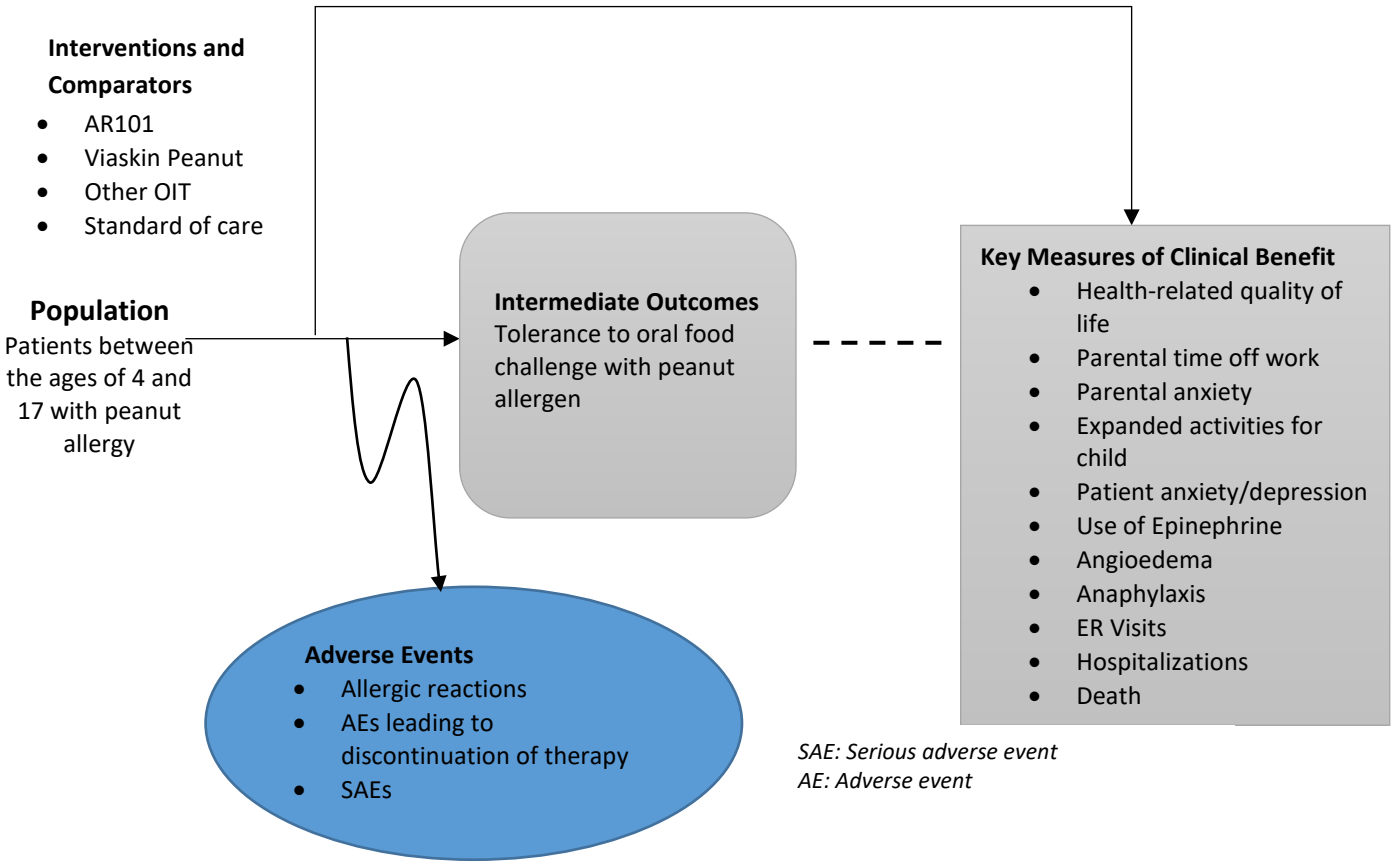
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence has been abstracted from randomized controlled trials. Our evidence review includes input from patients and patient advocacy organizations, information submitted by manufacturers, and other grey literature that meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

All relevant evidence was synthesized qualitatively because of important differences in the populations studied and in the primary outcomes of the trials. There were no head-to-head studies of the interventions of interest. Full details regarding the literature search, screening strategy, and data extraction, and evidence synthesis are provided in Appendix D.

Analytic Framework

The general analytic framework for assessment of therapies for peanut allergies is depicted in Figure 1.1.

Figure 1.1. Analytic Framework: Therapies for Peanut Allergy



The diagram begins with the population of interest on the left.[15] Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., tolerance on an oral food challenge), and those within the squared-off boxes are key measures of benefit (e.g., quality of life, reduction in anxiety, prevention of anaphylaxis). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.[15]

When available, outcomes are reported separately by type of exposure: iatrogenic versus accidental.

Populations

The population of focus for the review is children between the ages of four and 17 with peanut allergy.

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

- AR101
- Viaskin Peanut
- OIT with other peanut products

Comparators

Each of the interventions is compared to standard of care, which consists of strict avoidance of peanuts and rapid access to epinephrine, and to each other.

Outcomes

The outcomes of interest are described in Table 1.1. As noted above, when possible, we report the outcomes separately for iatrogenic and accidental exposure.

Table 1.1. Outcomes and Harms

Outcomes	Key Harms
Death	Systemic allergic reactions
ER/hospitalization for peanut allergy reactions	Skin reactions
Quality of life	Gastrointestinal reactions
Parental time off from work	Serious adverse events
Expanded activities for child	Adverse events leading to treatment discontinuation
Anaphylaxis	
Angioedema	
Bronchospasm/wheezing	
Urticaria	
Use of epinephrine	
Parental anxiety	
Patient anxiety/depression	
Tolerance to challenge with peanut allergen	

Timing

Evidence on intervention effectiveness was derived from studies of at least one year's duration and evidence on harms from studies of at least three month's duration.

Settings

All relevant settings were considered, with a focus on outpatient settings in the US.

1.3 Definitions

Oral food challenge (OFC): Exposing a patient with suspected food allergy to the food in a doctor's office in gradually increasing doses. The Practical Allergy (PRACTALL) consensus report recommends starting at 3 mg of food protein and then increasing the dose every 20 minutes using the following amounts: 10, 30, 100, 300, 1000, and 3000 mg.[16] The food challenge is stopped if there are objective symptoms of an allergic reaction or subjective symptoms on three consecutive doses.

Double blind placebo-controlled food challenge (DBPCFC): This is the gold standard recommended in the PRACTALL consensus report for both the diagnosis of food allergy and as an outcome in therapeutic trials.[16] The protocol for an OFC is performed as described above, but the patient is randomized to receive either the suspected food allergen or an identical placebo that does not contain the suspected allergen. Neither the patient nor the person administering the test knows the contents of the food being used in the OFC. The OFC is repeated on a subsequent day with the other food.

Eliciting Dose: This is the dose (grams of peanut protein) at which an oral food challenge is stopped due to either objective symptoms or significant subjective symptoms.

Tolerated Dose: This is the dose (grams of protein) just prior to the eliciting dose in an oral food challenge.

Cumulative Reactive Dose: This is the sum of all the doses in an oral food challenge including the eliciting dose.

Tolerance: an individual who no longer has symptoms when eating the food or during an OFC months to years after any treatment has stopped has tolerance to that food.

Desensitization: This is the goal of the immunotherapies evaluated in this report. Patients who are desensitized do not have an allergic reaction to low doses of the food, but have not developed tolerance. They require ongoing therapy to maintain desensitization. There is no standard eliciting or tolerated dose that defines desensitization.

Eosinophilic esophagitis (EoE) refers to localized eosinophilic inflammation of the esophagus. In some patients, avoidance of specific foods will result in normalization of histopathology. EoE can present with feeding disorders, vomiting, reflux symptoms, and abdominal pain in children; and dysphagia and esophageal food impactions in adolescents and adults. EoE is a known complication of OIT.

1.4 Insights Gained from Discussions with Patients and Patient Groups

Several themes emerged from speaking with patients and patient representatives. First was the burden of day-to-day living with peanut allergy. Patients and their caregivers experience tremendous anxiety, stress, and report poor quality of life. Caregivers frequently miss time from work or even leave the workplace to help manage the safety of the places that their loved ones visit. Patients with peanut allergy may feel they are restricted in where they live: some will not travel beyond a short distance from their specialist or tertiary care center. Some children do not go on field trips or to birthday parties or restaurants out of fear of exposure; patients and families may choose not to travel via airplane or travel abroad. Patients and their caregivers often lead a lifestyle that may be heavily impacted by fear and anxiety. An important goal for patients is to be able to live and eat more freely.

While death from a food allergy is rare, adolescents may be at the highest risk for death due to both their risk-taking nature and the movement away from environments that can be carefully managed by their parents and other caregivers. While food labeling has improved since 2006, it is still challenging to know if food items contain traces of allergens because so many products are labeled as either “may contain” peanuts or have been manufactured using equipment potentially exposed to peanuts, placing patients at risk from cross-contamination. All food labels must be read carefully and patients avoid many foods altogether, which may lead to restricted diet, extra expenses for food, and/or nutritional risks to the patient if avoidances are not carefully managed.

As noted above, many patients with peanut allergies suffer from other food allergies. Some of these patients expressed that decreasing just peanut sensitivity may have less impact on their quality of life.

Many within the patient community are excited to have FDA approved products with standardized treatment protocols because they perceive that they will be safer. Unregulated OIT that is practiced now may not always be reimbursed by insurance since it can be viewed as experimental

and the majority of Allergists do not offer it. As a result, patients who pursue OIT often pay out of pocket, which can limit access to those who can afford it. Patients with a peanut allergy are particularly sensitized to the cost of therapy because of the recent increases in the price of EpiPen autoinjectors. Out of pocket expenses are a major issue for patients, both with regard to medications and food, and can have potential impact on managing disease and adherence to new treatments.

1.5. Potential Cost-Saving Measures in Peanut Allergy

As described in its Final Value Assessment Framework for 2017-2019, ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by AR101 and Viaskin Peanut (e.g., emergency department management of an allergic reaction), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of peanut allergy beyond the potential offsets that arise from a new intervention.

Examples include relevant Choosing Wisely recommendations, such as the following from the AAAAI:

- *Don't perform unproven diagnostic tests, such as immunoglobulin G (IgG) testing or an indiscriminate battery of immunoglobulin E (IgE) tests, in the evaluation of allergy.*
- *Don't perform food IgE testing without a history consistent with potential IgE-mediated food allergy.*

ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient in order to offset the costs of desensitization therapy. We have not received any additional suggestions for the preliminary report.

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

To understand the insurance landscape for therapies for peanut allergy treatment and prevention, we reviewed publicly-available coverage policies for immunotherapy and epinephrine from the Centers for Medicare and Medicaid Services (CMS), California Department of Health Care Services (DHCS), and from regional and national commercial insurers (Aetna, Anthem, Blue Shield of California [BSCA], Cigna, Health Net, Humana, Kaiser Permanente, and United HealthCare [UHC]). At the time the draft Evidence report was published, we were unable to survey policies pertaining to AR101 and Viaskin Peanut because the FDA had not issued a decision regarding their applications for approval.

We were unable to locate any coverage criteria for oral immunotherapy from DHCS as well as Cigna, HealthNet, Kaiser Permanente, and UHC. CMS as well as Aetna, BSCA, and Humana do not cover oral immunotherapy.[17-20] Several patients and advocates suggested that oral immunotherapy is currently more likely to be paid for out-of-pocket by the patient or their family at specialized clinics that provide the treatment.

Each of the commercial payers included in our search covered and did not have utilization management policies for the use of generic epinephrine. While epinephrine is covered in all plans surveyed, patients are still subject to out-of-pocket costs, based on their benefit design. A 2017 study evaluating nearly 200 million commercially insured claims from 2007-2014, found that the percentage of patients paying more than $100 and $250, jumped from 3.9% to 18%, and 0.1% to 7.4% respectively over that time period.[21] Patients and advocates reflected sensitivity to growing out-of-pocket spending in interviews.

2.2 Clinical Guidelines

We reviewed guidelines on peanut allergy issued by major clinical societies. Although many of the organizations also provided recommendations on when and how peanut allergy testing should occur, we have only summarized the guidance that pertain to the prevention and treatment of peanut allergies. At the time this report was published, we were unable to locate any guideline statements that pertained to the use of AR101 or Viaskin Peanut.

American Academy of Allergy, Asthma and Immunology (AAAAI), 2011[22]

AAAAI summarized the available evidence for the practice of allergen immunotherapy for patients with allergic diseases. The Joint Task Force concluded that clinical trials do not support the use of subcutaneous immunotherapy for food hypersensitivity and that the safety and efficacy of oral and sublingual immunotherapy for food hypersensitivity is currently investigational. They recommend that allergen immunotherapy be administered with trained staff and on-hand medical equipment for treating and recognizing anaphylaxis.

National Academies of Sciences, Engineering, and Medicine (NASEM), 2017[23]

The National Academies of Sciences, Engineering, and Medicine in 2017 created a consensus study to clarify the nature of peanut allergy, its causes, and its current management. For individuals diagnosed with peanut allergy, they recommend strict-peanut avoidance to prevent a reaction. In cases of anaphylaxis, they recommend treatment with epinephrine, and additional therapies, such as bronchodilator medications, antihistamines, corticosteroids, vasopressors, glucagon, atropine, supplemental oxygen, intravenous fluids, and patient positioning. Furthermore, in cases of anaphylaxis, they recommend observation in the medical setting until complete resolution of symptoms, education on avoidance and management, and referral for additional testing and management.

National Institute of Allergy and Infectious Diseases (NIAID)/American Academy of Allergy, Asthma and Immunology (AAAAI), 2010, 2017[24,25]

The National Institute for Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), with support from more than thirty professional organizations in 2010, convened an expert panel to summarize the available evidence for the diagnosis and management of food allergies.

The expert panel did not recommend using allergen immunotherapy to treat food allergies. To treat anaphylaxis, they recommended epinephrine, and allowed for repeated use every five to 15 minutes. After epinephrine-use, they recommended immediate transfer to an emergency facility for observation for four to six hours or longer and possible further treatment. Bronchodilators (albuterol), antihistamines (diphenhydramine), supplemental oxygen therapy, and intravenous fluids can also be considered.

In 2017, the NIAID with support from the American Academy of Allergy, Asthma & Immunology (AAAAI) and twenty-four other organizations, issued an addendum to these guidelines that was informed by the Learning Early about Peanut Allergy (LEAP) trial. For infants at risk for peanut allergy, they recommended early introduction of peanut-containing food at four to six months of age (assessed as moderate quality evidence using GRADE).

British Society for Allergy and Clinical Immunology (BSACI), 2017[26]

The British Society for Allergy and Clinical Immunology (BSACI) in 2017 summarized the available evidence for the diagnosis and management of peanut and tree nut allergies. In their guidelines, they find that peanut oral immunotherapy can induce desensitization in peanut-allergic children. The BSACI considered the strength of this recommendation to be an "A" meaning that the evidence included a well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.

European Academy of Allergy and Clinical Immunology (EAACI), 2014[27]

In 2014 the European Academy of Allergy and Clinical Immunology developed a comprehensive set of documents on food allergy and severe allergic reactions. Food allergen immunotherapy is not currently recommended. Adrenaline, also known as epinephrine, must be promptly administered intramuscularly into the mid-outer thigh for emergency management of anaphylaxis. Repeat doses should be administered at least five minutes apart. If the patient does not respond to two or more doses of intramuscular adrenaline, adrenaline may be administered as an infusion with appropriate cardiac monitoring.

American Academy of Allergy, Asthma and Immunology (AAAAI), 2012[16]

In 2012, the AAAAI compiled the available evidence for the practice of oral food challenges in the PRACTALL consensus report. During immunotherapy, they recommend having immediate access to epinephrine, oxygen, antihistamines, beta-agonists, corticosteroids, and intravenous fluids.

In their report, they recommend processes for assessing and treating mild, moderate, and severe reactions during oral food challenges. Mild skin reactions can result in scratching continuously for two minutes or more and faint erythema, but do not necessarily require altering dosing, or resolution of trial. Moderate reactions require caution, with a judgment as to whether to proceed, delay, repeat, escalate, or stop dosing altogether. If symptoms persist or recur after three doses, they are considered moderate reactions. Moderate reactions include at least three of the following: hard continuous scratching; hives; sneezing; throat clearing, cough, or persistent throat tightness; nausea or abdominal pain that may include an itchy mouth or throat; frequent nausea or gastrointestinal pain; notable GI distress; emesis or diarrhea; and feeling weak or dizzy.

Severe reactions have objective symptoms likely to indicate a true reaction and usually an indication to stop dosing. Severe reactions include: more than three hives or significant lip or face edema; generalized urticaria or angioedema; generalized erythema; continuous rubbing of the nose or eyes; long bursts of sneezing; audible wheezing; hoarseness that may include a frequent dry cough; multiple episodes of emesis or diarrhea; drop in blood pressure; a significant change in mental status; cardiovascular collapse and/or unconsciousness.

3. Comparative Clinical Effectiveness

3.1 Overview

We abstracted evidence from RCTs of individuals ages four to 17 years with peanut allergy comparing desensitization therapy to strict peanut avoidance. Age is an important effect modifier for the efficacy of desensitization therapy. Early trial results led to a focus on children ages four to 11 years in the Phase 3 trial of Viaskin Peanut and ages four to 17 in the Phase 3 trial of AR101. Our review focused on clinical benefits (reduction in allergic reactions, epinephrine use, ER visits, hospitalizations, and quality of life) as well as potential harms (systemic allergic reactions due to the therapies, serious adverse events, and adverse events leading to discontinuation of therapy).

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on therapies for peanut allergy followed established best research methods.[28,29] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[30] The PRISMA guidelines include a checklist of 27 items, which are described further in Appendix Table A1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms that are presented in Appendix Tables A2 and A3.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/). Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-

confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer-review.org/use-of-in-confidence-data/).

Study Selection

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection was accomplished through two levels of screening, at the abstract and full-text level. Two reviewers independently screened the titles and abstracts of all publications using DistillerSR (Evidence Partners, Ottawa, Canada) and resolved any issues of disagreement through consensus. No study was excluded at abstract level screening due to insufficient information. For example, an abstract that did not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening were retrieved in full text for review. Reasons for exclusion were categorized according to the PICOTS elements during full-text review.

Data Extraction and Quality Assessment

Data were extracted into evidence tables (Appendix Tables D1-D6).

Data extraction was performed in the following steps:

1. Two reviewers extracted information from the full articles.
2. Extracted data was reviewed for logic, and data were validated by a third investigator for additional quality assurance.

We used criteria employed by the US Preventive Services Task Force ([USPSTF] see Appendix D) to assess the quality of clinical trials, using the categories "good," "fair," or "poor."[31]

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[32]

Assessment of Publication Bias

Given the emerging nature of the evidence base for these newer treatments, we scanned the ClinicalTrials.gov *web*site to identify studies completed more than two years ago. None were identified.

Data Synthesis and Statistical Analyses

The studies are summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. Evidence tables are presented in Appendix Tables D1-D6. Relevant data include those listed in the data extraction section. Important differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality are noted in the text of the report.

Given the heterogeneity of the patients included in the trials and the lack of a consistent primary outcome, we did not perform any meta-analyses or network meta-analyses.

3.3 Results

The results are organized within benefits by therapy, then harms by therapy.

Study Selection

Appendix Figure A1 summarizes the search results and study selection using a PRISMA flow diagram. In brief, we identified 635 potential references of which 363 met criteria for full text review. We excluded 357 of these references due to patient populations outside of our scope, interventions outside our scope and lack of relevant outcomes. This left two trials of AR101[33,34], three trials of Viaskin Peanut[35-37], two RCTs of other forms of OIT[38,39], and two observational studies of OIT.[40,41]

Key Studies

There are two key studies – the Phase 3 randomized trials for each of the therapies that have submitted documentation to the FDA for approval. They are summarized in detail below.

Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization (PALISADE) Trial[34]

The PALISADE trial randomized 551 participants four to 55 years of age with peanut allergy in a 3:1 ratio to AR101 or placebo (oat flour).[34] Patients were required to have an eliciting dose of 100 g or less on DBPCFC at study entry. Important exclusion criteria included severe or uncontrolled asthma, severe or life-threatening anaphylaxis in the past 60 days, and eosinophilic esophagitis. The primary outcome was the proportion of participants four to 17 years of age who could ingest 600 g or more of peanut protein without dose-limiting symptoms in a DBPCFC after approximately one-year follow-up. Note that the 600 mg dose is an exception from the PRACTALL OFC dose escalation protocol, which increases as follows: 3, 10, 30, 100, 300, 1000, and 3000 mg. Because the primary outcome focuses on patients four to 17 years of age and the expected FDA decision will

be for patients four to 17, the remainder of the results described here will be for that age group (n=496). For patients 18 to 55 years of age, please see Appendix Tables D1 to D11.

