

Response to ICER's Draft Background and Scope for Viaskin® Peanut and AR101 Immunotherapy for Peanut Allergy

Executive summary

Aimmune Therapeutics appreciates the opportunity to provide feedback and recommendations for the Institute for Clinical and Economic Review's (ICER's) draft scoping document for the assessment of treatments for peanut allergy (PA). Our response is divided into the following three categories:

1. ICER's evaluation should not consider non-FDA approved oral immunotherapy (OIT) because of the lack of a standard formulation, dose or schedule, and the uncertainty of the clinical impact of desensitization arising from different levels of antigens present. In addition, clinical studies for off-label OIT were conducted without robust study design and had substantial differences in outcome measures. Only AR101, Viaskin® Peanut, and standard of care are appropriate treatments for this review.
2. A societal perspective, which incorporates treatment-related improvement in patient and caregiver utility and productivity gains, should form the base case.
3. Additional direct comments on ICER's draft scoping document in the final section.

1. ICER's evaluation should not consider off-label OIT. Only AR101, Viaskin® Peanut and standard of care are relevant comparators for this review

Off-label peanut OIT is a group of unregulated, uncontrolled mixtures used for PA which involves administration of "home brew" OIT by increasing the amount of peanut protein given to patients. It can be administered with peanut protein from sources such as partially defatted peanut flour, lightly roasted peanut flour, or whole crushed roasted peanuts.¹⁻⁶ The antigen composition of these preparations is highly variable, which may affect clinical outcomes.⁷ No single standard exists for the preparation of off-label OIT products or for the administration protocol that should be followed, and none of these OIT products are the subject of a clinical development program that would meet the stringent requirements for FDA approval for PA. Trial designs, populations and clinical endpoints in the off-label OIT trials are also inconsistent. It is therefore neither appropriate nor feasible to combine clinical data and evaluate off-label OIT as a single product comparator for AR101^{8,9} and Viaskin® Peanut¹⁰. In addition, there is no standard approach to the pricing of off-label OIT because treatment is usually not covered by payers and is typically paid for out-of-pocket by patients. Including off-label OIT will reduce the quality of ICER's assessment, and a potential recommendation may compromise patient safety due to unregulated use.

Clinical Evidence Significant heterogeneity is evident across several aspects of study design in clinical trials for off-label OIT.^{11,12} Many clinical studies for off-label OIT are open-label trials^{1,2,4,5,13}, and some studies are non-randomized.^{1,2,5,14} These flaws in study design introduce selection bias and a lower quality of evidence when compared to large randomized, double-blind, placebo-controlled studies.¹⁵ A particularly concerning methodological limitation of these trials is that they were often conducted in one^{2,4,16} or two^{1,3,5} centers with very small sample sizes, ranging from 16¹⁶ to 99⁴ participants. This raises concerns regarding the robustness of the results and the generalizability of the findings for the broader population of peanut-allergic individuals. Trial designs for off-label OIT studies are also highly variable, with treatment durations ranging from nine weeks² to four years⁵, maintenance doses varying between 125mg⁶ and 4000mg^{3,5}, and up-dosing schedules ranging from one week² to almost one year.³ A wide range of efficacy endpoints were used in off-label OIT studies; for example, some studies used OFC threshold^{1,3,5,14,16}, and others used percent tolerating a specific dose^{2,4,6,13} or percent with specified desensitization levels achieved.¹ Heterogeneity across these studies prevents valid interpretations of the results or any high quality evidence synthesis to generate a comparative effectiveness estimate. Using off-label OIT as a comparator would therefore increase uncertainty and compromise the quality of ICER's evaluation of treatments in PA.

An additional concern regarding the inclusion of off-label OIT trials is that their safety reporting might not follow standards for regulatory submissions. These clinical studies are non-pivotal trials without consistent approaches to documenting adverse events (AEs). For example, the recent off-label peanut OIT trial from Blumchen *et al.* captured AEs as either objective or subjective events, which makes it less comparable with other trials.⁶ Rates of serious AEs are also unclear in many of these clinical studies, indicating a lack of rigor and potential risks associated with off-label OIT.

Clinical Guidelines and Opinions Two US clinical guidelines for food allergy do *not* recommend off-label OITs. The National Institute of Allergy and Infectious Diseases (NIAID) states that allergen-specific immunotherapy should not be used to treat food allergies because the evidence available for the benefits of [off-label] immunotherapy is of low quality.¹⁷ The American Academy of Allergy, Asthma and Immunology (AAAAI) cites Level A evidence that the risk-benefit profile of immunotherapies has not been properly established and strongly recommends against the use of immunotherapies.¹⁸ These guidelines were published prior to the recruitment of the pivotal Phase 3 studies examining AR101 and Viaskin[®] Peanut. Therefore, both guidelines are referring to off-label OIT.

