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

Final Background and Scope

December 20, 2018

Background

Peanut is a common childhood allergen in the United States. According to recent estimates approximately 1.4-4.5% of children suffer from peanut allergy.[1,2] In addition, peanut allergy is the leading cause of death from anaphylaxis due to food, particularly in teenagers.[3]

Food allergy reactions can range from mild cutaneous symptoms, to GI symptoms such as abdominal pain, nausea, vomiting, and diarrhea, on to anaphylaxis.[4,5] The allergy usually begins early in life and only a minority of patients outgrow their food allergy.[4] Furthermore, approximately one-third of patients with peanut allergy suffer from additional food allergies.[6] The economic cost of food allergies in the United States is estimated at $24.8 billion per year, of which only $4.3 billion was direct medical costs.[7] The remaining $20.5 billion represents costs borne by the families of affected children including out of pocket medical costs, the costs of special foods, and lost caregiver productivity.

The primary approach to managing food allergies is to avoid the trigger, though 40% or more of those with peanut allergy may experience an accidental exposure and reaction.[2,4,8] Antihistamines are used to manage mild to moderate symptoms and epinephrine autoinjectors (EpiPen®, Auvi-Q®) are used for severe reactions. Research has focused on desensitizing patients by exposing them to increasing amounts of the food, but no therapies are FDA approved.

This evidence review will examine the effectiveness and value of two technologies to desensitize patients with peanut allergy – AR101 and Viaskin® Peanut– as well as non-commercialized oral immunotherapy (OIT) for peanut allergy.[9]

- **AR101 (Aimmune Therapeutics)** is defatted, slightly roasted peanut flour, which comes in a capsule 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 either pudding, applesauce, or other foods as a vehicle. 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 (12 total visits). The 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. Viaskin® Peanut is being studied primarily in pediatric patients ages four to 11 years.

An FDA approval decision on AR101 is expected in the second half of 2019. The timeline for FDA review of Viaskin® Peanut is currently unknown.

Stakeholder Input

This scoping document was developed with input from diverse stakeholders, including patients and their families, clinicians, and researchers. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Several themes emerged from speaking with patients and patient representatives. First was the burden of day-to-day living with peanut allergy, the severity of which may be difficult to predict. Patients and their caregivers experience tremendous anxiety and may experience 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: many will not travel beyond a short distance from their specialist or tertiary care center. Some children do not go on field trips or birthday parties or to restaurants out of fear of exposure; patients and families may not 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 fatality 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 labeling has improved since 2006, it is 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, up to one third of patients with peanut allergies suffer from other food allergies. Some of these patients expressed that decreasing 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. As a result, patients who pursue OIT often pay out of pocket, which could 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 EpiPens®. 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.

Report Aim

This project will evaluate the health and economic outcomes of AR101 and Viaskin® Peanut for peanut allergy. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