On day one, participants underwent a dose escalation phase from 0.5 mg to 6 mg followed by an increasing-dose phase during which the dose was increased every two weeks from 3 mg to 300 mg a day over approximately 24 weeks. Each dose escalation was done under medical supervision and the participant was observed for a minimum of 90 minutes. This was followed by a 24-week dose maintenance phase of 300 mg of peanut protein per day. The study encouraged participants to take their dose with a meal at roughly the same time each day (within a four-hour period), to refrain from activities that can increase allergic reactivity (exercise, hot showers, or baths) within three hours of taking the dose, and not to go to sleep within two hours of taking the dose.

In the group of participants ages four to 17 years old, 66% were ages four to 11 years, and 34% were 12 to 17 years. There were more males (57%) and the majority had a history of peanut anaphylaxis (72%), asthma (53%), and multiple food allergies (66%). The median maximum tolerated dose at study entry was 10 mg of peanut protein.

In the active treatment group, 67.2% (250/372) of participants were able to tolerate 600 mg of peanut protein compared with 4.0% (5/124) in the placebo group (between group difference 63.2%, 95% CI 53.0% to 73.3%, p<0.001). The between group difference was slightly greater among participants ages four to 11 years (66.1%) compared with those ages 12 to 17 years (58.3%). No data on participant quality of life were reported.

Adverse events were graded using the National Cancer Institute Common Toxicity Criteria. Adverse events were common in both the active treatment and placebo groups (98.7% and 95.2%, respectively). Serious adverse events were more common in the active treatment group (2.2% vs. 0.8%). Systemic allergic reactions were more common in the active treatment group (14.2% vs. 3.2%) as was the use of epinephrine outside of the DBPCFC (14.0% vs. 6.5%). In the AR101 group 67% of epinephrine doses were administered at home. Withdrawal due to adverse events was more common in the active treatment group (11.6% vs. 2.4%) as was the overall withdrawal rate from the study (21.0% vs. 7.3%). The most common adverse events were GI, such as abdominal pain (52% AR101 vs. 24%) and vomiting (51% AR101 vs. 24%). Adverse event rates during the maintenance phase, which may reflect rates during long term follow-up remained high. For example, abdominal pain (15% AR101 vs. 6%), and vomiting (16% AR101 vs. 12%) remained common and higher in the AR101 group. This was also true for systemic allergic reactions (8.7% AR101 vs. 1.7%) during the maintenance phase.

In summary, the PALISADE trial demonstrated that AR101 markedly increased the percentage of patients who could tolerate a 600 mg dose of peanut protein (cumulative dose 1043 mg) in a DBPCFC (67.2% vs. 4.0%, p<0.001). However, there were significantly higher rates of GI side effects,

systemic allergic reactions and epinephrine use in the AR101 group even during the maintenance phase. In addition, the treatment requires a substantial investment in time for patients (at least 12 office visits over the initial 24 weeks with in office observation for at least 90 minutes) and continued consumption of AR101 to maintain desensitization.

Peanut EPIT Efficacy and Safety (PEPITES) Trial[35]

The PEPITES trial randomized 356 participants four to 11 years of age with peanut allergy in a 2:1 ratio to Viaskin Peanut 250 mcg patch or placebo patch.[35] Patients were required to have an eliciting dose of 300 g or less on DBPCFC at study entry. Important exclusion criteria included uncontrolled asthma and a history of severe anaphylaxis. The primary outcome was the proportion of participants with an eliciting dose at least 300 mg of peanut protein (tolerated dose of 100 g) in a DBPCFC after approximately one-year follow-up for those participants with a baseline eliciting dose of 10 mg or less or an eliciting dose at least 1000 mg (tolerated dose 300 mg) for those participants with a baseline eliciting dose of 30 mg or more.

On day one, the patch was applied for three hours under medical supervision. The length of time that the patch was applied was increased to six hours during week one, 12 hours during week two, and 24 hours thereafter. The dose escalation did not require additional visits to the physician's office, but the time to get to 24 hours of patch application could be extended additional weeks if needed.

The participants had a median age of seven years, 61% were male, and many had a history of asthma (47%), and multiple food allergies (85%). The median maximum tolerated dose at study entry was 30 mg of peanut protein (eliciting dose of 100 mg).

In the active treatment group, 35.3% (84/238) of participants met the primary outcome compared with 13.6% (18/118) in the placebo group (between group difference 21.7%, 95% CI 12.4% to 29.8%, $p<0.001$). No data on participant quality of life were reported.

Adverse events were graded using the International Conference on Harmonization-Good Clinical Practice definition. Adverse events considered related to the patch were common in both the active treatment and placebo groups (59.7% and 34.7% respectively). Overall adverse events were not reported for individual AEs, making comparisons with the PALISADES trial challenging. Serious adverse events related to the patch were more common in the active treatment group (1.3% vs. 0%). Systemic allergic reactions related to the patch were more common in the active treatment group (3.8% vs. 1.7%), but there were no serious systemic reactions. Epinephrine use was also more common in the Viaskin Peanut group (9.2% vs. 3.4%). Withdrawal due to adverse events was more common in the active treatment group (1.7% vs. 0%) as was the overall withdrawal rate from the study (10.5% vs. 9.3%). The most common adverse events were dermatologic such as itching (34.5% Viaskin vs. 11.9%) and erythema (28.2% Viaskin vs. 16.9%) at the patch administration site.

In summary, the PEPITES trial demonstrated that Viaskin Peanut modestly increased the percentage of patients who met the primary endpoint compared with a placebo patch in a DBPCFC (35.3% vs. 11.9%, p<0.001). The patch was well tolerated with low rates of adverse events – mostly cutaneous and few serious.

Key Differences Between the PALISADE and PEPITES Trials

It is challenging to compare the results in the PALISADE and PEPITES trials because of differences in the inclusion criteria of the trials, differences in the implementation in the DBPCFC, and differences in the systems used to categorize adverse events. However, several important differences should be highlighted (Table 3.1). First, the PALISADE trial included older patients (ages 12 to 17 years) who are less likely to respond to desensitization therapy. The PALISADE trial also enrolled participants with a lower eliciting dose (≤ 100 mg rather than 300 mg). Finally, the primary outcome in the PALISADE trial required a tolerated dose of 600 mg or higher compared with 100 mg for the low-eliciting dose group in PEPITES or 300 mg for the high-eliciting dose in PEPITES. Thus, if the study design for the PALISADE trial was the same as that of the PEPITES trial, the between group difference for AR101 compared to placebo would likely have been greater than the 63.2% observed in the PALISADE trial. Conversely, if the study design for the PEPITES trial was the same as that of the PALISADE trial, the between group difference for Viaskin Peanut would likely have been less than the 21.7% observed in the PEPITES trial.

Table 3.1. Comparison of the Phase 3 PALISADE and PEPITES Trials

	AR101	Viaskin Peanut
Key Study	PALISADE	PEPITES
Ages	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	ED 300 mg if baseline ED ≤10 mg ED 1000 mg if baseline ED ≥30 mg
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 for at least 90 minutes	Day 1 only
Met Primary Outcome, Active vs. Placebo	67.2% vs. 4.0%	35.3% vs. 13.6%
Overall Withdrawal Rate, Active vs. Placebo	21.0% vs. 7.3%	10.5% vs. 9.3%

DBPCFC: double-blind, placebo-controlled food challenge, ED: eliciting dose

* This dose escalation is the ideal if no complications, but may be slowed for adverse events and adherence issues.

However, the treatment burden for AR101 is much greater – requiring more than 12 office visits and restrictions on the timing of dose administration. Moreover, the adverse events associated with AR101 appear to be significantly greater than those of Viaskin Peanut, even during the maintenance dose phase of the trial. For some patients, the adverse event rates associated with daily AR101 may be higher than those they would experience by strict adherence to a peanut avoidance strategy. This may be why the proportion of patients who withdrew during the first year of therapy for AR101 (21.0%) was twice that for Viaskin Peanut (10.5%), though this is not a direct, randomized comparison (Table 3.1).

Quality of Individual Studies

The two randomized trials of AR101 and the three randomized trials of Viaskin Peanut were all of good quality/low risk of bias, though all of the trials were at risk for partial unblinding due to adverse events. For the other OIT trials, two were good quality and one was fair quality.

Clinical Benefits

AR101

There are two published studies of AR101: the Phase 3 PALISADE trial[34] described above in the Key Studies section and a multicenter phase 2 trial ARC001.[33]

The Phase 2 trial enrolled a slightly different population (55 participants ages four to 26 years of age) and used a different primary outcome from the Phase 3 trial (able to tolerate at least 300 mg rather than 600 mg of peanut protein during a DBPCFC).[33] In addition, the exit DBPCFC for the primary outcome was performed after only two weeks on the target daily maintenance dose of 300 mg of peanut protein rather than the 24 weeks of maintenance dosing in the PALISADE trial. Thus, the outcomes are not directly comparable.

In the Phase 2 trial, 79% of patients randomized to AR101 were able to tolerate 300 mg of peanut protein and 62% were able to tolerate 600 mg of peanut protein compared with 19% and 0% of participants randomized to placebo (oat protein). In the phase 3 PALISADE trial, 76.6% of patients randomized to AR101 were able to tolerate 300 mg of peanut protein and 67.2% were able to tolerate 600 mg of peanut protein compared with 8.1% and 4.00% of participants randomized to placebo.

Quality of life outcomes were not reported for either trial.

Viaskin Peanut

There are three published studies of Viaskin Peanut: the Phase 3 PEPITES trial[35] and two additional Phase 2 trials.[36,37] The PEPITES trial results are described in detail above in the Key Studies section.

The Phase 2 studies are both dose finding studies that randomized patients to 50 mcg patches, 100 mcg patches, 250 mcg patches, or identical placebo patches. They also included a wider range of ages (six to 55 years in one; four to 25 years in the other). The primary outcomes also differed. In one, the primary outcome was an increase of at least tenfold in the eliciting dose of peanut protein or reaching at least 1000 mg after one year of treatment. In the other, the primary outcome was passing a 5044 mg peanut protein OFC or at least a tenfold increase in the eliciting dose of peanut protein after one year of treatment. Thus, none of the outcomes are directly comparable with each other or with those used in the trials of AR101.

Focusing in on the population of interest, in children ages six to 11 years, 15/28 (53.6%) of those treated with the 250 mcg patch met the primary outcome compared with 6/31 (19.4%) of those treated with the placebo patch.[37] In children ages four to 11 in the other Phase 2 trial, 11/18 (61.1%) of those treated with the 250 mcg patch met the primary outcome compared with 1/18 (5.6%) of those treated with the placebo patch.[36] In both Phase 2 trials, the benefits of the Viaskin Peanut patch were smaller in the older participants.

Quality of life outcomes were not reported in any of the three trials.

Other Oral Immunotherapy

There have been many studies of OIT for peanut allergy using different peanut preparations, different dose escalation strategies, different maintenance doses (125 mg to 5,000 mg peanut protein per day), different primary outcomes and different target populations.[38,42-48] Two RCTs of OIT[38,39] met our inclusion criteria.[38,39]

The STOP II trial randomized 99 participants ages seven to 16 years with peanut allergy documented on DBPCFC to peanut flour (n=49) or strict peanut avoidance (n=50) in an open label study. The dose of peanut protein was increased every two weeks under MD observation from 2.5 mg to 5, 12.5, 25, 50, 100, 200, 400, then 800 mg and maintained at 800 mg for a total of 26 weeks (including the dose escalation phase). The primary outcome was defined as no reaction during a DBPCFC at a cumulative dose of 1400 mg. The PRACTALL guidelines were not cited and it is unclear what doses were used to reach a cumulative dose of 1400 mg. Ten patients randomized to the active intervention were excluded from the primary analysis because they did not complete the DBPCFC; and four of the controls were excluded because three declined participation when not randomized to the active arm, and one developed Crohn's disease. The reported successful desensitization rate was 62% (24/39) in the active treatment group and 0% (0/46 in the control

group). Because both the PEPITES and PALISADE trials used a strict intention to treat analysis and considered anyone who was randomized and did not complete the final DBPCFC as a treatment failure, the equivalent desensitization rate would be 49% (24/49). Quality of life was assessed using the Food Allergy Quality of Life Questionnaire – Parent Form, which is intended to be used for the parents of affected children ages zero to 12 years. Thus, it was reported for the subset of participants ages seven to 12 years. Scores on the questionnaire range from 0 to 6, with lower scores indicating better quality of life and a change of at least 0.5 points representing the minimum clinically important difference. The quality of life score on this scale improved significantly for both groups (-1.61 active group vs. 1-.41 control group). This study was considered poor quality because of the lack of blinding, differential loss to follow-up, and not following a strict intention to treat analysis.

Table 3.2. Comparison of the Outcomes of Other OIT Trials in Children

Trial	Desensitization	Immunotherapy	Control
Anagnostou 2014	Tolerate cumulative dose of 1400 mg in DBPCFC	62% reported, 49% ITT	0%
Reier-Nilsen 2017	Reach maintenance dose of 5000 mg	21%	NA

The TAKE-AWAY trial[39] randomized 77 children ages five to 15 years with peanut allergy confirmed reactive to 3 mg or more of peanut protein on DBPCFC to peanut flour (n=57) or observation only (n=20). The dose escalation phase had increasing doses of peanut flour every two weeks until about 65-100 mg when patients switched to eating roasted peanuts and continued to increase their dose to a goal of 5,000 mg per day over 50 to 78 weeks. Participants were maintained on their maximally tolerated maintenance dose for 36 months. The primary outcome was the feasibility of reaching a maximum maintenance dose of 5,000 mg per day. The primary outcome was reached by 21% of the participants (12/57). Of the remaining participants, 54.4% reached a lower maintenance dose and 24.5% discontinued therapy. The most common reason for not reaching 5,000 mg was taste aversion (66.7%). Taste aversion was a challenge for 77.2% of the participants. Quality of life outcomes were not reported. This study was considered poor quality because of the lack of blinding, lack of follow-up of the control group, and not following a strict intention to treat analysis.

Expert reviewers suggested the inclusion of two publications about real-world OIT for peanut allergy that did not meet our original inclusion and exclusion criteria.[40,41] We will include them in the final report. In brief, the first study is a retrospective cohort describing the experience of 352 patients 3 through 24 years of age treated at 5 centers that vary in the selection criteria for patients, the source of peanut protein, the dose escalation protocol, and the maintenance dose.[40] For example the target maintenance dose ranged from a low of 415 mg of peanut protein to a high of 8,000 mg daily. Overall, 85% of patients reached their maintenance dose. The rate of

epinephrine administration was 0.7 per 1,000 doses or 0.26 per person-year of treatment. No data on quality of life or reactions to accidental exposure were presented.

The second study summarizes additional data from 270 consecutive patients ages 4-19 treated at one of the five centers described in the first publication (Texas).[41] 81% of patients reached the target dose of 3,000 mg per day in a median of 25.8 weeks. Twenty-three percent of patients required epinephrine during dose escalation. Ten percent of patients required epinephrine during the maintenance phase (28/270). During dose escalation, 13.7% of patients experience symptoms consistent with eosinophilic esophagitis.

Harms

AR101

The harms of the Phase 3 PALISADE trial are summarized in the Key Studies section above and are detailed in Appendix Tables D7 – D11. The most common adverse events were GI (abdominal pain, nausea, vomiting) and though the incidence declined in the dose maintenance phase compared with the dose escalation phase, they remained high. Withdrawal rates overall (21.0%) and withdrawals due to adverse events (11.6%) were substantially higher than those observed in the placebo group. Systemic allergic reactions (14.2%) and the use of epinephrine (14.0%) were common.

The adverse events observed in the Phase 2 ARC001 trial were similar to those observed in the PALISADES trial.

Viaskin Peanut

The harms of the Phase 3 PEPITES trial are summarized in the Key Studies section above and are detailed in Appendix Tables D7 – D11. The most common adverse events were skin reactions at the site of the patches including itching (34.5%) and redness (28.2%). Most of these adverse events were mild to moderate. The specific adverse events reported in the PEPITES trial are those that the investigators thought could be related to the patch, which is different from most clinical trials. Grouped overall adverse event rates are reported in the supplementary online materials for the publication, but not the specific events, such as itching and redness. This can impact comparisons across trials. For instance, there were 27 adverse events leading to use of epinephrine in the Viaskin Peanut patch group, but only seven of these were considered related to the patch. Systemic allergic reactions related to the patch were uncommon (3.8%), though epinephrine use was more frequent (9.2%). Withdrawal due to adverse events was uncommon in the active treatment group (1.7%), but more than 10% withdrew from the study during one year of follow-up.

As in the Phase 3 trial, the majority of the adverse events were skin reactions related to the patch site and they were mild. One of the trials included a two-year, open-label extension during which 57/171 patients (31.6%) discontinued therapy. Skin reactions continued to be the most common adverse event, but they decreased with time.

Other Oral Immunotherapy

The harm in the OIT studies mirrored those of AR101. The primary adverse events leading to discontinuation were GI, including abdominal pain, nausea, and vomiting. In studies with very high maintenance doses, food aversion also played an important role. No new adverse events were identified.

Controversies and Uncertainties

The primary benefit of desensitization to peanuts in patients with peanut allergy is likely to be the improvements in quality of life for both the patient and caregivers. However, the quality of life outcomes for the phase 3 trials have not yet been published. It is challenging to fully evaluate the impact of these therapies without placebo-controlled assessments of the change in quality of life.

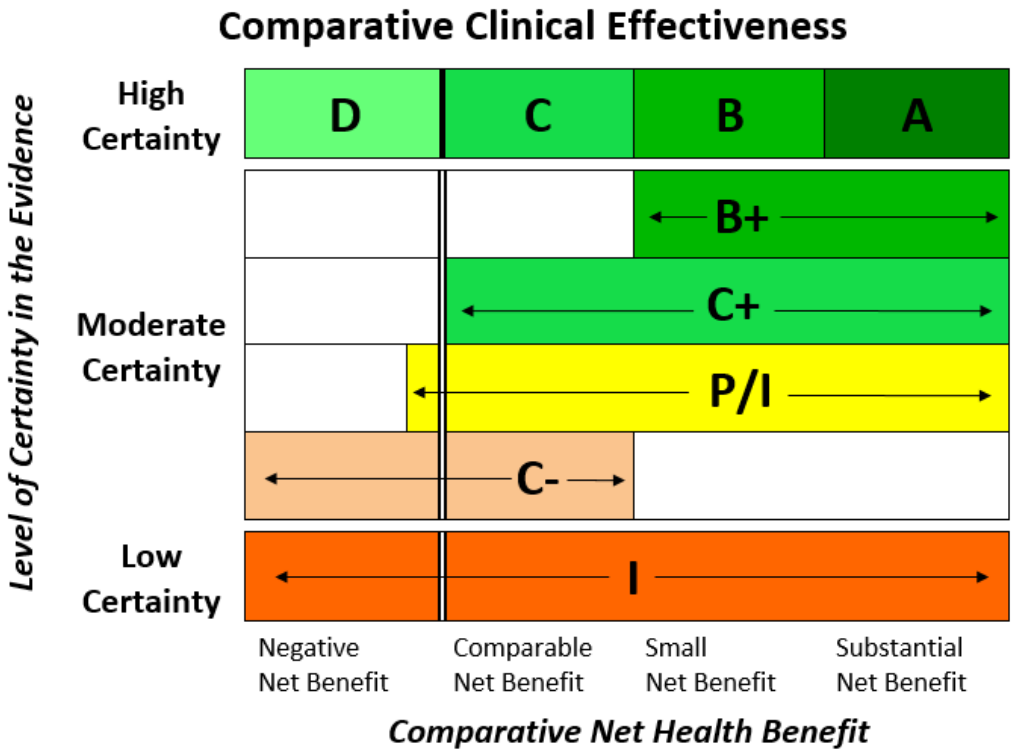
Despite the PRACTALL consensus guidelines and the use of the DBPCFC to evaluate the effectiveness of immunotherapy, there is no consensus on what tolerated dose represents a clinically meaningful outcome for desensitization. A recent review of immunotherapy trials for peanut allergy described 18 different studies with large variations in the definitions used for their primary outcomes.[49] In the PALISADE trial for AR101, successful desensitization was defined by tolerance of a 600 mg dose of peanut protein, which is equivalent to an eliciting dose of at least 1,000 mg. In the PEPITES trial for Viaskin Peanut, successful desensitization was defined at two different thresholds based on the baseline eliciting dose. For participants with a baseline eliciting dose ≤10 mg, successful desensitization was defined by a post-treatment eliciting dose of at least 300 mg, which is equivalent to a tolerated dose of at least 100 mg. For participants with a baseline eliciting does >10 mg, successful desensitization was defined by a post-treatment eliciting dose of at least 1,000 mg, which is equivalent to a tolerated dose of at least 300 mg. Modeling studies suggest that achieving the endpoint in the PEPITES trial will prevent reactions to between 95% and 99.9% of accidental exposures.[50] However, neither AR101 nor Viaskin Peanut has long term follow-up data demonstrating this degree of a reduction in allergic reactions. The FDA working with specialty societies could provide guidance on a standard outcome for future studies of immunotherapy for food allergies in general, not just peanut allergies.