In addition, practicing allergists hold strong opinions about the importance of FDA approval, safety and standardization of immunotherapy for PA. A survey published in 2015 reported that 86% of allergists (381 out of 442) do not offer off-label OIT to their patients.¹⁹ Among them, 74% were waiting for an FDA-approved product before they would offer it to patients. The most important factors for prescribing a product to patients included FDA approval (91%), a standardized product for therapy (92%), additional safety data (94%), and evidence-based guidelines (89%).¹⁹ These results also demonstrate that without FDA approval and an established risk/benefit profile, it is unlikely that off-label OITs can achieve major market penetration. The use of off-label OIT, which only exists in a small minority of practices, will likely be reduced after the approval of AR101 and is therefore irrelevant for ICER's evaluation.

Finally, we strongly encourage ICER to consider the implications of a potential positive recommendation for off-label peanut OIT. ICER must recognize its position as a leader in the field of health economics in the United States and its growing influence on payer and practice decisions. We caution ICER that there is insufficient evidence to review off-label peanut OIT and that the possibility of a recommendation may potentially lead to the ongoing unregulated and unsupervised use of PA treatments among peanut-allergic patients.

2. A societal perspective should be the base case and emphasized

ICER states that key measures of clinical benefits include health-related QoL, parental time off work, parental anxiety, and expanded activities for children, but that productivity losses and other indirect costs will be considered in a "separate societal perspective analysis".²⁰ Caregiver QoL ("family-spillovers") should be included in the model to more fully capture the impact of PA from a societal perspective. An online survey conducted in eight European countries found that social situations involving food caused extremely high or very high levels of anxiety in 60% of peanut allergic children and 71% of parents and caregivers.²¹ Another cross-sectional study indicated 31% of parents/carers of children with PA reported moderate/severe anxiety and 9% reported depression, both of which are higher than population norms in the UK.^{22,23} Severity of anxiety and depression was also correlated with the severity of the child's allergy.²² In addition, parents of peanut-allergic children have reported considerable disruption to daily activities and family relations.²⁴ Given the young age of the population and the resulting substantial QoL burden of PA on both patients and caregivers, Aimmune strongly recommends that ICER incorporate any patient and caregiver improvement in utility and productivity gains in the base case. We would also strongly encourage ICER to model its impact quantitatively rather than including it in a qualitative checklist item under "Potential Other Benefits."