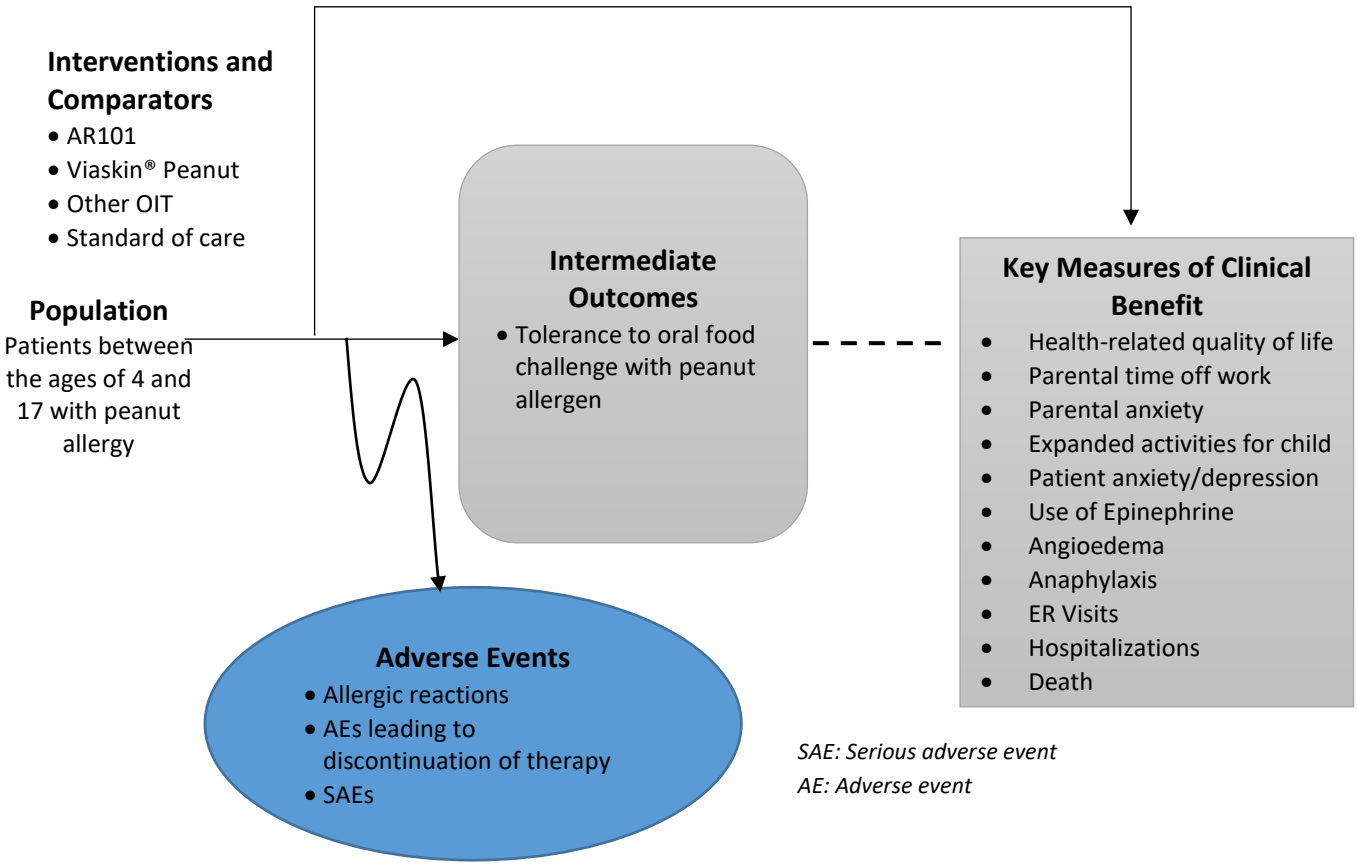
All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction,

and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

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.[10] 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.[10]

When available, outcomes will be 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

Data permitting, we intend to compare the interventions to each other and to placebo/usual care.

Outcomes

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

Table 1.1. Outcomes and Harms

Outcomes	Key Harms
Death	Systemic 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	Skin reactions
Angioedema	
Bronchospasm/wheezing	
Urticaria	
Use of epinephrine	
Parental anxiety	
Patient anxiety/depression	
Tolerance to challenge with peanut allergen	

Timing

Evidence on intervention effectiveness will be 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 will be considered, with a focus on outpatient settings in the United States.

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. These elements are listed in the table below.

Table 1.2. Potential Other Benefits and Contextual Considerations

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 standard treatment, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to standard treatment, 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.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop a *de novo* health economic simulation model to assess the lifetime cost-effectiveness of AR101, Viaskin® Peanut, and non-commercialized OIT relative to placebo/usual care. The model structure will be based in part on a literature review of prior published models of peanut allergy,[11-13] as well as the interventions' clinical trials and other observational studies of peanut allergy treatments.[14-16] The base case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only). Data permitting, productivity losses (i.e., lost wages for parents/caregivers) and other indirect costs will be considered in a separate societal perspective analysis.

The target population will consist of children between the ages of four and 17 with peanut allergy. Subject to change upon our upcoming evidence review, the model will consist of health states including but not limited to (1) well without peanut desensitization, (2) well with peanut desensitization, (3) allergic reaction (stratified by type, data permitting), and (4) death. In the model, a cohort of patients will transition between states during predetermined cycles (current assumption: one month) over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness may be estimated for shorter time horizons (e.g., five years) in a scenario analysis. Cost and disutilities associated with treatment, and adverse events (AEs) resulting from treatment, will be applied in the two "well" health states.

Key model inputs will include clinical probabilities, quality of life estimates, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using the AR101 and Viaskin® Peanut clinical trial outcomes, and through data obtained in the systematic review. Health outcomes and costs will be dependent on time spent in each health state, clinical events, AEs, and direct medical costs. The outcomes of each intervention will be evaluated in terms of life-years and quality-adjusted life years (QALYs) gained, health care costs, the incremental cost per life-year gained, and the incremental cost per QALY gained. Data permitting, we may also estimate health outcomes such as number of allergic reactions prevented and the incremental cost per allergic reaction prevented. Quality of life weights will be applied to each health state, including quality of life decrements for anxiety related to peanut allergy, allergic reactions, and serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity losses for parents/caregivers and other indirect costs will be included in a separate analysis, data permitting.

In separate analyses, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the simulation model for treatment

costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2018/05/ICER-value-framework-v1-21-18.pdf.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include 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.

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