Finally, there is considerable uncertainty about the long-term outcomes for both AR101 and Viaskin Peanut. There is hope that a subset of patients may develop sustained unresponsiveness, but for now the assumption is that patients will remain on these therapies indefinitely. This raises issues about long-term adherence to therapy, particularly during adolescence and young adulthood. If

patients are not adherent, they may no longer be desensitized and could have a serious allergic reaction to the therapy itself. With oral immunotherapy, food aversion can be an issue in a subset of patients and eosinophilic esophagitis may become more common. The true incidence of eosinophilic esophagitis is unknown as most patients do not undergo endoscopy with biopsy. Other unexpected adverse events may occur during long follow up or with larger numbers of patients undergoing therapy.

3.4 Summary and Comment

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable" *- High certainty of a comparable net health benefit*
D = "Negative" *- High certainty of an inferior net health benefit*
B+ = "Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C- = "Comparable or Inferior" *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
I = "Insufficient" *- Any situation in which the level of certainty in the evidence is low*

AR101

The substantial increase in patients treated with AR101 who are able to tolerate 600 mg of peanut protein compared with those treated with placebo (67.2% vs. 4.0%) is balanced by the large numbers of patients with ongoing gastrointestinal symptoms, systemic allergic reactions, and epinephrine use. The net health benefits of AR101 will be driven by changes in quality of life, which have not yet been reported. Thus, there is only moderate certainty of a comparable, small, or substantial net health benefit of AR101 compared with strict avoidance and rapid use of epinephrine (C+, comparable or better). Given the need for frequent visits to doctors during the dose escalation phase and the frequent adverse events, it will be important to ensure that patients receive adequate informed consent and that their preferences are carefully elicited prior to initiating desensitization therapy with AR101.

Viaskin Peanut

The small increase in patients able to tolerate 100 to 300 mg of peanut protein compare with those treated with placebo (35.3% vs. 13.6%) is balanced by relatively few adverse events. As with AR101, the net health benefits are likely to be driven by changes in quality of life, which have not been reported. Thus, there is only moderate certainty of a comparable, small, or substantial net health benefit of Viaskin Peanut compared with strict avoidance and rapid use of epinephrine (C+, comparable or better).

Oral immunotherapy (OIT)

The studies of OIT, other than AR101, were relatively small, unblinded poor quality studies that used peanut protein not subject to Good Manufacturing Practices. There were differences in the dose escalation phase and in the maintenance dose as well as differences in the outcomes used to define desensitization. Finally, there were significant adverse events associated with OIT and no clear net improvements in quality of life. Thus, the level of certainty in the evidence for OIT is low (I, insufficient).

Comparisons among therapies

There are no head to head trial between these agents, and the patient populations and primary outcomes differed sufficiently to preclude indirect comparisons. Based on surrogate outcomes (oral food challenges), AR101 appears more efficacious than Viaskin Peanut, but appears to have more adverse effects. However, the level of certainty in the comparative evidence is low (I, insufficient).

4. Long-Term Cost Effectiveness

4.1 Overview

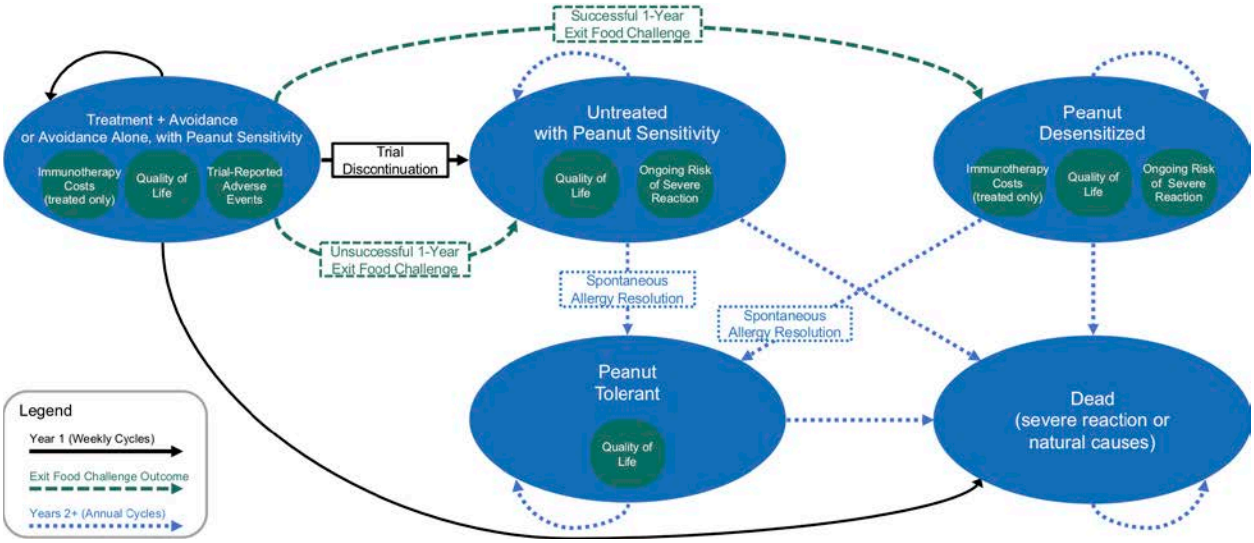
The primary aim of this analysis was to estimate the lifetime cost-effectiveness of the two peanut allergy immunotherapies from a US health care sector perspective. The cost-effectiveness model included two comparisons: 1) AR101 oral immunotherapy plus avoidance compared to avoidance alone, and 2) Viaskin Peanut plus avoidance compared to avoidance alone. These two immunotherapies were modeled independently; i.e., all incremental values, including incremental cost-effectiveness ratios (ICERs), solely reflect comparisons to the placebo control from the respective trials. Participant survival, quality-adjusted survival, serious adverse events (anaphylaxis), and health care costs were summarized over a lifetime time horizon for each treatment option. All costs and outcomes were discounted at 3% per year. We modeled a variety of scenarios beyond the base case, including a modified societal perspective to capture the quality of life and economic impacts of peanut allergy on parents and/or caregivers. The analytic framework for this assessment is depicted in Figure 4.1 below.

4.2 Methods

Model Structure

We developed a *de novo* decision analytic model in Microsoft Excel (version 1902) that includes five health states: 1) on treatment or placebo with peanut sensitivity, 2) untreated with peanut sensitivity, 3) peanut desensitized, 4) peanut tolerant, and 5) death (Figure 4.1). Health states and transitions among them are modeled using a Markov model approach, a type of economic model used to follow a hypothetical cohort of participants through time as they move among a set of mutually exclusive heath states. The number of cycles that individuals reside in each state was used in conjunction with health state values (e.g., life-years, health-related quality-of-life, rate of allergic reactions, and cost) to estimate life expectancy, quality-adjusted life expectancy, and expected costs.[51]

Figure 4.1. Model Framework



The first year was modeled with weekly cycles to more accurately capture immunotherapy costs, adverse events, and treatment discontinuation as reported by the clinical trials. All transitions beyond the first year were modeled with annual cycles. The two immunotherapies were evaluated in separate models that utilize the same model structure. For each treatment regimen, a hypothetical peanut-allergic population began the model in health state (1) on treatment or placebo with peanut sensitivity, where they remain until they:

a) became desensitized to peanuts at the end of the first modeled year, then remained desensitized and on treatment;
b) discontinued treatment within or at the end of year one and were not desensitized to peanuts at the end of year one;
c) spontaneously became peanut tolerant (allergy resolves); or
d) died from a severe allergic reaction or other causes (i.e., age-specific mortality).

At one year, all surviving individuals who had not discontinued immunotherapy and successfully passed the exit food challenge were transitioned to the peanut desensitized health state; the remainder who failed the exit food challenge were transitioned to the untreated with peanut sensitivity health state. During subsequent cycles some individuals transitioned to the peanut tolerant health state from both the untreated with peanut sensitivity and peanut desensitized states. Individuals were allowed to transition to death from any of the alive health states.

The first year of the model was created using the clinical trial data separately for AR101 and Viaskin Peanut. In that year, the placebo patients from each trial experienced the events and the food challenges that were recorded in the trials, with these events being used to estimate the avoidance alone patient's experience. After the first year, all placebo patients who were not successful in completing the exit food challenge moved to the untreated with peanut sensitivity health state.

Treatments

The list of modeled interventions was developed with input from patient organizations, clinicians, manufacturers, and payers. The full list of interventions considered in the model was:

- AR101 oral immunotherapy plus avoidance versus avoidance alone, based on the PALISADE trial[34]
- Viaskin Peanut plus avoidance versus avoidance alone, based on the PEPITES trial[35]

Target Population

The population of focus was children between the ages of four to 17 years with peanut allergy. For the AR101 comparison, the modeled population represented the PALISADE trial's prespecified primary analysis population, comprised of children age four to 17 years who had a clinical history of peanut allergy.[34] The primary analysis in the Viaskin Peanut Phase 3 trial was for participants age four to 11 years.[35] We lacked direct estimates of the mean ages in the trials; therefore, due to the similarities in age ranges, we assumed a starting age of seven years in both models for all comparators.

Table 4.1. Clinical Trial Population Characteristics[34,35]

Participant Population	Median Maximum Peanut Protein Dose	Median Peanut-Specific IgE	Multiple Food Allergies
AR101[34]	10 mg (tolerated dose)*	69 kUA/liter	65.9%
Placebo[34]	10 mg (tolerated dose)*	75 kUA/liter	64.5%
Viaskin Peanut[35]	100 mg (eliciting dose)†	78 kUA/liter	86.1%
Placebo[35]	100 mg (eliciting dose)†	101 kUA/liter	84.7%

*Maximum peanut protein ingested in a single dose without dose-limiting symptoms.
†Maximum peanut protein dose at which a patient exhibited objective signs or symptoms of an immediate hypersensitivity reaction.

Key Model Characteristics and Assumptions

The first modeled year reproduced trial-reported outcomes. Model cycle length was one week in the first year (52 cycles in year one) to capture dose escalation-related costs and adverse events, as well as immunotherapy discontinuation. Subsequent model cycle lengths (year 2+) were one year.

Survival was weighted by health state utilities to model quality of life. The model included separate utilities for participants: 1) with peanut sensitivity, 2) peanut desensitized, and 3) peanut tolerant. Additionally, disutility decrements were applied based on rates of severe treatment-emergent side effects and the rate of epinephrine utilization.

The model included all treatment costs associated with each individual immunotherapy regimen, including drug acquisition costs, clinical visit costs, and food challenge costs. The model also included adverse event costs for events that occurred in at least 5% of participants in at least one of the included regimens.

Other key model assumptions are listed in Table 4.2, along with the rationale for each.

Table 4.2. Key Model Assumptions

Assumption	Rationale
Individuals who successfully complete AR101 or Viaskin Peanut regimens and pass the exit food challenge at one year are assumed to remain on maintenance immunotherapy for the remainder of the modeled time horizon.	Real-world treatment and adherence rates beyond the trials' follow-up periods are currently unknown. We also include a scenario in which individuals discontinue immunotherapy after the first year, no longer incurring treatment costs but maintaining desensitization based on trial-reported rates.
Avoidance alone (placebo arm) participants who pass the exit food challenge at one year are assumed to have the same health state utility and risk of future allergic reactions in years 2+ as desensitized participants who received and continue administration of immunotherapy.	Although it is plausible that desensitized participants who received immunotherapy are different from desensitized participants who did not, we are unaware of sufficient long-term data to make this distinction in the model.
Epinephrine use will be based on trial-reported usage rates, independent of modeled adverse events.	There is a lack of epinephrine usage data stratified by type of adverse event.
Participant behavior, e.g., increased risk tolerance for or aversion to peanut exposure, does not change based on modeled health state.	Participants are expected to continue avoidance of peanut exposure and maintain access to epinephrine regardless of desensitization.

Model Inputs

Clinical Inputs

Clinical Trial Evidence

In the AR101 comparison, the transition from the treatment plus avoidance with peanut sensitivity health state to the peanut desensitized health state at the end of year one was modeled using the primary efficacy end point of the PALISADE trial, with data from the placebo arm used for the transition from the avoidance alone with peanut sensitivity health state to the peanut desensitized health state. In the trial, 250 of 372 participants (67.2%) who received AR101 were able to ingest a dose of 600 mg or more of peanut protein without dose-limiting symptoms at the exit food challenge, compared to five of 124 participants (4.0%) who received placebo. The between-group difference was 63.2% (95% CI, 53.0% to 73.3%; P<0.001) (Table 4.3). In the model, the between-group difference was added to the proportion of desensitized placebo participants at one year to derive the proportion of desensitized AR101 participants at one year. We used the secondary end points in a scenario analysis, including tolerating the 300 mg dose and the 1,000 mg dose during the exit food challenge; the response rates in the treatment group were 76.6% and 50.3%, respectively, as compared with 8.1% and 2.4%, respectively, for the placebo control.

Table 4.3. Results of the PALISADE Trial[34] (AR101)

Dose of Peanut Protein Ingested without Dose-Limiting Effects	Placebo Proportion Tolerating Single Dose	AR101 Between-Group Difference vs. Placebo
600 mg (Base Case)	4.0% (95% CI: 0.6% - 7.5%)	63.2% (95% CI: 53.0% - 73.3%)
300 mg	8.1% (95% CI: 3.3% - 12.9%)	68.5% (95% CI: 62.1% - 74.9%)
1000 mg	2.4% (95% CI: 0.0% - 5.1%)	47.9% (95% CI: 42.1% - 53.7%)

CI: confidence interval

The primary efficacy end point of the Viaskin Peanut PEPITES trial was used in the Viaskin Peanut comparison to model the transition from the treatment plus avoidance with peanut sensitivity health state to the peanut desensitized health state at the end of year one, and data from the placebo arm for transition from the avoidance alone with peanut sensitivity health state to the peanut desensitized health state. Of the 238 Viaskin Peanut recipients in the PEPITES trial, 35.3% were treatment responders after 12 months of therapy, compared to 13.6% who received placebo. The between-group risk difference was 21.7% (95% CI: 12.4% - 29.8%) (Table 4.4). As in the AR101 comparison, the between-group difference was added to the proportion of desensitized placebo participants at one year to derive the proportion of desensitized Viaskin Peanut participants at one year.

Table 4.4. Results of the PEPITES Trial[35]

	Placebo Treatment Response at Month 12	Viaskin Peanut Between-Group Difference vs. Placebo
Eliciting Dose of 1000+ mg or 10x Initial Eliciting Dose	13.6% (95% CI: 7.4% - 19.8%)	21.7% (95% CI: 12.4% - 29.8%)

CI: confidence interval

Survival

Participant survival was modeled using United States Centers for Disease Control (CDC) life tables[52] for age-based background mortality, and we also applied a small (5.77×10^{-7}) annual probability of death from an allergic reaction to the peanut sensitivity and desensitized health states (but not the peanut tolerant health state) in years 2+ of the model; both estimates were converted to and applied as a weekly probability for year one.[53]

Spontaneous Peanut Tolerance

The rate of spontaneous tolerance to peanuts (resolution of the allergy) was applied to both the untreated with peanut sensitivity and peanut desensitized health states in years 2+. The same transition probability of 1.1% per year was applied to each state.[54]

Discontinuation of Immunotherapy

The rate of immunotherapy discontinuation in the first year reflects the trial-reported number of participants who did not complete the trial. In the case of AR101 versus avoidance alone, we utilized available discontinuation data stratified by dose escalation phase from the PALISADE trial.[34] For Viaskin Peanut, discontinuation rates were based on the reported discontinuation rates at year one in the PEPITES trial.[35] The rates of discontinuation for each time period were converted to weekly transition probabilities (Tables 4.5 and 4.6) that were used to transition participants from the treatment or avoidance alone with peanut sensitivity health state to the untreated with peanut sensitivity health state during modeled year one.

Table 4.5. Derivation of Trial Discontinuation Transition Probabilities (AR101 vs. Avoidance Alone)[34]

	Discontinuations/ Total Participants	Weeks in Phase	Calculated Weekly Rate	Conversion to Weekly Transition Probability†
AR101 Initial Phase to Updosing Phase	6/372	0.14 (1 day)	--	--
AR101 Updosing Phase to Maintenance Phase	56/366	20	0.00903	0.00899
AR101 Maintenance Phase to 1-Year Exit Food Challenge	18/310	32*	0.00193	0.00192
Placebo Initial Phase to Updosing Phase	1/124	0.14 (1 day)	--	--
Placebo Updosing Phase to Maintenance Phase	5/123	20	0.00212	0.00212
Placebo Maintenance Phase to 1-Year Exit Food Challenge	4/118	32	0.00110	0.00110

*The stated maintenance duration in the PALISADE trial is 24 weeks. However, the primary outcome was measured at approximately one year. We have based treatment discontinuation rates on the exit food challenge occurring at exactly one year, not at 44 weeks as could be implied.
†Some weekly transition probabilities appear equal to their rates due to rounding.

Table 4.6. Derivation of Trial Discontinuation Transition Probabilities (Viaskin Peanut vs. Avoidance Alone)[35]

	Discontinuations/ Total Participants	Weeks in Phase	Calculated Weekly Rate	Conversion to Weekly Transition Probability*
Viaskin Peanut at 1 Year	25/238	52	0.00225	0.00225
Placebo at 1 Year	11/118	52	0.00197	0.00197

*Some weekly transition probabilities appear equal to their rates due to rounding.

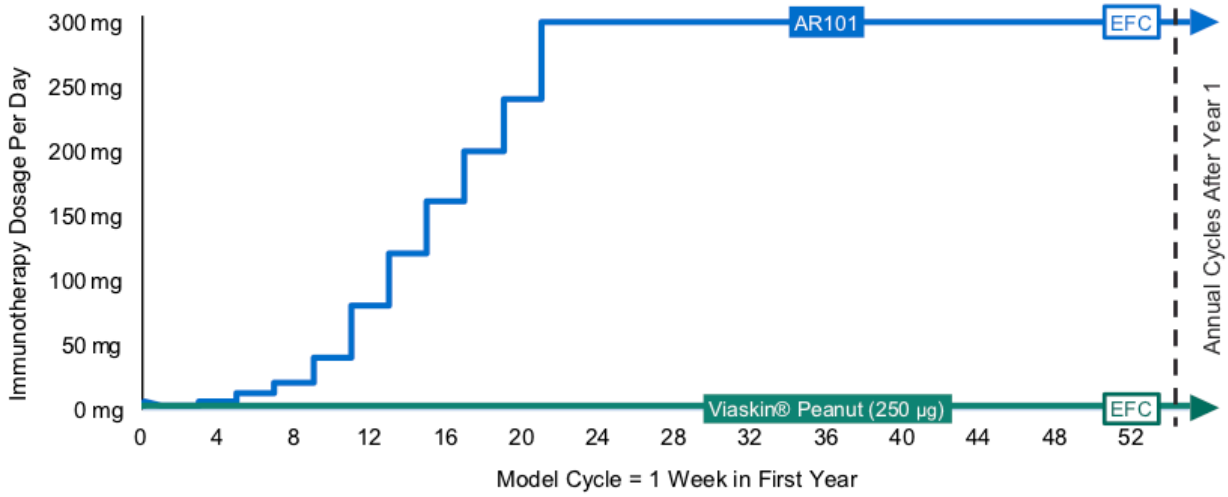
Immunotherapy Utilization

The estimation of drug utilization was derived from dosing schedules reported in the trials (Table 4.7 and Figure 4.2). Each regimen was assumed to be administered over a lifetime for participants who remain in the peanut desensitized health state post-trial, though a scenario analysis also evaluated continued treatment discontinuation in years 2+. Drug unit costs were applied to the utilization estimates to calculate total estimated treatment costs per model cycle. AR101's dose escalation was modeled based on Table 4.7 whereas Viaskin Peanut will use a 250-µg dose throughout treatment.

Table 4.7. Immunotherapy Regimen Recommended Dosage

	AR101[34]	Viaskin Peanut[35]
Manufacturer	Aimmune Therapeutics	DBV Technologies
Route of Administration	Oral	Epicutaneous
Regimen	1 day supervised initial escalation phase Increasing-dose phase, dose increased gradually every 2 weeks, up to 300 mg daily Ongoing maintenance of 300 mg daily	250-µg patch administered daily

Figure 4.2. Modeled Dosing of AR101 and Viaskin Peanut



EFC: Exit Food Challenge

Health State Utilities

Health state utilities were derived from publicly available literature and applied to the four alive disease states. The model base case used the same health state utility estimates across the two treatments evaluated in the model. The preference-weighted health-related quality of life literature in food allergy is extremely limited. While many manuscripts report changes in quality of life using various instruments, those instruments lack proper modeling studies to cross-walk them to preference weights that can be used to estimate QALYs.[55-57] We identified only one study across the food allergy literature that included a preference-weighted measure. The age-specific estimates, from Protudjer et al.,[58] compared a sample of children in Sweden with food allergies to a convenience sample of non-food allergic children aged zero to 17 years (stratified into two groups: children age zero to 11 years and adolescents age 12-17 years). The estimates of utility were derived using parent-reported (for children) and adolescent-reported EuroQol-5-Dimension (EQ-5D) responses.

Participants in peanut sensitivity health states received the utility value of food allergy participants, and peanut tolerant participants received the non-food allergic utility value from Protudjer et al. (Table 4.8). We also assumed that participants in the peanut desensitized health state had utility equal to the average of the utilities for the untreated with peanut sensitivity and peanut tolerant health states. This is a conservative assumption based on the available data and with the expectation that while desensitization reduces risk, there is still an underlying potential risk of reaction to exposure and the need to avoid exposure to peanuts and to carry epinephrine. We also noted that the utility values for ages 12+ were higher than those for the same health state for children age 0-11, which is difficult to reconcile. However, the differences between the health states within each age group are approximately equal. Thus, for the purpose of the model, this difference in absolute utility values between the age groups does not result in differences in incremental QALYs. Using the 0-11-year-old utility values for the entire model time horizon or switching values at age 12 results in the same incremental difference in QALYs between the two treatments.

The assumptions for the utility values were explored in the one-way sensitivity analysis using broad ranges for all three utility input values. Uncertainty in the utility values, where overlap occurs between the bounds and the next health state, were programmatically handled in the probabilistic sensitivity analysis. Forcing health states assumed to be ordinal to each other was accomplished by selecting the larger of either a) the maximum drawn from the health state's utility distribution, or b) the value drawn for the next worse health state.

The length of time that treatment-emergent AEs impacted participants was unknown but expected to be relatively short-lived. Therefore, we did not incorporate AE-related disutilities in the model.

Table 4.8. Quality of Life (Utility) Inputs

Health State	Utility Value Estimate	Lower Bound	Upper Bound
Children (Age 0-11) Treatment or Avoidance Alone with Peanut Sensitivity[58]	0.840	0.819	0.861
Children (Age 0-11) Treatment or Avoidance Alone with Peanut Desensitization*	0.890	0.868	0.912
Children (Age 0-11) Peanut Tolerant[58]	0.940	0.917	0.964
Adolescents/Adults (Age 12+) Treatment or Avoidance Alone with Peanut Sensitivity[58]	0.910	0.887	0.933
Adolescents/Adults (Age 12+) Treatment or Avoidance Alone with Peanut Desensitization*	0.955	0.931	0.979
Adolescents/Adults (Age 12+) Peanut Tolerant[58]	1.0	0.975	1.0

*Assumption that participants in the peanut desensitized health state received the average of the utilities for the untreated with peanut sensitivity and peanut tolerant health states.

Economic Inputs

Immunotherapy Cost Inputs

The costs of immunotherapy with AR101 and Viaskin Peanut are currently unknown as they have not been made commercially available. However, analyst estimates have recently forecasted an expected cost for AR101 of $5,000 to $10,000 for the first six months of use, and $300 to $400 per month after. Analysts also predict that Viaskin Peanut will cost more than $6,000 for a year's supply.[59] Based on these estimates, we assumed AR101 placeholder costs of $350 per month ($6,595 for months 1-6 including clinical visits for dose escalation; $4,200 per year thereafter).[59] For Viaskin Peanut, we assumed a placeholder cost of $6,500 per year.[59] We also present the model-calculated, value-based prices necessary to meet the willingness-to-pay thresholds of $50,000, $100,000, and $150,000 per QALY for each of the two comparisons.

Health Care Resource Utilization Inputs

Health care resource utilization was modeled based on available data from the trials and published sources. Health care resource use included the maintenance of an on-hand prescription for an epinephrine auto-injector (replaced upon use) and the administration of epinephrine for an allergic reaction (using a probability of epinephrine administration per cycle, Table 4.9). In non-desensitized participants, we assumed a rate of accidental peanut exposure of 11.7% per year, with

52% of those exposures resulting in a moderate-to-severe reaction requiring use of a single epinephrine pen, a 0.18% per year risk of hospitalization from a severe allergic reaction, and a 20.4% per year likelihood of outpatient visit per year with an allergic reaction.[54] We assumed a 95% risk reduction in moderate-to-severe reactions (and thus epinephrine use) in participants who were desensitized.[60] In scenario analyses, we present a range of decreased risks of moderate-to-severe reaction in the treatment with desensitization health state, as well as a modeled increased risk of accidental exposure in the treatment with desensitization health state to explore increased risk tolerance.

Table 4.9. Epinephrine Utilization

	Count of Epinephrine Uses	Person-Years of Trial Exposure	Annual Rate	Conversion to Weekly Probability	Administrations: 1 2 3
AR101 Year 1 [34]	82	307.0	0.267	0.0051	92.7% 6.1% 1.2%
Placebo Year 1 [34]	9	108.8	0.083	0.0016	100% 0% 0%
Viaskin Peanut Year 1 [35]	27	235.8	0.115	0.0022	100% 0% 0%
Placebo Year 1 [35]	5	115.2	0.043	0.0008	100% 0% 0%

The cost of the epinephrine auto-injector was taken from Redbook/IBM Micromedex.[61] Unit costs for medical services utilized estimates from the peer-reviewed literature and the Centers for Medicare and Medicaid Services fee schedules. [62 62 60]

Table 4.10. Other Healthcare Resource Utilization and Costs

Healthcare Costs		Cost
Exit Food Challenge Cost[62]		$345
Annual Physician Visit[54]		$98
Annual Immunotherapy Services[54]		$146
Allergic Reaction Events & Costs (Years 2+)	Probability	Cost
Annual Accidental Peanut Exposure[54]	11.7%	--
└> Moderate to Severe Reaction (Epinephrine Use) [54]	52.0%	--
└> Hospitalization after Severe Reaction[54]	0.18%	$5,360*
└> Emergency Department Visit[63]	2.7%	$661
└> Ambulance Transport[63]	0.50%	$561
└> Outpatient Treatment[63]	20.4%	$231
Epinephrine Pen Replacement (2-Pack)[61]	--	$300

*Assuming that the cost of hospitalization after a severe AE is the average cost for anaphylactic reaction, systemic allergic reaction, and asthma exacerbation (see Table 4.11).

All participants who had not yet discontinued treatment or avoidance alone (placebo rates from the trials) at one year accrued the cost of the exit food challenge during the last weekly cycle of year one.

Adverse Events

For each of the two comparisons, the model included all reported treatment-related serious adverse events (AEs) that occurred in >5% of participants in at least one of the comparators. Each serious AE had an associated cost that was applied for each occurrence of the event. Costs of serious AEs were based on resource utilization associated with appropriate treatments as reported in previous analyses, and unit prices from the Centers for Medicare and Medicaid Services (CMS) Final Rule and Correction Notice Tables for the fiscal year 2018.[62]

The PALISADE trial reported a detailed list of AEs stratified by dose escalation phase (Table 4.11). For the AR101 comparison, we assessed the full cost estimates of each AE in the first model cycle of each dose escalation phase (initial: model cycle 0; increasing: model cycle 1; maintenance: model cycle 21). The PEPITES trial did not report any severe anaphylactic reactions or asthma exacerbation, but did report that no systemic allergic reactions were severe.[35]

Table 4.11. Modeled Severe Adverse Events

	CMS Diagnosis-Related Group	Serious AE Cost[62]	AR101[34] N = 372	Placebo[34] N = 124	Viaskin Peanut[35]	Placebo[35]
Anaphylactic Reaction	DRG 915: Allergic Reactions with MCC	$8,897.68	0.3%	0%	0%	NR
Systemic Allergic Reaction	DRG 916: Allergic Reactions Without MCC	$3,301.02	0.5%	0%	0%	0%
Asthma Exacerbation	DRG 203: Bronchitis & Asthma without CC/MCC	$3,880.15	0.5%	0%	0%	NR

CC: complications and comorbidities, DRG: Diagnosis Related Group, MCC: major complications and comorbidities, NR: not reported

Model Analysis

The model estimated the average amount of time each participant spent desensitized to peanut exposure, as well as the time that participants remained sensitive to peanut exposure and time tolerant to peanut exposure. Time spent in each health state was summed to provide estimates of life expectancy and quality-adjusted life expectancy. In addition to presenting undiscounted results, long-term estimates of costs, QALYs, and life-years were discounted at 3% per year. We calculated the ICERs for each intervention versus avoidance alone as the incremental cost per quality-adjusted life year and also incremental cost per serious adverse event (anaphylaxis) avoided.

Societal Perspective Analysis

Peanut allergy results in significant medical, out-of-pocket, and opportunity costs to payers, parents, and employers. We explored the societal impact due to caregiver co-payments and deductibles, special diets, and childcare costs related to peanut allergy, as well as annual opportunity costs due to lower caregiver work productivity. These costs were derived from a recent economic and burden of disease study (Table 4.12).[64]

Table 4.12. Annual Costs for Societal Perspective Analysis

Societal Cost	Estimate
Annual Out-of-Pocket Costs [64]	$931
Annual Productivity Loss [64]	$2,399
Total Annual Cost	$3,330

Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We also performed threshold analyses for drug costs to estimate the price for each immunotherapy that would achieve specific willingness-to-pay thresholds (from $50,000 to $150,000 per QALY).

Scenario Analyses

Multiple scenario analyses were conducted to evaluate the impact of key model choices and assumptions on the robustness of the results and conclusions, including the following:

- Time horizon
- Post-year-one discontinuation and impact on desensitization (repeating the discontinuation rates from year one through the remaining time horizon)
- PALISADE secondary outcomes (for 300 mg, 1000 mg)
- No post-year-one spontaneous peanut tolerance
- Increased risk of accidental exposure in the treatment with desensitization health state to explore the relationship between value and the possibility of increased risk tolerance
- Range of 50% increase/decrease in rate of epinephrine use in years 2+
- Modified societal perspective: Caregiver utility added to the societal perspective
    - Similar to challenges with patient utility estimates, many manuscripts report changes in parent/caregiver quality of life using various instruments but lack proper modeling studies to cross-walk them to preference weights that can be used to estimate QALYs.[57,65-67] We did not identify any studies across the food allergy literature that included a preference-weighted measure. Therefore, we continue to explore methods for incorporating estimates of parent/caregiver benefit in this analysis.

Model Validation

We used several approaches to validate the model. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. Finally, we compared results to other cost-effectiveness models in this therapy area.

4.3 Results

Base Case Results

Immunotherapy with AR101 resulted in increased QALYs due to the utility benefit of more patients having peanut desensitization, with 0.63 incremental QALYs versus avoidance alone (Table 4.13). We did not model a difference in mortality among comparators, therefore both AR101 and avoidance alone resulted in 28.69 life years gained and there was no gain in overall survival for AR101. Using the available placeholder price, the total lifetime cost was $79,000 for AR101 versus $7,000 for avoidance alone, and the incremental cost-effectiveness ratio was $116,000.

Table 4.13. Discounted Base Case Results: AR101 versus Avoidance Alone Using Placeholder Price

Treatment	Immunotherapy Cost	Total Cost	QALYs	Life Years	Incremental Cost per QALY
AR101	$65,000	$79,000	27.06	28.69	
Avoidance Alone	$0	$7,000	26.43	28.69	
Incremental	$65,000	$72,000	0.63	0.00	$116,000

Immunotherapy with Viaskin Peanut resulted in increased QALYs due to the utility benefit of increased peanut desensitization, with 0.22 incremental QALYs versus avoidance alone (Table 4.14). As noted above, there was no difference in overall survival, therefore both Viaskin Peanut and avoidance alone resulted in 28.69 life years gained. Using the available placeholder price, the total cost was $62,000 for Viaskin Peanut versus $7,000 for avoidance alone, and the incremental cost-effectiveness ratio was $259,000.

Table 4.14. Discounted Base Case Results: Viaskin Peanut versus Avoidance Alone Using Placeholder Price

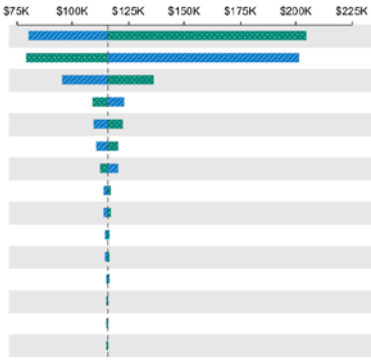
Treatment	Immunotherapy Cost	Total Cost	QALYs	Life Years	Incremental Cost per QALY
Viaskin Peanut	$56,000	$62,000	26.74	28.69	
Avoidance Alone	$0	$7,000	26.53	28.69	
Incremental	$56,000	$56,000	0.22	0.00	$259,000

Sensitivity Analysis Results

We performed one-way sensitivity analysis to evaluate the impact of single parameter uncertainty on the incremental cost-effectiveness ratios for immunotherapy versus avoidance alone (Figure 4.3). For the comparison of AR101 versus avoidance alone, the parameters with the greatest impacts on the ICER were utilities associated with peanut sensitivity and peanut desensitization, the cost of immunotherapy, and results of the exit food challenge. For the comparison of Viaskin Peanut versus avoidance alone, the parameters with the greatest impacts on the ICER were very similar to those driving the AR101 comparison. We performed probabilistic sensitivity analyses to evaluate the impacts of joint parameter uncertainty over 5,000 model simulations; detailed results of the probabilistic sensitivity analysis can be found in the Appendix, Tables E4 and E5.

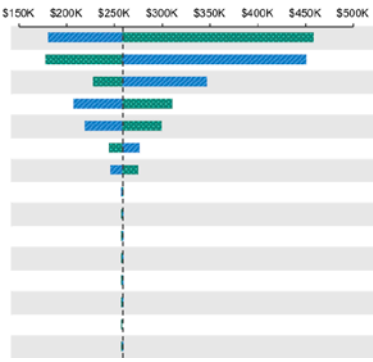
Figure 4.3. One-Way Sensitivity Analyses for Immunotherapy versus Avoidance Alone Using Placeholder Prices

AR101 vs. Avoidance Alone



Parameter	Low Value	High Value	Low Result	High Result	Spread
Utility on treatment/placebo with sensitivity (12+)	0.887	0.933	$80,557	$204,757	$124,199
Utility desensitized (12+)	0.933	0.979	$201,010	$79,368	$121,642
AR101 annual cost	$3,360	$5,040	$94,977	$136,272	$41,294
Utility desensitized (0-11)	0.868	0.912	$123,092	$109,011	$14,082
Utility on treatment/placebo with sensitivity (0-11)	0.819	0.861	$109,362	$122,647	$13,285
Placebo proportion pass EFC (600 mg)	0.6%	7.5%	$110,599	$120,650	$10,052
AR101 EFC difference vs. placebo (600 mg)	53.0%	73.3%	$120,274	$112,295	$7,979
Number of weekly outpatient office visits	0.40	0.60	$114,069	$117,180	$3,111
Cost of outpatient treatment for allergic reaction	$185	$277	$114,091	$117,157	$3,066
Number of weekly immunotherapy clinic visits	0.40	0.60	$114,641	$116,607	$1,966
Cost of annual immunotherapy services	$117	$175	$114,648	$116,601	$1,953
Annual probability of allergy resolution years 2+	0.009	0.013	$114,869	$116,390	$1,521
Duration of severe AE disutility (days)	1.000	5.000	$115,873	$115,376	$497
AR101 discontinuation: initial phase (day 1)	0.3%	2.9%	$115,873	$115,376	$496
Annual accidental peanut exposure probability	0.094	0.140	$115,762	$115,487	$275

Viaskin Peanut vs. Avoidance



Parameter	Low Value	High Value	Low Result	High Result	Spread
Utility on treatment/placebo with sensitivity (12+)	0.887	0.933	$180,598	$459,037	$278,439
Utility desensitized (12+)	0.933	0.979	$450,639	$177,933	$272,706
Viaskin® Peanut EFC difference vs. placebo	12.4%	29.8%	$347,350	$227,273	$120,077
Viaskin® Peanut annual cost	$5,200	$7,800	$207,318	$311,111	$103,793
Placebo proportion pass EFC	7.4%	19.8%	$218,749	$299,680	$80,932
Utility desensitized (0-11)	0.868	0.912	$275,957	$244,387	$31,569
Utility on treatment/placebo with sensitivity (0-11)	0.819	0.861	$245,175	$274,959	$29,784
Annual probability of allergy resolution years 2+	0.009	0.013	$258,085	$260,360	$2,275
Duration of severe AE disutility (days)	1.000	5.000	$259,773	$258,658	$1,115
Annual accidental peanut exposure probability	0.094	0.140	$259,455	$258,974	$480
Accidental exposure y-2+: ppn mod-sev reaction	0.416	0.624	$259,455	$258,974	$480
Disutility severe AEs	0.002	0.003	$259,382	$259,047	$334
Risk reduction of severe reaction if desensitized	0.760	1.000	$259,455	$259,151	$303
Duration of epinephrine disutility (days)	1.000	3.000	$259,214	$259,036	$178
Epinephrine cost/pen	$120	$180	$259,243	$259,186	$56

Scenario Analyses Results

Time Horizon

The incremental costs and outcomes for AR101 were sensitive to the model time horizon with both growing in a logarithmic form, stabilizing at between a 50 and 70-year time horizon. In the Viaskin Peanut analysis, the time horizon length was less impactful on the model results than the above analysis. See Tables E2 and E3 in the Appendix for results of the time horizon scenario analysis.

Extending discontinuation beyond one year

The base case above includes only the discontinuation rates seen in the trials during year 1. This scenario replicates those rates beyond one year, by assuming that same discontinuation rate each subsequent year. In these scenarios, the treatment discontinuation rates observed in the clinical trials were repeated annually to simulate treatment discontinuation, with no change in the baseline assumption of maintenance of treatment effect. Thus, the QALYs estimated for both AR101 and Viaskin Peanut are the same in their respective scenarios as in the base case. However, the immunotherapy treatment costs are lower than the base case due to the continuous rate of treatment discontinuation.

Table 4.15. Post-Year-One Treatment Discontinuation Scenario: AR101 versus Avoidance Alone Using Placeholder Price

Treatment	Immunotherapy Cost	Total Cost	QALYs	Life Years	Incremental Cost per QALY
AR101	$61,000	$76,000	27.06	28.69	
Avoidance Alone	$0	$7,000	26.43	28.69	
Incremental	$61,000	$69,000	0.63	0.00	$110,000

Table 4.16. Post-Year-One Treatment Discontinuation Scenario: Viaskin Peanut versus Avoidance Alone Using Placeholder Price

Treatment	Immunotherapy Cost	Total Cost	QALYs	Life Years	Incremental Cost per QALY
Viaskin Peanut	$51,000	$57,000	26.74	28.69	
Avoidance Alone	$0	$7,000	26.53	28.69	
Incremental	$51,000	$51,000	0.22	0.00	$235,000

PALISADE Secondary Outcomes (for 300 mg, 1000 mg)

These two secondary outcome scenarios involved using alternative definitions for the health state transition probabilities. However, we did not assume any incremental quality of life benefit between people who passed food challenges at different levels. Therefore, the same utility value was used for the desensitized health state across both scenarios. We based this assumption on the quantitative risk reduction literature, which indicated minimal difference in relative risk beyond 300mg.

The scenario using the proportion of patients who tolerated an exposure to 300 mg of peanut protein results in slightly more people being classified as desensitized at one year. The impact of this scenario is that more patients continue treatment throughout the time horizon. Thus, this scenario results in slightly more incremental QALYs relative to the base case, and more treatment costs at each threshold price.

Table 4.17. PALISADE Secondary Outcome Scenario: 300 mg Using Placeholder Price[34]

Treatment	Immunotherapy Cost	Total Cost	QALYs	Life Years	Incremental Cost per QALY
AR101	$73,000	$88,000	27.15	28.69	
Avoidance Alone	$0	$7,000	26.47	28.69	
Incremental	$73,000	$81,000	0.68	0.00	$119,000

The scenario using the proportion of patients who tolerated an exposure to 1,000 mg of peanut protein results in fewer people being classified as desensitized at one year. The impact of this scenario is fewer patients being treated, so lower overall costs for AR101 and a 24% decrease in incremental QALYs relative to the base case at each threshold.

Table 4.18. PALISADE Secondary Outcome Scenario: 1000 mg Using Placeholder Price[34]

Treatment	Immunotherapy Cost	Total Cost	QALYs	Life Years	Incremental Cost per QALY
AR101	$49,000	$64,000	26.89	28.69	
Avoidance Alone	$0	$7,000	26.41	28.69	
Incremental	$49,000	$57,000	0.48	0.00	$120,000

Post-Year-One Spontaneous Tolerance Turned Off

These scenarios evaluated the impact of the assumption that 1.1% of people per year experience total resolution of their peanut allergy spontaneously in both the immunotherapy treated and avoidance alone groups. Assuming no spontaneous resolution, the incremental differences in QALYs were slightly larger than the base case estimates, with less improvement in the avoidance alone groups. Immunotherapy costs were estimated to be higher because more patients continued on treatment rather than being transitioned to the tolerant (and untreated) health state.

Table 4.19. Spontaneous Tolerance Scenario: AR101 versus Avoidance Alone Using Placeholder Price

Treatment	Immunotherapy Cost	Total Cost	QALYs	Life Years	Incremental Cost per QALY
AR101	$82,000	$98,000	26.70	28.69	
Avoidance Alone	$0	$8,000	25.90	28.69	
Incremental	$82,000	$90,000	0.80	0.00	$112,000

Table 4.20. Spontaneous tolerance scenario: Viaskin Peanut versus Avoidance Alone Using Placeholder Price

Treatment	Immunotherapy Cost	Total Cost	QALYs	Life Years	Incremental Cost per QALY
Viaskin Peanut	$70,000	$78,000	26.29	28.69	
Avoidance Alone	$0	$8,000	26.02	28.69	
Incremental	$70,000	$70,000	0.27	0.00	$254,000

Increase/Decreased Risk of Accidental Exposure in the Treatment with Desensitization Health State

We modeled a range of relative differences in the probability of accidental exposure, from -100% to 100%. However, the impact of risky behavior, in either direction, was minimal given the already low probability of moderate-severe adverse events from exposures due to the 95% risk reduction conferred by peanut desensitization.[60] We also note that as seen in the one-way sensitivity analyses, varying the probability of annual accidental peanut exposure had very little impact on model results.

Range of 50% Increase/Decrease in Rate of Epinephrine Use Scenarios in Year 2+

We explored scenarios evaluating a range of increased and decreased rates of epinephrine use relative to the base case. These scenarios did not influence the model results in an appreciable way. As expected, total costs decreased slightly in the scenarios with decreased epinephrine use and increased slightly in the scenarios with increased epinephrine use.

Table 4.21. 50% Decrease in Epinephrine Use in Years 2+: AR101 versus Avoidance Alone Using Placeholder Price

Treatment	Immunotherapy Cost	Total Cost	QALYs	Life Years	Incremental Cost per QALY
AR101	$65,000	$79,000	27.06	28.69	
Avoidance Alone	$0	$6,000	26.43	28.69	
Incremental	$65,000	$73,000	0.63	0.00	$116,000

Table 4.22. 50% Decrease in Epinephrine Use in Years 2+: Viaskin Peanut versus Avoidance Alone Using Placeholder Price

Treatment	Immunotherapy Cost	Total Cost	QALYs	Life Years	Incremental Cost per QALY
Viaskin Peanut	$56,000	$62,000	26.74	28.69	
Avoidance Alone	$0	$6,000	26.53	28.69	
Incremental	$56,000	$56,000	0.21	0.00	$260,000

Table 4.23. 50% Increase in Epinephrine Use in Years 2+: AR101 versus Avoidance Alone Using Placeholder Price

Treatment	Immunotherapy Cost	Total Cost	QALYs	Life Years	Incremental Cost per QALY
AR101	$65,000	$79,000	27.06	28.69	
Avoidance Alone	$0	$7,000	26.43	28.69	
Incremental	$65,000	$72,000	0.63	0.00	$115,000

Table 4.24. 50% Increase in Epinephrine Use in Years 2+: Viaskin Peanut versus Avoidance Alone Using Placeholder Price

Treatment	Immunotherapy Cost	Total Cost	QALYs	Life Years	Incremental Cost per QALY
Viaskin Peanut	$56,000	$62,000	26.74	28.69	
Avoidance Alone	$0	$7,000	26.52	28.69	
Incremental	$56,000	$56,000	0.22	0.00	$259,000

Modified Societal Perspective

For this analysis, we included the annual societal costs listed in Table 4.12. The addition of societal costs notably decreased the incremental cost-effectiveness ratios at each value-based price anchor point, as seen in Tables 4.25 and 4.26.

Table 4.25. Modified Societal Perspective: AR101 versus Avoidance Alone Using Placeholder Price

Treatment	Immunotherapy Cost	Total Cost	QALYs	Life Years	Incremental Cost per QALY
AR101	$65,000	$106,000	27.06	28.69	
Avoidance Alone	$0	$79,000	26.43	28.69	
Incremental	$65,000	$27,000	0.63	0.00	$43,000

Table 4.26. Modified Societal Perspective: Viaskin Peanut versus Avoidance Alone Using Placeholder Price

Treatment	Immunotherapy Cost	Total Cost	QALYs	Life Years	Incremental Cost per QALY
Viaskin Peanut	$56,000	$112,000	26.74	28.69	
Avoidance Alone	$0	$72,000	26.53	28.69	
Incremental	$56,000	$40,000	0.22	0.00	$186,000

Threshold Analysis Results

The annual cost at which the immunotherapies would reach cost-effectiveness thresholds ranging from $50,000 to $150,000 per QALY gained are presented below.

Table 4.27. Threshold Analysis Results

	Annual Cost to Achieve $50,000 per QALY	Annual Cost to Achieve $100,000 per QALY	Annual Cost to Achieve $150,000 per QALY
AR101	$1,530	$3,564	$5,599
Viaskin Peanut	$1,259	$2,512	$3,764

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

In our review of prior economic models, we found no existing models that assessed the cost-effectiveness of AR101 or Viaskin Peanut in peanut allergy.

We found an economic analysis of an oral immunotherapy study in 62 children with peanut allergy (age one to 10 years), with 56 completing the trial.[63] The primary outcome was possible sustained unresponsiveness which occurred in 82.1% of those receiving immunotherapy and in 3.6% in the avoidance group (p<.001).[68] Desensitization occurred in 89.7% of the treated patients and 7.1% of those in the avoidance group (p<.001).[68] A mean number of 12.3 (95% CI, 12.0-12.5) and 2.0 (95% CI, 1.9-2.1) allergic reactions occurred in the immunotherapy and avoidance groups over 20 years of simulation, with 2.3 (95% CI, 2.2-2.3) episodes of anaphylaxis treated with intramuscular epinephrine per subject in the immunotherapy group and 1.1 (95% CI, 1.0-1.2) episodes per subject in the avoidance group.[68] At a $50,000 per QALY threshold, oral immunotherapy was cost-effective (ICER: $2,142 per QALY gained), although it was reported that treated patients may experience a greater rate of peanut-associated allergic reactions and anaphylaxis. In sensitivity analyses, oral immunotherapy was associated with lower rates of anaphylaxis than strict avoidance when the annual rate of accidental allergic reactions in the peanut avoidance group exceeded 25%; the

annual rate of anaphylaxis in the immunotherapy group dropped below 6%; or the probability of sustained unresponsiveness after four years of immunotherapy was 68% or greater.[68] The analysis was sensitive to the cost of therapy increases overtime, rates of accidental allergic reactions, therapy-associated adverse events, and likelihood of therapy-induced tolerance.[68]

Other published economic evaluations included a threshold analysis which calculated the value-based price of epinephrine autoinjectors for children with peanut allergy,[69] and an evaluation of immediate versus non-immediate activation of emergency medical services after epinephrine use for peanut-induced anaphylaxis.[70]

The results of our literature search also yielded a number of studies that were aimed to focus solely on costs not cost-effectiveness analysis. The most relevant studies that reported costs (i.e., direct, indirect, societal) were considered and included in our cost-effectiveness model analysis.[10,53,54,58,64]

4.4 Summary and Comment

Our analysis indicates that the long-term cost-effectiveness of AR101 or Viaskin Peanut is dependent on the prices at which these technologies come to market. The analysis estimated that treatment with AR101 resulted in 0.63 incremental QALYs compared to no immunotherapy treatment over a lifetime time horizon. The analysis of Viaskin Peanut estimated that it resulted in 0.22 incremental QALYs compared to no immunotherapy treatment over a lifetime time horizon. The results of both analyses were most sensitive to the health state utility values and the proportion of patients who passed the exit food challenge at the end of the first year.

Using placeholder prices of $350 per month ($6,595 for months 1-6 including clinical visits for dose escalation; $4,200 per year thereafter) for AR101 and $6,500 per year for Viaskin Peanut, we estimated the total cost of AR101 to be $84,000 over a lifetime, and an incremental cost-effectiveness ratio of $109,000. The estimated lifetime cost for Viaskin Peanut was $56,000, and its incremental cost-effectiveness ratio to be $259,000.

Our scenario analyses indicate that the proportion of patients who are assumed to have responded (choice of threshold for desensitization) and continue treatment is an important parameter, as this predicts the size of the treated population. Furthermore, the background rate of spontaneous tolerance among patients with peanut allergy may be a key driver in the estimation of incremental value for new immunotherapies.

Limitations

We undertook this analysis in the presence of several important limitations that relate to assumptions and uncertainties. First, the utility estimates used for the base case model come from a food allergy, but not necessarily peanut allergy, patient population. It is possible that peanut allergy patients specifically hold slightly different preferences for treatment. Unfortunately, the literature has a paucity of preference-weighted health-related quality of life estimates in food allergy patients and their caregivers. This represents a valuable opportunity for technology developers and policy makers alike.

Second, we lacked any long-term treatment data to inform decisions such as the length of treatment. Therefore, we took the conservative assumption of continuing lifetime treatment for those who were desensitized and acknowledge that this parameter may influence the calculation of value-based prices. We also modeled a scenario with treatment discontinuation with the maintenance of benefit for a lifetime.

Third, the analysis assumes a high level of risk reduction associated with desensitization measured in the two products' clinical trials, based on post-hoc analyses of trial data. While we recognize this potential limitation, it must be considered in the context that the events being avoided are already of very low incidence rate. Therefore, the assumption does not produce a large influence on the findings of the analysis.

Conclusions

Both AR101 and Viaskin Peanut are predicted to produce incremental benefit for people with peanut allergy relative to standard care (no desensitization treatment). These benefits are due to improved subjective quality of life despite the relative rarity with which serious events occur. The ultimate value of these products will be determined by the prices that are set by the manufacturers and their long-term effectiveness.

5. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that influence the relative value of illnesses and interventions. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to AR101 and Viaskin Peanut. We sought input from stakeholders, including individual patients, patient advocacy organizations, clinicians, and manufacturers, to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting Council of clinicians, patients, and health services researchers. As part of their deliberations, Council members will judge whether a treatment may substantially impact the considerations listed in Table 5.1. The presence of substantial other benefits or contextual considerations may shift a council member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a council member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Council member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Council member to vote for a lower value category. A Council member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's value assessment framework. The content of these deliberations is described in the last chapter of ICER's Final Evidence Report, which is released after the public meeting.

This section, as well as the Council's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision-making between patients and clinicians, coverage policy development, and pricing negotiations.

Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
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.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to strict allergen avoidance, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to strict allergen avoidance, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

5.1 Potential Other Benefits

Both AR101 and Viaskin Peanut have the potential to reduce the economic disparities that lead to higher emergency department visits and hospitalization in patients from low income households if they are given access to these therapies.

Viaskin Peanut uses a novel mechanism of action by delivering immunotherapy transcutaneously. Prior immunotherapy approaches have been oral, sublingual, or subcutaneous.

There are inadequate data to assess whether these therapies will reduce caregiver psychosocial burden, physical burden, and anxiety, as well as improve quality of life and productivity, though both therapies have the potential to do so.

5.2 Contextual Considerations

Both AR101 and Viaskin Peanut will be the first therapies approved by the FDA to treat peanut allergy. The current method to manage peanut allergy is avoidance, which is not treatment and can result in potentially life-threatening accidental exposure to peanut allergens.

Peanut allergy has a significant, lifelong impact on patients' and families and caregivers' quality of life and these therapies have the potential to improve their quality of life.

There is significant uncertainty about the long-term risks and benefits for both therapies as the placebo-controlled comparisons are only one year in length and the data from the extension trials are sparse.

6. Value-Based Price Benchmarks

Value-based price benchmarks will be included in the revised Evidence Report that will be released on/about May 28, 2019.

7. Potential Budget Impact

7.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impact of AR101 and Viaskin Peanut in children with peanut allergy, ages four to 17 years and ages four to 11 years, respectively. We calculated the budget impact using the prices to achieve willingness-to-pay (WTP) thresholds between $50,000 to $150,000 per QALY gained. As in the cost-effectiveness analysis, we also used placeholder prices from publicly available analysts' estimates. We assumed a placeholder price of $350 per month for AR101 (i.e., $6,595 for months 1-6 including clinical visits for dose escalation; $4,200 per year thereafter).[59] For Viaskin Peanut, we assumed a placeholder price of $6,500 per year.[59] Note that these placeholder prices for both AR101 and Viaskin Peanut may not reflect the actual prices at launch, and therefore the actual budget impact of these technologies may differ from our estimates.

7.2 Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new technology, rather than relevant existing treatments, for the eligible population in this indication, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. We assumed that all children ages four to 17 years with peanut allergy would be eligible for AR101, and that all children ages four to 11 years with peanut allergy would be eligible for Viaskin Peanut, based on the trial populations. All costs were undiscounted and estimated over a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of children eligible for these technologies.

For AR101, the potential budget impact analysis included children ages four to 17 years with peanut allergy. To estimate the size of the potential population for our budget impact analysis, we first used an estimate of the prevalence (2%) of peanut allergy in children from the guidelines for the prevention of peanut allergy in the United States.[25] We then applied this estimate to the projected 2019 to 2023 US population estimates for children ages four to 17 years to derive the average population over the next five years. This resulted in an eligible population size for AR101 of 1,152,930 children over five years, or an estimated 230,586 children each year.

For Viaskin Peanut, the potential budget impact analysis included children ages four to 11 years with peanut allergy. We used the same estimate of the prevalence (2%) of peanut allergy in children from the guidelines for the prevention of peanut allergy in the United States.[25] We then

applied this estimate to the projected 2019 to 2023 US population estimates for children ages four to 11 years to derive the average population over the next five years. This resulted in an eligible population size for Viaskin Peanut of approximately 650,480 children over five years, or an estimated 130,096 children each year.

ICER's methods for estimating potential budget impact are described in detail elsewhere[71] and have been recently updated. The intent of our revised approach to budgetary impact is to document the percentage of patients who could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. For 2018-19, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $991 million per year for new drugs.

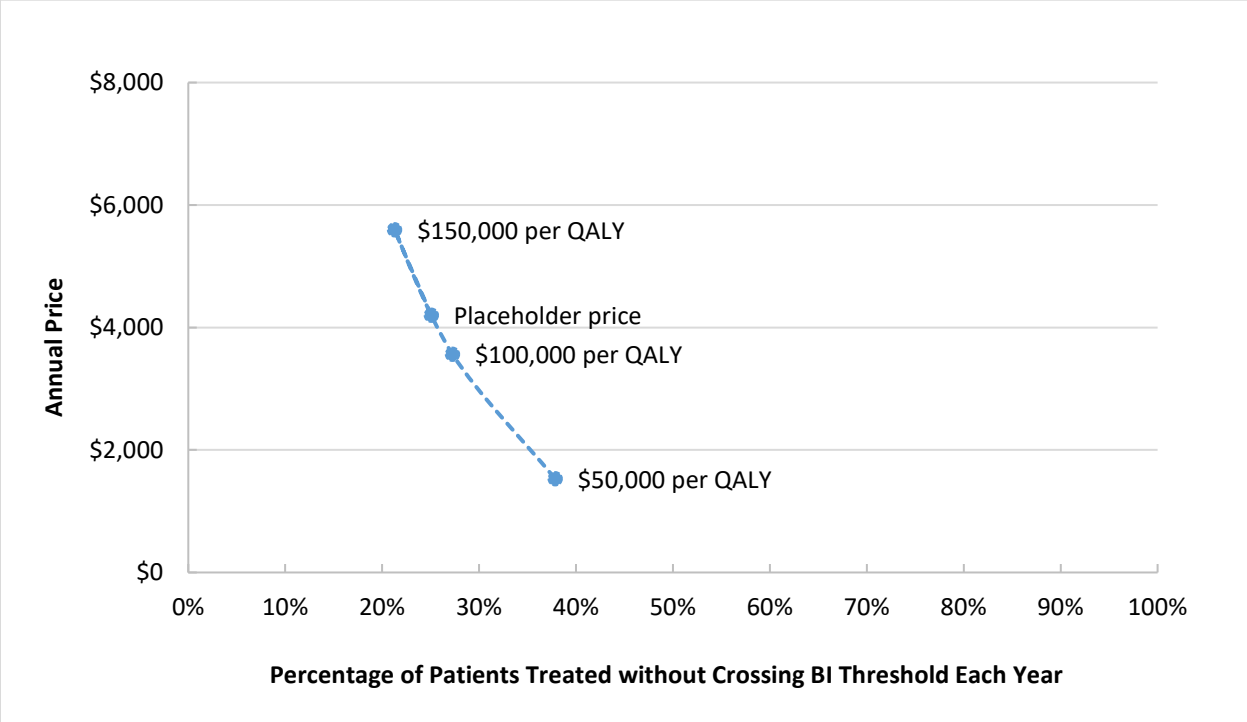
To estimate potential budget impact, we evaluate a new therapy that would take market share from one or more existing therapies/treatments and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. For this analysis, we evaluated the potential budget impact of AR101 and Viaskin Peanut, each compared to avoidance in children with peanut allergy. For each treatment, we assumed equal uptake over five years (20% each year), with treatment duration ranging from one year (for the year-five cohort) to five years (for the year-one cohort). In other words, patients initiating therapy in year one would accrue all drug costs and cost offsets over the full five years, but those initiating in other years would only accrue a proportional amount of five-year costs.

7.3 Results

For AR101, per-patient budget impact calculations are based on the placeholder price of $4,200 per year and the prices to reach $150,000, $100,000, and $50,000 per QALY thresholds ($5,599, $3,564, and $1,530 per year, respectively). The average five-year annualized potential budgetary impact when using the placeholder price was approximately $6,800 per patient. The average five-year annualized potential budgetary impact at the three cost-effectiveness threshold prices ranged from approximately $7,900 per patient using the annual price to achieve $150,000 per QALY to approximately $4,800 using the annual price to achieve a $50,000 per QALY cost-effectiveness threshold.

As shown in Figure 7.1, approximately 25% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $991 million at the placeholder price ($4,200/year). Approximately 38%, 27% and 21% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000, $100,000, and $50,000 per QALY threshold prices (at $5,599, $3,564, and $1,530 per year, respectively).

Figure 7.1. Budget Impact of AR101 at Placeholder* and Threshold Prices



*Placeholder price is used until list or net prices become available.

For Viaskin Peanut, per-patient budget impact calculations were based on the placeholder price ($6,500 per year) and the prices to reach $150,000, $100,000, and $50,000 per QALY thresholds ($3,764, $2,512 and $1,259 per year, respectively). Across the five-year timeframe, the weighted annualized potential budgetary impact (i.e., adjusted for differing periods of drug utilization and associated cost offsets) when using the placeholder price was approximately $4,100 per patient. The average five-year annualized potential budgetary impact at the three cost-effectiveness threshold prices ranged from approximately $2,400 per patient using the annual price to achieve $150,000 per QALY to approximately $790 using the annual price to achieve a $50,000 per QALY cost-effectiveness threshold.

At the placeholder price ($6,500/year) for Viaskin Peanut, approximately 71% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $991 million. Despite the assumption of a higher placeholder price for Viaskin Peanut, more patients could be treated than with AR101, largely due to AR101's higher administration and monitoring costs in the first year of treatment. As shown in Table 7.1, the annual potential budgetary impact of treating the entire eligible population over five years did not exceed the $991 million ICER budget impact threshold at the prices to achieve $150,000, $100,000, and $50,000 per QALY, reaching 81%, 54%, and 27% of the budget impact threshold, respectively.

Table 7.1. Budget Impact of Viaskin Peanut at Threshold Prices

	Viaskin Peanut Percent of Budget Impact Threshold
$150,000 per QALY Threshold Price	81%
$100,000 per QALY Threshold Price	54%
$50,000 per QALY Threshold Price	27%

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This is the first ICER review of oral immunotherapy and Viaskin Peanut for peanut allergy.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.

Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of Bias Across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of Bias within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Search Strategies for Peanut Allergy

Table A2. Search Strategy of MEDLINE 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials

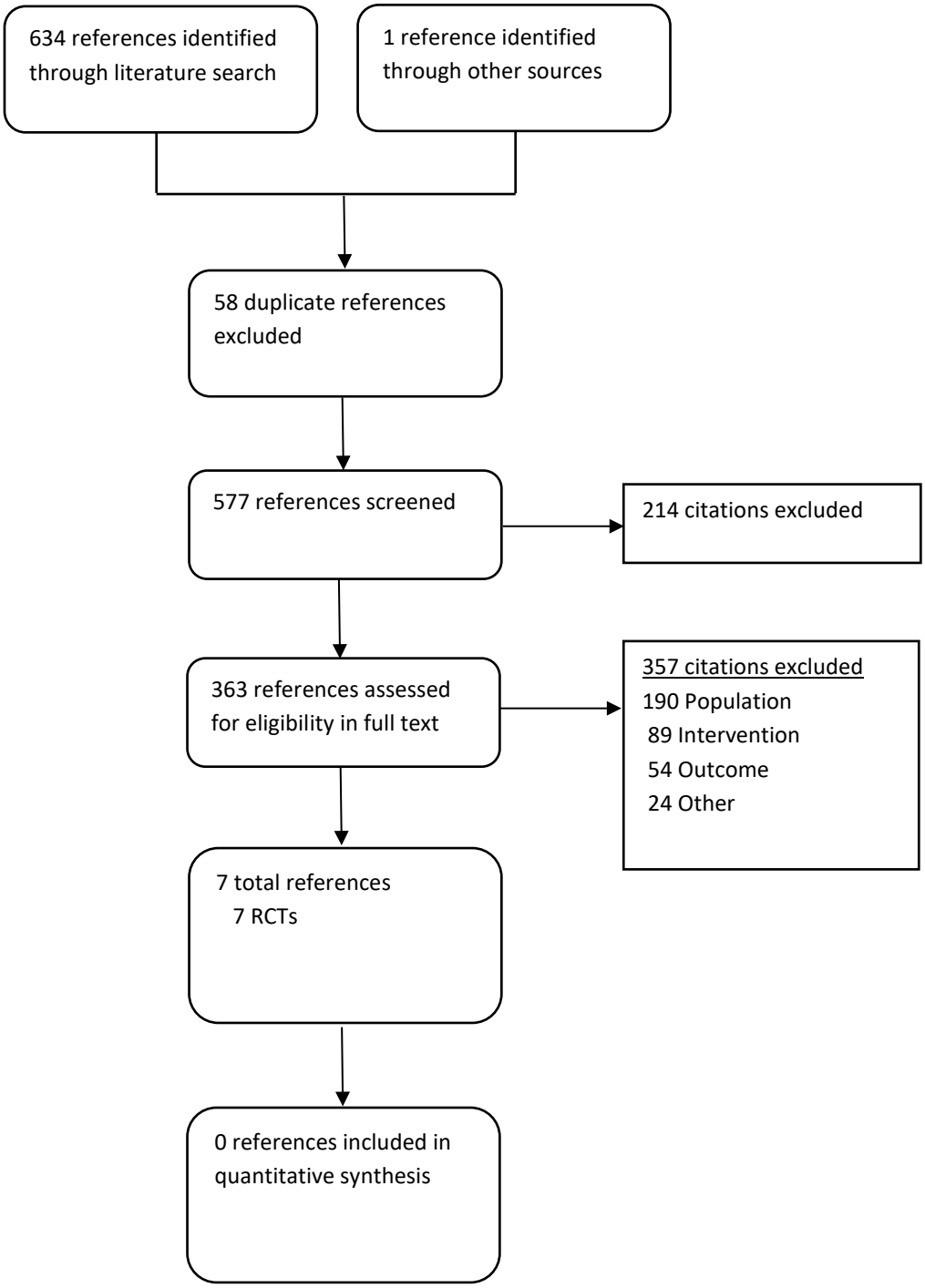
No.	Search Terms
#1	Exp peanut hypersensitivity/ or exp peanut allergy/
#2	(peanut* or groundnut* or arachis hypogaea).ti,ab.
#3	(allerg* or hypersen*).ti,ab.
#4	(peanut* and allerg*).ti,ab.
#5	(peanut-allerg* or peanut allerg* or peanut-hypersen* peanut hypersen* or groundnut-allerg* or groundnut-hypersen* or groundnut allerg* or groundnut hypersen* or arachis hypogaea allergy or legume-allerg* or legume-hypersen*).ti,ab.
#6	((peanut* adj2 allerg*) or (peanut* adj2 hypersen*) or (groundnut* adj2 allerg*) or (groundnut* adj2 hypersen*) or (legume* adj2 allerg*) or (legume* adj2 hypersen*)).ti,ab
#7	(viaskin or 'dbv712' or 'dbv 712' or 'dbv-712').ti,ab
#8	('ar101' or 'ar 101' or 'ar-101').ti,ab.
#9	('arc-101' or 'arc 101' or 'acr101').ti,ab.
#10	('viaskin peanut' or 'peanut patch' or 'peanut-patch').mp.
#11	exp immunotherapy/
#12	('oral immune tolerance' or 'oral tolerance').ti,ab.
#13	2 and 3
#14	1 or 13
#15	4 or 5 or 6 or 10
#16	7 or 8 or 9
#17	11 or 12
#18	14 and 17
#19	15 and 16
#20	18 or 19
#21	(clinical trial or clinical trial, phase I or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or multicenter study or randomized controlled trial).pt. or double-blind method/ or clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or early termination of clinical trials as topic/ or multicenter studies as topic/ or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab,kw. or (4 arm or four arm).ti,ab,kw.
#22	cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab. or case-control studies/ or control groups/ or matched-pair analysis/ or retrospective studies/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab,kw.
#23	21 or 22
#24	20 or 23
#25	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or

	in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt.
#26	24 not 25

Table A3. Search Strategy of EMBASE Search

No.	Search Term
#1	'peanut allergy' /exp
#2	'peanut' and (allerg* OR hypersens*)
#3	'oral immune tolerance' OR 'oit' OR 'oral tolerance' OR 'immune tolerance' OR 'immunological tolerance
#4	'dvb712' OR 'dbv 712' OR 'dbv-712'
#5	'viaskin' OR 'viaskin peanut'
#6	'transdermal patch' OR 'viaskin peanut'
#7	'viaskin' AND 'patch'
#8	'ar-101' or 'ar 101' or 'ar101'
#9	'arc-101' OR 'arc 101' OR 'arc101'
#10	1 OR 2
#11	3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
#12	10 AND 11
#13	'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it
#14	12 NOT 13

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Viaskin Peanut, AR101, and Other OIT for Peanut Allergy



Appendix B. Previous Systematic Reviews and Technology Assessments

We identified one systematic review for the treatment of Peanut Allergy summarized below.

Nurmatov, U., et al. (2012). "Allergen-Specific Oral Immunotherapy for Peanut Allergy." Cochrane Database for Systematic Reviews.[72]

Cochrane conducted a systematic review to evaluate the current treatments for peanut allergy. Only one trial matched their inclusion criteria and was summarized in the review. The US-based study, Varshney 2011, enrolled 28 children ages one to 16 years who had a clinical history of peanut allergy. Patients with a history of severe peanut anaphylaxis and moderate-to-severe persistent asthma were excluded from the study. Patients were randomized to receive either peanut flour (n=19) or oat flour placebo (n=9). Dosing began on day one with an escalation of 0.1 mg of peanut flour, doubled every 30 minutes until 6 mg was reached or the patient showed symptoms. Day two started at the dose reached during day one, and continued to be ingested daily in food, with dose escalation occurring every two weeks (50 to 100% increase until 75 mg dose, 25-33% increase until 400 mg maintenance dose). The primary endpoint, tolerating the maximum cumulative dose (5,000 mg) in a double-blind, placebo-controlled food challenge, was achieved by 16 participants in the intervention arm and no participants in the placebo arm. Three of the 19 participants in the intervention arm withdrew from the study. Two participants failed the dose escalation phase and one additional patient withdrew due to gastrointestinal symptoms. Nine (47%) of the patients in the intervention arm experienced treatment-related adverse events during the initial day one escalation. At the end of study oral food challenge (OFC), one participant in the peanut flour arm showed upper respiratory symptoms and moderate urticaria. The reviewers note that the limited evidence based makes it difficult to inform care decisions, and with safety concerns there may be limited applicability of the evidence. The small trial size may also affect external validity and there was no evidence found on the management of treatment for peanut allergy in adults.

Note: the trial that met criteria for this Cochrane review, did not meet the inclusion trial for the ICER review because the age range included patients younger than those in the scope of the ICER review.

Appendix C. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
AR101					
ARTEMIS Peanut Allergy in Children Aimmune Therapeutics, Inc. NCT03201003	Phase III, randomized, parallel assignment, quadruple masking Study Duration: 9 -14 months Estimated enrollment : 175	Intervention : AR101	Inclusions: 4-17 years Clinical history of allergy to peanuts Serum SPT > 3 mm greater than control Dose limiting symptoms at or before 444 mg peanut protein at the screening DBPCFC Exclusions: History of cardiovascular disease History of severe or life-threatening episode of anaphylaxis History of eosinophilic esophagitis History of mass cell disorder Any other condition that precludes participation for reasons of safety	Primary Outcome Efficacy of AR101 : proportion of subjects who tolerate specified challenge doses with on AEs of mild severity at the exit DBPCFC.	Press Release Announcing results (March 2019)[73]

AR101 Real-World Open-Label Extension Study Aimmune Therapeutic, Inc. NCT03337542	Phase III, multicenter, open-label, long-term, safety extension, single group assessment Study Duration: 6 months Estimated Enrollment: 330	Intervention: AR101	Inclusion Criteria Received AR101 in study ARC007 Completed ARC007 study Use of effective birth control by sexually active female subjects of childbearing age Exclusion Criteria Developed a clinically significant change in health status during the ARC007 study Receiving prohibited medication or anticipated use of prohibited medication Currently in the buildup phase of immunotherapy for any nonfood allergen Currently participating in any other interventional clinical study outside of the ARC007 study that was just completed	Primary Outcomes Incidence of treatment-emergent adverse events including serious adverse events during the overall study period	April 2019
PALISADE Follow-On Study (ARC004) Aimmune Therapeutics, Inc. NCT02993107	Phase III, international, multicenter, open-label, 2 arm follow-on study Study Duration: 9 – 14 months Estimated enrollment : 500	Intervention : AR101	Inclusion Criteria Completion of the ARC003 study Written informed consent Effective birth control Exclusion Criteria Early discontinuation from the ARC003 trial Meets any longitudinally applicable ARC003 study exclusion criteria (Group 2 only) failure to tolerate > 443 mg cumulative peanut protein with no or mild symptoms in ARC003 study exit DBPC	Primary Outcomes Incidence of adverse events including serious adverse events	December 2020

Study in Pediatric Subjects with Peanut Allergy to Evaluate the safety and Efficacy of Dupilumab as Adjunct to AR101 Sanofi Aimmune Therapeutics, Inc. NCT03682770	Phase II, randomized, parallel assignment, quadruple masking Study Duration: 28 weeks Estimated enrollment : 156	Arm 1: Dupilumab + AR101 Arm 2: Placebo + AR101	Inclusion Criteria Experience dose-limiting symptoms at or before the challenge dose of peanut protein on screening and not experiencing dose-limiting symptoms to placebo Serum Immunoglobulin E (IgE) to peanut of ≥24 kUA/L and/or a skin prick test (SPT) to peanut ≥10 mm compared to a negative control Participants with other known food allergies must agree to eliminate these other food items from their diet so as not to confound the safety and efficacy data from the study Exclusion Criteria History of other chronic disease (other than asthma, Atopic Dermatitis (AD), or allergic rhinitis) History of frequent or recent severe, life-threatening episode of anaphylaxis or anaphylactic shock Asthma at time of enrollment Use of systemic corticosteroids within 2 months prior to screening	Primary Outcomes Change in cumulative tolerated dose of peanut protein Proportion of participants treated with Dupilumab plus AR101 vs. placebo plus AR101 who reach the dose of AR101 Patients who "pass" DBPCFC Percent change in peanut specific IgE Proportion of participants experiences mild, moderate, or severe symptoms	March 2021
Peanut Oral Immunotherapy Study of Early Intervention for Desensitization Aimmune Therapeutics, Inc. NCT03736447	Phase III, randomized, parallel alignment, triple masking Study Duration: Estimated Enrollment: 105	Intervention: AR101	Inclusion Criteria Aged 1 to < 4 years at randomization Written informed consent Documented history of physician-diagnosed IgE mediated peanut allergy Exclusion Criteria History of severe or life-threatening anaphylaxis History of hemodynamically significant cardiovascular or renovascular disease Moderate or severe asthma Mild asthma that is uncontrolled	Primary Outcomes The proportion of subjects treated with AR101 compared with placebo who tolerate at least 600 mg single dose peanut protein with no more than mild allergy symptoms at the exit DBPCFC.	November 2021

Long-term Safety Study of AR101 in Subjects who Participated in a Prior AR101 study (ARC008) Aimmune Therapeutics, Inc. NCT03292484	Multicenter, open-label, long-term safety study Study Duration: 3 years Estimated Enrollment : 1100	Intervention: AR101	Inclusion Criteria Prior participation in an Aimmune AR101 clinical study that identifies ARC008 a follow-on study option in the protocol Written informed consent Use of effective Birth control Exclusion Criteria Did not complete a minimum of 3 months of AR101 maintenance therapy if the subject was assigned to AR101 in the parent study Early discontinuing from the parent study Currently receiving or received within 5 years prior to screening any time of peanut or other food allergen immunotherapy.	Primary Outcome The frequency of treatment-related adverse events and serious adverse events during the overall study period	December 2021
Viaskin Peanut					
Safety and Efficacy Study of Viaskin Peanut in Peanut-Allergic young children 1-3 years of age (EPITOPE) DBV Technologies NCT03211247	Phase 3, randomized, parallel assignment, triple masking Study Duration: 12 months Estimated enrollment: 331	Arm 1 Viaskin Peanut 250 mcg Arm 2: Viaskin Peanut 100 mcg Arm 3: Placebo	Inclusion Criteria Male or female 1-3 years of age Physician-diagnosed peanut allergy Peanut specific IgE level >0.7 kU/L Positive peanut SPT with a largest wheel diameter ≥6mm Positive DBPCFC at ≤300 mg peanut protein Exclusion Criteria Uncontrolled asthma History of severe anaphylaxis to peanut Prior immunotherapy to any food or other immunotherapy Generalized severe dermatologic disease	Differences between the percentage of treatment responders in the selected active Viaskin Peanut group compared to the placebo group	May 30, 20202

Follow-up of the EPITOPE Study to Evaluate Long-Term Efficacy and Safety of DBV712 in Young Children (EPOPEX) DBV Technologies NCT03859700	Phase 3, single group, open-label Study Duration: 32 months Estimated enrollment: 330	Intervention: DBV712 250 mcg	Inclusion Criteria Completion of the EPITOPE study Exclusion Criteria Generalized dermatologic disease Diagnosis of asthma that evolved to severe, unstable, or uncontrolled asthma	Proportion of subjects reaching an ED ≥1000 mg in 12, 24, and 36 months	June 2023
Follow-up of the PEPITES Study to Evaluate Long-Term Efficacy and Safety of Viaskin Peanut in Children (PEOPLE) DBV Technologies NCT03013517	Phase 3, single group, open-label Study Duration: 24 months Estimated enrollment: 300	Intervention: Viaskin Peanut 250ug	Inclusion Criteria Subjects who completed the PEPITES study Exclusion Criteria Generalized dermatologic disease extending widely on the skin and especially on the back or arms with no intact zones to apply the Viaskin patches Diagnosis of asthma that evolved to severe, unstable, or uncontrolled asthma	% of subjects originating from the active arm of PEPITES reaching an eliciting dose (ED) ≥ 1,000 mg after 24 months of additional treatment in PEOPLE	February 2020
Safety Study of Viaskin Peanut to Treat Peanut Allergy (REALISE) DBV Technologies NCT02916446	Phase 3, parallel assignment, triple masking Study Duration: 3 years Estimated enrollment: 393	Arm 1: Viaskin 250 mcg Arm 2: Placebo	Inclusion Criteria Physician-diagnosed peanut allergy A peanut skin prick test (SPT) with a wheal largest diameter ≥8 mm A peanut-specific immunoglobulin E (IgE) ≥ 12 kU/L Subjects follow a strict peanut-free diet Exclusion Criteria Generalized dermatologic disease Spirometry forced expiratory volume in second <80% receiving beta-blocking agents, angiotensin-converting enzyme inhibitors etc. Prior or concomitant history of an immunotherapy to any food allergy	Adverse events (AEs), treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)	September 22, 2017 (Last Update posted: February 21, 2019)

Other					
The Grown-Up Peanut Immunotherapy Study (GUPI) Guy's and St. Thomas' NHS Foundation Trust NCT03648320	Phase 2, single arm, open-label Study Duration: 7 – 8 months Estimated Enrollment: 40	Intervention: Peanut oral immunotherapy - daily dose of peanut flour	Inclusion Criteria Adults aged 18-40 years A positive skin prick test to peanut abstract Elevated (>0.35) serum specific Immunoglobulin (IgE) to Ara h 2 major peanut allergen Positive DBPCFC to 30mg or less of peanut protein Well controlled asthma Exclusion Criteria Anaphylaxis to food other than peanut History of life-threatening anaphylaxis or angioedema Asthmatic treated with higher than moderate dose of ICS Any asthmatic if uncontrolled or difficult to control Non-adherence with asthma treatment from general practitioner Participants who react to placebo during DBPCFC On-going use of beta-blockers Regular use of NSAIDs for a chronic condition	Tolerance of cumulative dose of 1.4g peanut protein without reaction on DBPCFC post OIT after minimum of 1-month maintenance dosing on peanut OIT	September 30, 2020

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2)[31] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

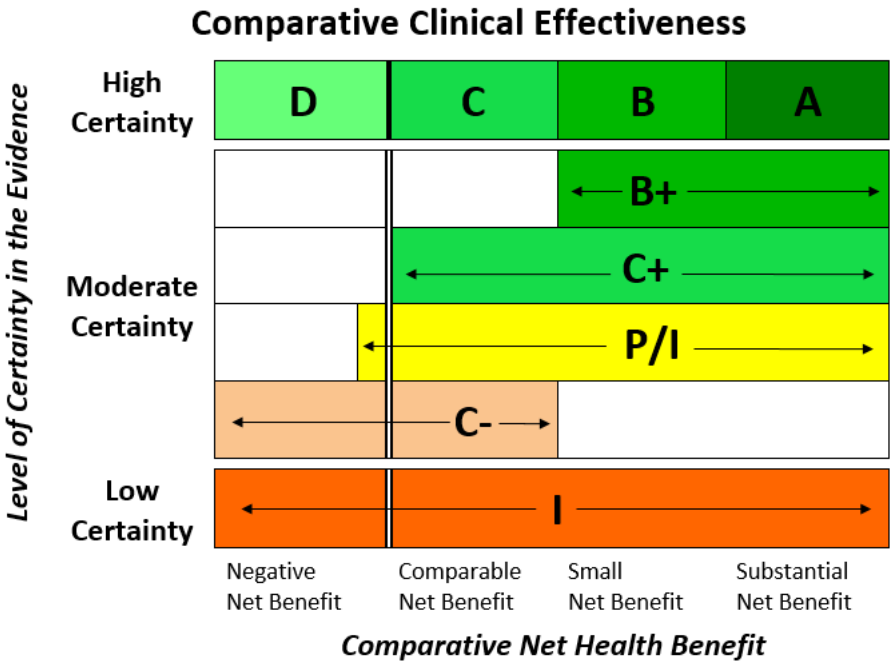
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[32]

Figure D1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable"*- High certainty of a comparable net health benefit*
D = "Negative"*- High certainty of an inferior net health benefit*
B+ = "Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C- = "Comparable or Inferior" *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
I = "Insufficient" *- Any situation in which the level of certainty in the evidence is low*

Table D1. Study Quality Metrics

Quality										
Study	**Comparable Groups**	**Adequate Randomization**	**Adequate Concealment**	**Patient Blinding**	**Physician Blinding**	**Outcome Adjudication Blinding**	**Non-Differential Follow-Up**	**ITT Analysis**	**Handling of Missing Data**	**Overall Quality**
AR101/Aimmune										
Bird 2017	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
PALISADE 2018[34] (age 4-17)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
PALISADE 2018[34] Age 18-55	--	--	--	--	--	--	--	--	PALISADE 2018 Age 18-55	--
Viaskin Peanut/DBV Technologies										
Jones, 2016[36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Sampson, 2017[37]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Fleischer 2019[74] PEPITES										
Other Oral Immunotherapy										
Anagnostou, 2014[55] STOP II	Yes	Yes	Yes	No	No	No	No	No	No	Poor
Reier-Nilsen, 2018[75]	Yes	Yes	No	No	No	No	No	No	No	Poor

Supplemental Data

Table D2. Study Design

Author, Journal Year	Phase	Funding	Total Follow-Up (Weeks)	Primary Outcome	Inclusion Criteria (List Subgroups)	Exclusion Criteria
AR101/Aimmune						
Bird 2017[33]	2	Industry	6-9 months	The response rate, defined as the proportion of subjects who were able to successfully consume a single dose of ≥300 mg of peanut protein with no dose-limiting symptoms	Subjects aged 4 – 26 with a clinical history of peanut allergy and either serum peanut-specific IgE ≥0.35 kU/L or peanut skin prick test wheel diameter ≥3 mm	History of frequent or repeated, sever or life-threatening anaphylaxis, Gi disease or sever or uncontrolled asthma.
PALISADE, 2018[34] (age 4-17)	3	Industry	48-68 weeks	Proportion of participants 4 to 17 years of age who could ingest a challenge dose of 600 mg or more, without dose-limiting symptoms.	Peanut allergy age 4-17, serum IgE level at least 0.35 kUA per liter, mean wheal diameter at least 3 mm larger than negative control, allergic reaction to no more than 100 mg peanut protein	Clinical history of a severe anaphylactic reaction known or suspected to be caused by ingestion of peanut that required treatment with 2 or more administrations of epinephrine or hospitalization, moderate or severe asthma, poorly controlled asthma, diagnosis of other severe or complicating medical problems.
PALISADE, 2018[34] (age 18-55)	3	Industry	48-68 weeks	Proportion of participants 18 to 55 years of age who could ingest a challenge dose of 600 mg or more, without dose-limiting symptoms.	Peanut allergy age 18-55, serum IgE level at least 0.35 kUA per liter, mean wheal diameter at least 3 mm larger than negative control, allergic reaction to no more than 100 mg peanut protein	Clinical history of a severe anaphylactic reaction known or suspected to be caused by ingestion of peanut that required treatment with 2 or more administrations of epinephrine or hospitalization, moderate or severe asthma, poorly controlled asthma, diagnosis of other severe or complicating medical problems.

Author, Journal Year	Phase	Funding	Total Follow-Up (Weeks)	Primary Outcome	Inclusion Criteria (List Subgroups)	Exclusion Criteria
Viaskin Peanut/DBV Technologies						
Jones, 2016[36]	2	NIH and DBV technologies	52 weeks	Proportion of participants with a successful outcome after 52 weeks defined as either passing a double-blind, placebo-controlled food challenge with 5044 mg of peanut protein at week 52 or by a 10-fold or greater increase in successfully consumed dose (SCD) of peanut protein compared with the baseline OFC.	Age 4-25 and physician diagnosed peanut allergy or convincing clinical history of peanut allergy and response to peanut (≥3 mm greater than control) or peanut specific IgE >.35 kU/l and positive baseline OFC result to a cumulative dose of 1044 mg or less of peanut protein	Severe anaphylaxis (previous hypotension, neurologic compromise or mechanical ventilation) to peanut; severe or poorly controlled atopic dermatitis or Severe asthma (2017 NHLBI criteria steps 5 or 6; mild to moderate asthma that is uncontrolled or difficult to control (FEV 1 <80% predicted or FEV1/FVC <75% with or without controller OR inhaled ICS >500 mcg fluticasone or one asthma hospitalization in the past year or ER visit in past 6 months , steroids for more than a month in past year or burst within past 3 months OR inability to discontinue antihistamines OR other chronic disease
Sampson, 2017[37]	2b	DBV technologies Industry	12 months (2-year open label extension)	Percentage of treatment responders (1000mg or more initial dose at exit food challenge and/or 10-times or greater eliciting dose) after 12 months of therapy	Peanut allergy age 6-55; peanut skin prick test wheal 8 mm or greater; peanut specific IgE level >0.7 Ku/L and eliciting dose of 300 mg or less of peanut protein	chronic disease, unstable asthma, and Severe anaphylaxis to peanut
Fleischer 2019[74] PEPITES	3	DBV technologies Industry	12-month treatment + 2-week follow-up	Response (post-treatment eliciting dose of 300 mg or more or 1000 mg or more of peanut protein for low or high groups respectively) rate difference between active and placebo treatment groups after 12 months	Age 4-11 years with a physician diagnosis of peanut allergy or well documented medical history of IgE-medicated symptoms. Peanut specific IgE level >0.7kU/L	History of severe anaphylaxis to peanut with any of the following symptoms: hypotension, hypoxia, neurological compromise. Uncontrolled persistent asthma.

Author, Journal Year	Phase	Funding	Total Follow-Up (Weeks)	Primary Outcome	Inclusion Criteria (List Subgroups)	Exclusion Criteria
Other Oral Immunotherapy						
Anagnostou, 2014[38]	2	Medical Research Council National Institute for Health Research	26 weeks	Proportion of desensitized (no reaction during peanut DBPCFC with cumulative dose of 1400 mg peanut protein) participants in each group at the end of the first phase	7-16 with immediate hypersensitivity reaction after peanut ingestion, positive skin prick test to peanuts and positive by double blind placebo-controlled food challenge	major chronic illness (except eczema, rhinitis, or asthma) , care provider or present household member had suspected or diagnosed allergy to peanuts, unwillingness, or inability to comply with study procedures (those with severe asthma, tree nut allergy or previous life threatening reaction not excluded)
Reier-Nilsen, 2018[75]	3	Foundations and Norwegian Health Authority	--	Feasibility of reaching MMD, defined as the proportion of children who reached the predefined MMD of 5000 mg peanut protein.	Age 5-15 with history of systemic reaction to peanut and or sensitization to peanut by a peanut skin prick test ≥3 mm or a peanut IgE≥0.35 kUA/L	Uncontrolled asthma or sever chronic disease

Table D3. Baseline Characteristics

Author, Year	Intervention	N	Age, Mean (SD) or Median [IQR]	Male, n (%)	Median Size Average Wheal on Skin Prick Testing [IQR} (mm)	Median Level of Peanut Specific IGE kUA/liter	Median Maximum Tolerated Dose of Peanut Protein [OQR] mg	History of Peanut Anaphylaxis no (%)	Previous or Current Asthma no (%)	Multiple Food Allergies no (%)	Lost to Follow Up n (%)
AR101/Aimmune											
Bird 2017[33]	AR101	29	7 y (4-21)	20 (69)	14 (5-30)	63.4	13 (3-43)	15 (52)	12 (41)	7 (24) other food, drug	NR
	Placebo	26	8 y (4-14)	16 (62)	13 (5-26)	100.0	28 (3-43)	15 (56)	11 (41)	4 (15) other food, drug	NR
PALISADE, 2018[34] (age 4-17)	AR101 in escalating dose program to achieve 300 mg per day for 24 weeks	372	--	208 (56%)	11 (9,.0, 14.0)	69	10 mg (3-30)	72	53.8	64.6	21.00%
	placebo	124	--	76 (61%)	12 (9.0, 15.0)	75	10 mg (3-30)	72	55.8	65.2	7.30%
PALISADE, 2018[34] (age 18-55)	AR101 in escalating dose program to achieve 300 mg per day for 24 weeks	42	--	--	--	--	--	74.30%	--	--	9.50%
	placebo	14	--	--	--	--	--	72.50%	--	--	0%

Author, Year	Intervention	N	Age, Mean (SD) or Median [IQR]	Male, n (%)	Median Size Average Wheal on Skin Prick Testing [IQR} (mm)	Median Level of Peanut Specific IGE kUA/liter	Median Maximum Tolerated Dose of Peanut Protein [OQR] mg	History of Peanut Anaphylaxis no (%)	Previous or Current Asthma no (%)	Multiple Food Allergies no (%)	Lost to Follow Up n (%)
Viaskin/DBV Technologies											
Jones, 2016[36]	Epicutaneous peanut patch 100 MCG	24	8.4 (4.1, 16.6)	58%	11.8 (4.5,32)	84.6	44 mg	only severe excluded	16 (66.7%)	20 (80%)	0
	Epicutaneous peanut patch Peanut 250 MCG	25	7.7 (4.2,14.4)	64%	12.5 (6.0,25.5)	92.1	14 mg	NR	13 (52%)	21 (87.5%)	0
	placebo	25	8.5 (4.8, 20.3)	64%	13.5 (3,29.5)	58	44 mg	NR	12 (48%)	20 (80%)	1 (4%)
Sampson, 2017[37]	Epicutaneous peanut patch 50 MCG (daily for 12 months)	53	10 [8.0,16.0]	31 (58.5%)	12.0 [9.5, 15.0]	83	100 mg	0	NR	NR	0
	Epicutaneous peanut patch 100 Mcg (daily for 12 months)	56	12 [10.0,17.0]	33 (58.9%	11.6 [9.0,13.8]	66.1	100 mg	0	NR	NR	1
	Epicutaneous peanut patch 250 mcg (daily for 12 months)	56	11.5 [9.0, 16.0]	38 (67.9%)	12.0 [10.0, 13.3]	79.9	100 mg	0	NR	NR	0
	placebo (daily for 12 months)	56	11 [8.7, 14.0]	36 (64.3%	11.0 [9.5, 13.3]	68.5	100 mg	0	NR	NR	0
PEPITES 2019[74]	Peanut Patch	238	7 (6,9)	149 (62.6)	NR	77.9 (20,192)	NR	NR	117 (49.2)	205 (86.1)	3

Author, Year	Intervention	N	Age, Mean (SD) or Median [IQR]	Male, n (%)	Median Size Average Wheal on Skin Prick Testing [IQR} (mm)	Median Level of Peanut Specific IGE kUA/liter	Median Maximum Tolerated Dose of Peanut Protein [OQR] mg	History of Peanut Anaphylaxis no (%)	Previous or Current Asthma no (%)	Multiple Food Allergies no (%)	Lost to Follow Up n (%)
	Placebo Patch	118	7 (5,9)	69 (58.5)	NR	101 (29.1, 232)	NR	NR	52 (44.1)	100 (84.7)	3
	Placebo	12	5.8	100%	7 (5.5,13)	57	NR	NR	78%	89%	0
Other OIT											
Anagnostou, 2014[55]	oral immunotherapy in up dosing phase to achieve 800 mg daily	49	12.4 (2.2)	34 (69%) %	8.92 (3.02)	37.9	151.9	NR	29 (59%)	10 (20%)	0
	Placebo	50	11.9 (2.67)	36 (72%) %	8.43 (3.08)	41.6	99.8	NR	29 (58%)	13 (26%)	0
	Placebo SLOT/active ORIT up to 2000 mg peanut protein/day	11	11.1 (7.2,12.4)	64%	12 (7.5,19)	169	21 mg	6/11 (55%)	9/11 (82%)	10/11 (91%)	NR
Reier-Nilsen, 2018[75]	OIT with biweekly step up to goal of 5000 mg	57	10.1 (5.2,15.2)	31 (54%)	9.8 (8.6, 11.0)	110.6	18.4 mg	79%	42%	47%	NR
	Observation	20	8.9 (5.1,13.3)	13 (65^))	9.3 (7.4, 11.7)	52.2	5 mg	90%	45%	58%	NR

Table D4. Outcomes I

Author, Year	Intervention	N	Timepoint	Proportion of Participants who Could Tolerate Challenge Dose of 600 mg or More	Proportion of Participants who Could Tolerate 1400 mg Peanut Protein	Proportion of Patients who Could Tolerate Challenge ≥10 Times Increase and or Reaching ≥1000 mg
AR101						
Bird 2017[33]	AR101	29	6-9 months	62% ITT, 78% completer	NR	NR
	Placebo	26	6-9 months	NR	NR	NR
PALISADE 2018[34] (age 4-17)	AR101 in escalating dose program to achieve 300 mg	372	24 weeks	67.2%	NR	50.3%
	placebo	124	24 weeks	4.0%	NR	2.4%
PALISADE 2018[34] (age 18-55)	AR101 in escalating dose program to achieve 300 mg	42	24 weeks	41.5%	NR	NR
	placebo	14		14.3%	NR	NR
Viaskin /DBV Technologies						
Jones, 2016[36]	Epicutaneous peanut patch 100 MCG	24	12 months	NR	NR	NR
	Epicutaneous peanut patch250 MCG	25	12 months	NR	NR	NR
	placebo	25	12 months	NR	NR	NR
Sampson, 2017[37]	Epicutaneous peanut patch 50 MCG	53	12 months	NR	NR	45.3
	Epicutaneous peanut patch 100 Mcg	56		NR	NR	41.1
	Epicutaneous peanut patch 250 mcg	56		NR	NR	50.0
	placebo (daily for 12 months)	56		NR	NR	25
PEPITES 2019[74]	Peanut Patch	238	12 months	NR	NR	NR
	Placebo Patch	118		NR	NR	NR
	placebo	12	12 months	NR	NR	NR

Author, Year	Intervention	N	Timepoint	Proportion of Participants who Could Tolerate Challenge Dose of 600 mg or More	Proportion of Participants who Could Tolerate 1400 mg Peanut Protein	Proportion of Patients who Could Tolerate Challenge ≥10 Times Increase and or Reaching ≥1000 mg
Other OIT						
Anagnostou, 2014[55]	oral immunotherapy in up dosing phase to 800 mg daily	49	6 months	NR	62%	NR
	placebo	50		NR	0%	NR
	Placebo SLOT/active ORIT up to 2000 mg peanut protein/day	11		NR	NR	NR
Reier-Nilsen, 2018[75]	OIT with biweekly step up to goal of 5000 mg	57	time to reach MMD	NR	NR	NR
	Observation	20	time to reach MMC	NR	NR	NR

Table D5. Outcomes II

Author, Year	Intervention	N	Timepoint	Proportion of Patient Who Could Tolerate 5044 mg Peanut Challenge or ≥10-fold Increase from Baseline	Proportion of Patients Who Could Tolerate Daily Ingestion of 800 mg Peanut Protein Up to 26 weeks	Proportion Who Could Tolerate Maximum Dose 10-Fold Increase Compared with Baseline	Proportion of Participants who Could Reach Max Maintenance Dose of 5000 mg
AR101							
Bird 2017[33]	AR101	29	6-9 months	NR	NR	NR	NR
	Placebo	26	6-9 months	NR	NR	NR	NR
PALISADE 2018[34] (age 4-17)	AR101 in escalating dose program to achieve 300 mg per day	372	24 weeks	NR	NR	NR	NR
	placebo	124		NR	NR	NR	NR
PALISADE 2018[34] (age 18-55)	AR101 in escalating dose program to achieve 300 mg per day for 24 weeks	42	24 weeks	NR	NR	NR	NR
	placebo	14	24 weeks	NR	NR	NR	NR
Viaskin/DBV Technologies							
Jones, 2016[36]	Epicutaneous peanut patch 100 MCG	24	12 months	46.00%	NR	NR	NR
	Epicutaneous peanut patch 250 MCG	25		48%	NR	NR	NR
	placebo	25		12%	NR	NR	NR
Sampson, 2017[37]	Epicutaneous peanut patch 50 MCG	53	12 months	NR	NR	NR	NR
	Epicutaneous peanut patch 100 Mcg	56		NR	NR	NR	NR
	Epicutaneous peanut patch 250 mcg	56		NR	NR	NR	NR
	placebo	56		NR	NR	NR	NR
	Peanut Patch	238	12 months	NR	NR	NR	NR

Author, Year	Intervention	N	Timepoint	Proportion of Patient Who Could Tolerate 5044 mg Peanut Challenge or ≥10-fold Increase from Baseline	Proportion of Patients Who Could Tolerate Daily Ingestion of 800 mg Peanut Protein Up to 26 weeks	Proportion Who Could Tolerate Maximum Dose 10-Fold Increase Compared with Baseline	Proportion of Participants who Could Reach Max Maintenance Dose of 5000 mg
PEPITES, 2019[74]	Placebo Patch	118		NR	NR	NR	NR
Other OIT							
Anagnostou, 2014[55]	oral immunotherapy in up dosing phase to achieve 800 mg daily	49	6 months	NR	84%	NR	NR
	placebo	50	6 months	NR	0%	NR	NR
Reier-Nilsen, 2018[75]	OIT with biweekly step up to goal of 5000 mg	57	time to reach MMD	NR	NR	NR	21%
	Observation	20	time to reach MMC	NR	NR	NR	NA

Table D6. Outcomes III

Author, Year	Intervention	N	Timepoint	Percentage Reaching an Individual Maintenance Dose	Median Dose of Peanut Protein Ingested at End of Study	Maximum Severity of Symptoms during Exit Challenge Moderate (%)	Maximum Severity of Symptoms During Exit Challenge Severe (%)	Peanut Specific IgE
AR101								
Bird 2017[33]	AR101	29	6-9 months	23/29 (79)	218.15 (5.895)	3 (13) mild	NR	NR
	Placebo	26	6-9 months	5/26 (19)	32.30 (5.674)	≥1	10 (38)	NR
PALISADE 2018[34] (age 4-17)	AR101 in escalating dose program to achieve 300 mg per day for 24 weeks	372	24 weeks	NR	NR	25%	5%	NR
	placebo	124		NR	NR	59%	11%	NR
PALISADE 2018[34] (age 18-55)	AR101 in escalating dose program to achieve 300 mg per day for 24 weeks	42	24 weeks	NR	NR	NR	NR	NR
	placebo	14		NR	NR	NR	NR	NR
Viaskin /DBV Technologies								
Jones, 2016[36]	Epicutaneous peanut patch 100 MCG	24	12 months	NR	144mg	NR	NR	NR
	Epicutaneous peanut patch250 MCG	25		NR	144mg	NR	NR	NR
	placebo	25		NR	14 mg	NR	NR	NR
Sampson, 2017[37]	Epicutaneous peanut patch 50 MCG	53	12 months	NR	244 mg	NR	NR	NR
	Epicutaneous peanut patch 100 Mcg	56		NR	444 mg	NR	NR	NR
	Epicutaneous peanut patch 250 mcg	56		NR	444 mg	NR	NR	NR
	placebo	56		NR	144 mg	NR	NR	NR
PEPITES, 2019[74]	Peanut Patch	238	12 months	62.6		NR	NR	

Author, Year	Intervention	N	Timepoint	Percentage Reaching an Individual Maintenance Dose	Median Dose of Peanut Protein Ingested at End of Study	Maximum Severity of Symptoms during Exit Challenge Moderate (%)	Maximum Severity of Symptoms During Exit Challenge Severe (%)	Peanut Specific IgE
	Placebo Patch	118		28	297 mg (44, 444) median cumulative reactive dose difference	NR	NR	
Other OIT								
Anagnostou, 2014[55]	oral immunotherapy in up dosing phase to achieve 800 mg daily	49	6 months	NR	1400 mg (ag 6 months)	NR	NR	NR
	placebo	50	6 months	NR	5 mg (at 6 months)	NR	NR	NR
Reier-Nilsen, 2018[75]	OIT with biweekly step up to goal of 5000 mg	57	time to reach MMD	NR	NR	NR	NR	NR
	Observation	20	time to reach MMC	NR	NR	NR	NR	NR

Table D7. Safety I

Author, Year	N	Timepoint (Months)	ANY AE (%)	AE Mild (%)	AE Moderate (%)	AE Severe (%)
AR101						
Bird 2017[33]	29	6-9 months	28 (96.6)	96%	4%	NR
	26		22 (84.6)	94%	6%	NR
PALISADE 2018[34] (age 4-17)	372	24 weeks	98.7%	34.7%	59.7%	4.3%
	124		95.2%	50.0%	44,4%	0.8%
PALISADE 2018[34] (age 18-55)	--	--	--	--	--	--
Viaskin/DBV Technologies						
Jones, 2016[36]	24	12 months	68%	68%	0	0
	24		80%	72%	4%	0
	25		24%	36%	0	0
Sampson, 2017[37]	53	12 months	96.2%	NR	NR	3.8
	56		94.6%	NR	NR	17.9
	56		96.4%	NR	NR	14.3
	56		48.2%	NR	NR	7.1
PEPITES, 2019[74]	238	12 months	227 (95.4)	220 (92.4)	127 (53.4)	14 (5.9)
	118		105 (89)	97 (82.2)	53 (44.9)	2 (1.7)
Other OIT						
Anagnostou, 2014[55]	39	6 months	68%	68%	0	0
	46		80%	72%	4%	0
Reier-Nilsen, 2018[75]	57	time to reach max dose	time to reach max dose	98%	98.2%	38.6%
	20	NR	NR	n/a	NR	NR

Table D8. Safety II

Author, Year	Intervention	N	Timepoint (Months)	All-Cause Discontinuation, n (%)	AE Leading to Discontinuation, n (%)	Systemic Allergic Reaction (%)	Epinephrine Administered During Trial (%)	GI Symptom Related Withdrawal	Mild Treatment Emergent AE During Initial Escalation
AR101									
Bird 2017[33]	AR101	29	6-9 months	27 (93)	6 (NR)	26 (90) immune system	4 (screening); 2 (9) exit	66% (GI symptoms)	NR
	Placebo	26		12 (46)	0 (0)	10 (38) immune system	4 (screening), 11 (42) exit	27% (GI symptoms)	NR
PALISADE 2018[34] (age 4-17)	AR101 in escalating dose program to achieve 300 mg per day for 24 weeks	372	24 weeks	NR	11.6%	14.2%	14.0%	6.5%	45.7%
	placebo	124			2.4%	3.2%	6.5%	1.6%	26.8%
PALISADE 2018[34] (age 18-55)	--	--	--	--	--	--	--	--	--
Viaskin/DBV Technologies									
Jones, 2016[36]	Epicutaneous peanut patch 100 MCG	24	12 months	NR	13%	NR	NR	NR	NR
	Epicutaneous peanut patch 250 Mcg	24		NR	0%	NR	NR	NR	NR
	Placebo	25		NR	8%	NR	NR	NR	NR
Sampson, 2017[37]	Epicutaneous peanut patch 50 MCG	53	12 months	NR	0%	2/53 (4%)	NR	NR	NR
	Epicutaneous peanut patch 100 Mcg	56		NR	1.8%	0	NR	NR	NR

Author, Year	Intervention	N	Timepoint (Months)	All-Cause Discontinuation, n (%)	AE Leading to Discontinuation, n (%)	Systemic Allergic Reaction (%)	Epinephrine Administered During Trial (%)	GI Symptom Related Withdrawal	Mild Treatment Emergent AE During Initial Escalation
	Epicutaneous peanut patch 250 mcg	56		NR	0%	1/56 (2%)	NR	NR	NR
	placebo	56		NR	0	0	NR	NR	NR
PEPITES, 2019[74]	Peanut Patch	238	12 months	10.5%	4 (1.7)	NR	22 (9.2)	NR	NR
	Placebo Patch	118		9.3%	0 (0)	NR	4 (3.4)	NR	NR
Other OIT									
Anagnostou, 2014[55]	oral immunotherapy in up dosing phase to achieve 800 mg daily	39	6 months	NR	13%	NR	NR	NR	NR
	placebo	46		NR	0%	NR		NR	NR
Reier-Nilsen, 2018[75]	OIT with biweekly step up to goal of 5000 mg	57	time to reach max dose	24.5%	14/57 (25%)	6 (10.5%)	24.5%	NR	NR
	Observation	20		NR	NR	NR	NR	NR	NR

Table D9. Safety III

Author, Year	Intervention	N	Timepoint (Months)	Mild Treatment Related AE During Up-Dosing	Mild Treatment Related AE During Maintenance	Moderate Treatment Emergent AE During Initial Escalation	Moderate Treatment Related AE During up-Dosing
AR101							
Bird 2017[33]	AR101	29	6-9 months	NR	NR	NR	NR
	Placebo	26	6-9 months	NR	NR	NR	NR
PALISADE 2018[34] (age 4-17)	AR101 in escalating dose program to achieve 300 mg per day for 24 weeks	372	24 weeks	40.2%	51.9%	5.1%	53.8%
	placebo	124		56.1%	48/3%	2.4%	30.9%
PALISADE 2018[34] (age 18-55)	--	--	--	--	--	--	--
Viaskin/DBV Technologies							
Jones, 2016[36]	Epicutaneous peanut patch 100 MCG	24	12 months	NR	NR	NR	NR
	Epicutaneous peanut patch 250 Mcg	24		NR	NR	NR	NR
	Placebo	25		NR	NR	NR	NR
Sampson, 2017[37]	Epicutaneous peanut patch 50 MCG	53	12 months	NR	NR	NR	NR
	Epicutaneous peanut patch 100 Mcg	56		NR	NR	NR	NR
	Epicutaneous peanut patch 250 mcg	56		NR	NR	NR	NR
	placebo	56		NR	NR	NR	NR
PEPITES, 2019[74]	Peanut Patch	238	12 months	NR	NR	NR	NR
	Placebo Patch	118		NR	NR	NR	NR

Author, Year	Intervention	N	Timepoint (Months)	Mild Treatment Related AE During Up-Dosing	Mild Treatment Related AE During Maintenance	Moderate Treatment Emergent AE During Initial Escalation	Moderate Treatment Related AE During up-Dosing
Other OIT							
Anagnostou, 2014[55]	oral immunotherapy in up dosing phase to achieve 800 mg daily	39	6 months	NR	NR	NR	NR
	placebo	46		NR	NR	NR	NR
Reier-Nilsen, 2018[75]	OIT with biweekly step up to goal of 5000 mg	57	time to reach max dose	NR	NR	NR	NR
	Observation	20		NR	NR	NR	NR

Table D10. Safety IV

Author, Year	Intervention	N	Timepoint (Months)	Moderate Treatment Related AE During Maintenance	Treatment Emergent Severe AE During Initial Escalation	Treatment Related Severe AE During Up-Dosing	Treatment Related Severe AE During Up-Dosing
AR101							
Bird 2017[33]	AR101	29	6-9 months	NR	NR	NR	NR
	Placebo	26	6-9 months	NR	NR	NR	NR
PALISADE 2018[34] (age 4-17)	AR101 in escalating dose program to achieve 300 mg per day for 24 weeks	372	24 weeks	32.6%	0%	2.5%	2.6%
	placebo	124	24 weeks	31.4%	0%	0.8%	0%
PALISADE 2018[34] (age 18-55)	--	--	--	--	--	--	--
Viaskin/DBV Technologies							
Jones, 2016[36]	Epicutaneous peanut patch 100 MCG	24	12 months	NR	NR	NR	NR
	Epicutaneous peanut patch 250 Mcg	24		NR	NR	NR	NR
	Placebo	25		NR	NR	NR	NR
Sampson, 2017[37]	Epicutaneous peanut patch 50 MCG	53	12 months	NR	NR	NR	NR
	Epicutaneous peanut patch 100 Mcg	56		NR	NR	NR	NR
	Epicutaneous peanut patch 250 mcg	56		NR	NR	NR	NR
	placebo	56		NR	NR	NR	NR
PEPITES, 2019[74]	Peanut Patch	238	12 months	NR	NR	NR	NR
	Placebo	118		NR	NR	NR	NR

Author, Year	Intervention	N	Timepoint (Months)	Moderate Treatment Related AE During Maintenance	Treatment Emergent Severe AE During Initial Escalation	Treatment Related Severe AE During Up-Dosing	Treatment Related Severe AE During Up-Dosing
Other OIT							
Anagnostou, 2014[55]	oral immunotherapy in up dosing phase to achieve 800 mg daily	39	6 months	NR	NR	NR	NR
	placebo	46		NR	NR	NR	NR
Reier-Nilsen, 2018[75]	OIT with biweekly step up to goal of 5000 mg	57	time to reach max dose	NR	NR	NR	NR
	Observation	20	--	NR	NR	NR	NR

Table D11. Safety V

Author, Year	Intervention	N	Timepoint (Months)	Treatment Related AE During Initial Day Escalation	Treatment Related AE During Build Up Doses	Treatment Related AE During Maintenance
AR101						
Bird 2017[33]	AR101	29	6-9 months	NR	NR	NR
	Placebo	26	6-9 months	NR	NR	NR
PALISADE 2018[34] (age 4-17)	AR101 in escalating dose program to achieve 300 mg per day for 24 weeks	372	24 weeks	NR	NR	NR
	placebo	124		NR	NR	NR
PALISADE 2018[34] (age 18-55)	--	--	--	NR	NR	NR
Viaskin/DBV Technologies						
Jones, 2016[36]	Epicutaneous peanut patch 100 MCG	24	12 months	NR	NR	NR
	Epicutaneous peanut patch 250 Mcg	24		NR	NR	NR
	Placebo	25		NR	NR	NR
Sampson, 2017[37]	Epicutaneous peanut patch 50 MCG	53	12 months	NR	NR	NR
	Epicutaneous peanut patch 100 Mcg	56		NR	NR	NR
	Epicutaneous peanut patch 250 mcg	56		NR	NR	NR
	placebo	56		NR	NR	NR
PEPITES, 2019[74]	Peanut Patch	238	12 months	NR	NR	NR
	Placebo Patch	118		NR	NR	NR
Other OIT						
Anagnostou, 2014[55]	oral immunotherapy in up dosing phase to achieve 800 mg daily	39	6 months	NR	NR	NR
	placebo	46	6 months	NR	NR	NR
Reier-Nilsen, 2018[75]	OIT with biweekly step up to goal of 5000 mg	57	time to reach max dose	NR	NR	NR
	Observation	20	--	NR	NR	NR

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in This Analysis from… Perspective?	
		Health Care Sector	Societal
Health Outcomes	Longevity effects	☑	☑
	Health-related quality of life effects	☑	☐*
	Adverse events	☑	☐
Medical Costs	Paid by third-party payers	☐	☑
	Paid by patients out-of-pocket	NA	☑
	Future related medical costs	☑	☑
	Future unrelated medical costs	☐	☐
Health-Related Costs	Patient time costs	NA	☐
	Unpaid caregiver-time costs	NA	☑
	Transportation costs	NA	☐
Productivity	Labor market earnings lost	NA	☑
	Cost of unpaid lost productivity due to illness	NA	☑
	Cost of uncompensated household production	NA	☐
Consumption	Future consumption unrelated to health	NA	☐
Social Services	Cost of social services as part of intervention	NA	☐
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐
	Cost of crimes related to intervention	NA	☐
Education	Impact of intervention on educational achievement of population	NA	☐
Housing	Cost of home improvements, remediation	NA	☐
Environment	Production of toxic waste pollution by intervention	NA	☐
Other	Other impacts (if relevant)	NA	☐

NA: not applicable

*Forthcoming pending further exploration of approaches to modeling caregiver utility in lieu of published estimates.

Adapted from Sanders et al.[76]

Table E2. Cost per QALY Gained for AR101 (Placeholder Cost) versus Avoidance Alone Over a Range of Time Horizons

Time Horizon	Treatment	Total Cost	QALYs	ICER (QALYs)
1 year	**AR101**	$13,000	0.83	$19,520,000
	Avoidance Alone	$1,000	0.83	
	Incremental	$11,000	0.00	
3 years	**AR101**	$18,000	2.45	$284,000
	Avoidance Alone	$2,000	2.39	
	Incremental	$17,000	0.06	
5 years	**AR101**	$23,000	4.04	$196,000
	Avoidance Alone	$2,000	3.93	
	Incremental	$21,000	0.11	
10 years	**AR101**	$35,000	7.77	$148,000
	Avoidance Alone	$3,000	7.56	
	Incremental	$32,000	0.21	
20 years	**AR101**	$51,000	13.75	$128,000
	Avoidance Alone	$4,000	13.39	
	Incremental	$47,000	0.37	
50 years	**AR101**	$74,000	23.79	$117,000
	Avoidance Alone	$6,000	23.21	
	Incremental	$68,000	0.58	

Table E3. Cost per QALY Gained for Viaskin Peanut (Placeholder Cost) versus Avoidance Alone Over a Range of Time Horizons

Time Horizon	Treatment	Total Cost	QALYs	ICER (QALYs)
1 year	**Viaskin Peanut**	$7,000	0.83	$30,480,000
	Avoidance Alone	$1,000	0.83	
	Incremental	$6,000	0.00	
3 years	**Viaskin Peanut**	$12,000	2.42	$514,000
	Avoidance Alone	$1,000	2.40	
	Incremental	$10,000	0.02	
5 years	**Viaskin Peanut**	$16,000	3.99	$378,000
	Avoidance Alone	$2,000	3.95	
	Incremental	$14,000	0.04	
10 years	**Viaskin Peanut**	$25,000	7.66	$308,000
	Avoidance Alone	$3,000	7.59	
	Incremental	$23,000	0.07	
20 years	**Viaskin Peanut**	$39,000	13.57	$277,000
	Avoidance Alone	$4,000	13.44	
	Incremental	$35,000	0.13	
50 years	**Viaskin Peanut**	$58,000	23.50	$261,000
	Avoidance Alone	$6,000	23.30	
	Incremental	$52,000	0.20	

Table E4. Results of Probabilistic Sensitivity Analysis, AR101 (Placeholder Price) versus Avoidance Alone

AR101 Outcomes	PSA Mean	Credible Range	Avoidance Alone Outcomes	PSA Mean	Credible Range	Incremental Outcomes	PSA Mean	Credible Range
						ICER	**$136,787**	**($64,336 - $324,336)**
Total Costs	**$79,138**	**($63,304 - $96,645)**	**Total Costs**	**$6,602**	**($5,742 - $7,458)**	**Incremental Costs**	**$72,536**	**($56,701 - $89,772)**
Treatment	$64,760	($48,952 - $81,996)	**Treatment**	--	--	**Treatment**	$64,760	($48,952 - $81,996)
Healthcare	$14,177	($12,148 - $16,347)	**Healthcare**	$6,313	($5,468 - $7,164)	**Healthcare**	$7,864	($6,320 - $9,621)
Serious AEs	$86	($43 - $160)	**Serious AEs**	$87	($59 - $120)	**Serious AEs**	$0	(-$49 - $76)
Epi Use	$115	($80 - $160)	**Epi Use**	$203	($141 - $279)	**Epi Use**	-$88	(-$139 - -$45)
Total QALYs	**27.08**	**(26.68 - 27.47)**	**Total QALYs**	**26.43**	**(25.97 - 26.84)**	**Incremental QALYs**	**0.64**	**(0.21 - 1.12)**
On Treatment or Placebo	0.68	(0.66 - 0.70)	**On Treatment or Placebo**	0.78	(0.76 - 0.80)	**On Treatment or Placebo**	-0.10	(-0.11 - -0.09)
Untreated Peanut Sensitive	6.55	(4.59 - 8.70)	**Untreated Peanut Sensitive**	18.80	(17.57 - 19.95)	**Untreated Peanut Sensitive**	-12.25	(-14.22 - -10.14)
Peanut Desensitized	13.81	(11.48 - 16.19)	**Peanut Desensitized**	0.83	(0.27 - 1.68)	**Peanut Desensitized**	12.99	(10.76 - 15.18)
Peanut Tolerant	6.03	(5.06 - 7.02)	**Peanut Tolerant**	6.03	(5.06 - 7.01)	**Peanut Tolerant**	0.00	(0.00 - 0.04)
Epi Use & AEs	0.00	(0.00 - 0.00)	**Epi Use & AEs**	0.00	(-0.01 - 0.00)	**Epi Use & AEs**	0.00	(0.00 - 0.00)
Societal	0.00	(0.00 - 0.00)	Societal	0.00	(0.00 - 0.00)	Societal	0.00	(0.00 - 0.00)
Total Life Years	**28.71**	**(28.69 - 28.87)**	**Total Life Years**	**28.69**	**(28.69 - 28.69)**	**Incremental Life Years**	**0.02**	**(0.00 - 0.18)**

Figure E1. Results of Probabilistic Sensitivity Analysis: Cost-Effectiveness Acceptability Curve for AR101 (Placeholder Price) versus Avoidance Alone

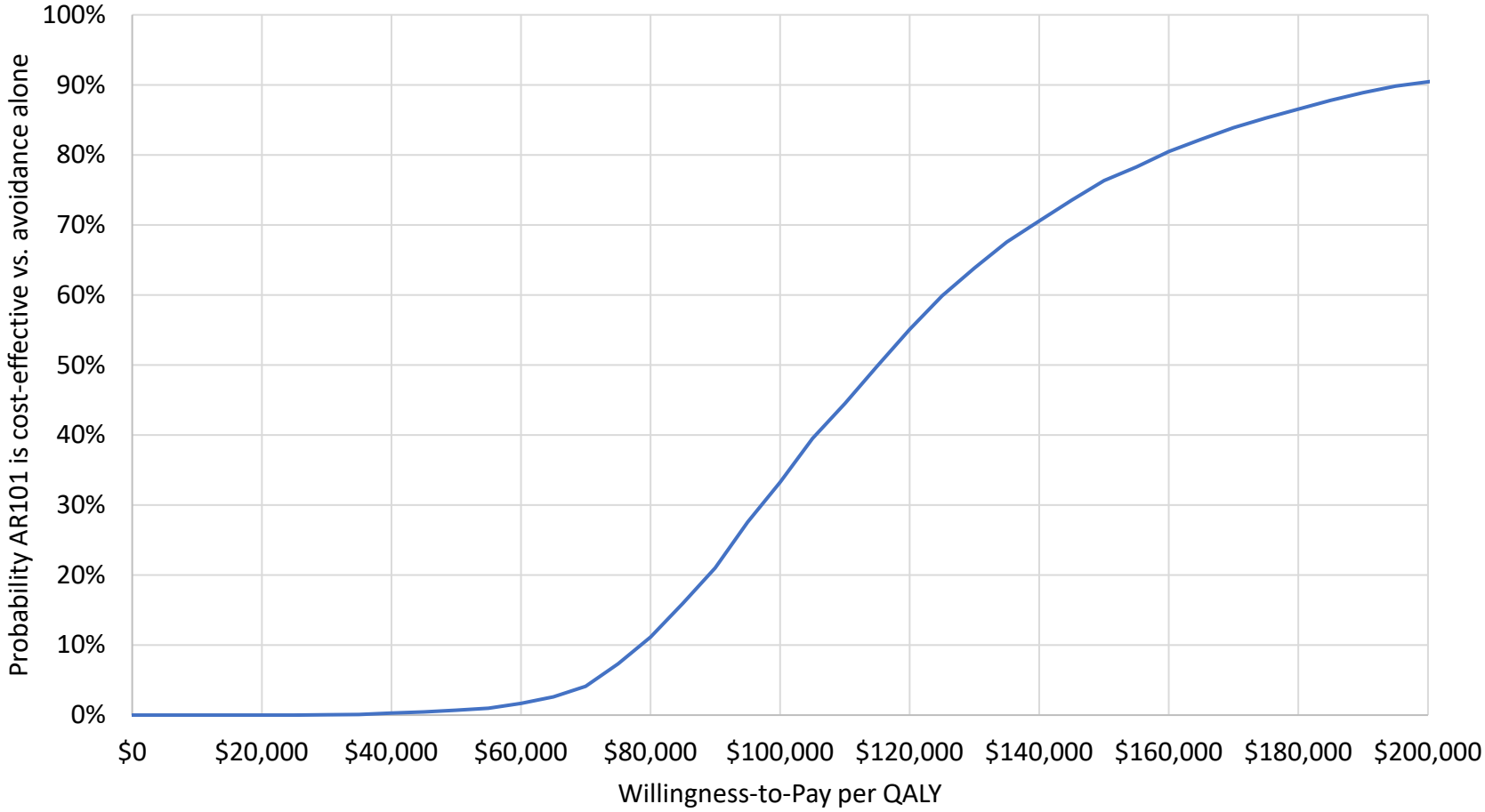


Table E5. Results of Probabilistic Sensitivity Analysis, Viaskin Peanut (Placeholder Price) versus Avoidance Alone

Viaskin® Peanut Outcomes	PSA Mean	Credible Range	Avoidance Alone Outcomes	PSA Mean	Credible Range	Incremental Outcomes	PSA Mean	Credible Range
						ICER	**$306,567**	**($143,420 - $761,701)**
Total Costs	**$60,843**	**($43,751 - $81,108)**	**Total Costs**	**$6,562**	**($5,703 - $7,416)**	**Incremental Costs**	**$54,281**	**($37,305 - $74,534)**
Treatment	$54,339	($37,356 - $74,612)	**Treatment**	--	--	**Treatment**	$54,339	($37,356 - $74,612)
Healthcare	$6,292	($5,448 - $7,146)	**Healthcare**	$6,301	($5,457 - $7,155)	**Healthcare**	-$9	(-$10 - -$8)
Serious AEs	$61	($40 - $87)	**Serious AEs**	$79	($54 - $111)	**Serious AEs**	-$19	(-$31 - -$10)
Epi Use	$151	($103 - $208)	**Epi Use**	$181	($124 - $250)	**Epi Use**	-$31	(-$57 - -$11)
Total QALYs	**26.73**	**(26.36 - 27.06)**	**Total QALYs**	**26.52**	**(26.09 - 26.89)**	**Incremental QALYs**	**0.21**	**(0.07 - 0.39)**
On Treatment or Placebo	0.77	(0.75 - 0.79)	**On Treatment or Placebo**	0.78	(0.76 - 0.80)	**On Treatment or Placebo**	-0.01	(-0.01 - -0.01)
Untreated Peanut Sensitive	12.89	(10.69 - 14.93)	**Untreated Peanut Sensitive**	17.14	(15.70 - 18.50)	**Untreated Peanut Sensitive**	-4.24	(-6.10 - -2.66)
Peanut Desensitized	7.04	(5.01 - 9.35)	**Peanut Desensitized**	2.57	(1.51 - 3.87)	**Peanut Desensitized**	4.47	(2.80 - 6.43)
Peanut Tolerant	6.03	(5.06 - 7.01)	**Peanut Tolerant**	6.03	(5.06 - 7.01)	**Peanut Tolerant**	0.00	(0.00 - 0.00)
Epi Use & AEs	0.00	(-0.01 - 0.00)	**Epi Use & AEs**	0.00	(-0.01 - 0.00)	**Epi Use & AEs**	0.00	(0.00 - 0.00)
Societal	0.00	(0.00 - 0.00)	**Societal**	0.00	(0.00 - 0.00)	**Societal**	0.00	(0.00 - 0.00)
Total Life Years	**28.69**	**(28.69 - 28.69)**	**Total Life Years**	**28.69**	**(28.69 - 28.69)**	**Incremental Life Years**	**0.00**	**(0.00 - 0.00)**

Figure E2. Results of Probabilistic Sensitivity Analysis: Cost-Effectiveness Acceptability Curve for Viaskin Peanut (Placeholder Price) versus Avoidance Alone