3. Direct comments on draft scoping document

- We alert ICER to the differences between immune tolerance and desensitization (Page 4, Figure 1.1; Page 7, Paragraph 2). Research has focused primarily on desensitization and sustained unresponsiveness. “Immune tolerance” is considered a permanent state, which equates to a cure and has not been achieved by treatments to date. We recommend the health states described as “well without peanut tolerance” and “well with peanut tolerance” are changed to “well without peanut desensitization” and “well with peanut desensitization.” It will be crucial to take into account the level of desensitization, and include risks associated with accidental exposure as well as associated QoL considerations. The ability to confirm protection following desensitization is also an important consideration, as this has implications both for QoL and patient safety. Patients who believe they are protected, but have not confirmed that they are, may be particularly at risk.
- While the exit double-blind placebo-controlled food challenge (DBPCFC) is the FDA-accepted gold standard for measuring efficacy of food allergy treatment, there are critical differences between trial endpoints using this standard in the recent Phase 3 studies.^{8,10} An understanding of these distinctions are key: **1) reactive or eliciting** doses provoke a reaction and are therefore not tolerated or safe to consume, **2) tolerated** doses can be safely consumed, and **3) cumulative** doses represent a sum of all the **single** doses used in a food challenge. These outcomes are not directly comparable and must be carefully interpreted for meaningful comparisons. The use of the single tolerated dose in the assessment of the DBPCFC for AR101 is clearly outlined in the recent Phase 3 trial publication.⁸
- Page 1, Paragraph 3: The use of epinephrine during DBPCFC in trials is a supportive measure of the outcome of desensitization. During a controlled trial, in which patients are aware that they may be exposed to their allergen on a daily basis, the prompt use of epinephrine to prevent a possible severe course is both counseled and expected. The result of this recommendation is that there can be a low threshold for epinephrine deployment, with epinephrine often used for mild to moderate reactions. As a consequence, epinephrine use cannot be used as a surrogate for severe reactions without running the risk of an inaccurate prediction of clinical benefit in the economic evaluation.²⁵⁻²⁹
- Page. 1, Paragraph 3: The goal of desensitization therapy is to protect patients during accidental exposure to peanut. Accidental exposures are common, occurring in approximately 60% of patients³⁰, a higher frequency than the 39% stated in the document, which refers to severe reactions only. The risk of an allergic reaction to therapy is likely to occur with greatest frequency during the up-dosing period when the patient is carefully monitored by the provider or caregiver. This risk should be weighed against the risk of allergic reactions due to unpredictable accidental exposure, which may occur away from careful supervision.³⁰
- Given the nature of immunotherapy dose escalation, we suggest that ICER consider a 1-year cycle length for modeling the transition. Desensitization does not occur within a month and up-dosing for OIT takes place over at least 6 months. Full desensitization will take place over a much longer time period, and patients should not be considered desensitized as soon as they achieve maintenance dosing. The 1-year period that is available in the clinical studies provides the best data in a reasonable time frame to assess the effect of the therapy. In addition, it will allow for the use of the FDA-accepted surrogate for accidental exposure, the DBPCFC, to be appropriately used in modeling exposure.
- The benefits of immunotherapy are to reduce the burden of allergy by improving QoL in alleviating anxiety for patients and caregivers in their daily lives. Therefore, it is not reasonable to assume that decreasing peanut sensitivity in patients with multiple food allergies will have little impact on QoL (Page 3, Paragraph 1). There are a number of factors affecting QoL (i.e. type of allergen, perceived severity, ease of avoidance)³¹⁻³³ where multiple food-allergic patients can benefit from immunotherapy to one allergen.
- AR101 is a peanut allergen powder, a product developed to Good Manufacturing Practice (GMP) standards that is not merely peanut flour. AR101 can be sprinkled over any refrigerated or room temperature age-appropriate semi-solid food, not just pudding and applesauce.

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December 12, 2018

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic
Review One State Street, Suite1050
Boston, MA 02109

RE: DBV recommendations on the proposed scope for ICER's value assessment of peanut allergy therapies

Dear Dr. Pearson,

DBV Technologies is pleased to submit comments on the proposed scope of ICER's value assessment of peanut allergy therapies. DBV Technologies is a clinical stage biopharmaceutical company dedicated to improving the lives of patients with food allergies. We strive to deliver transformative treatments for patients suffering from the burden and life-threatening risk of food allergies and related allergic diseases.

DBV Technologies believes that it is premature to assess Viaskin Peanut at this time. The lack of FDA-approved therapeutic options for peanut allergy and associated absence of health state utility and long-term treatment data, combined with patient heterogeneity, precludes an accurate and reliable cost effectiveness assessment.

Despite our concerns with the timing of this review, DBV technologies would like to comment on key parameters of the draft scope. Our comments are structured into three categories as detailed below.

Head-to-Head Treatment Comparisons: In its draft scoping document, ICER suggested where possible, Viaskin Peanut, AR101 and peanut oral immunotherapy will be compared head-to-head. Any direct or indirect comparisons utilizing clinical trial data associated with these treatments is fundamentally inappropriate due to major differences in study design that include, but are not limited to:

- Patient study populations (i.e. PEPITES 4-11¹; PALISADE 4-55²)
- Inclusion and exclusion criteria
- Trial protocols and clinical measurement (i.e., Eliciting dose vs Tolerated dose)
- Definitions of safety measures (i.e. anaphylaxis, serious adverse events, systemic hypersensitivity)
- Study periods

Such clinical or cost effectiveness comparisons among investigational treatments for peanut allergy would be unreliable and misleading. DBV Technologies recommends that any comparison in this assessment be limited to study trial comparators, which are the standard of care, of strict avoidance and readiness to manage accidental ingestion reactions.

Key Clinical and Economic Recommendations:

Modeling Clinical Effectiveness: Risk reduction to reactions from accidental exposure to peanut is an appropriate measure for outcomes.

Oral Food Challenge (OFC) is used as a surrogate marker for the probability of reducing the risk of reactions from accidental food allergen exposure. A Quantitative Risk Reduction Model³ exists to predict the risk of allergic reactions following accidental exposure to peanut. In this model, changes in sensitivity thresholds predict reduction in the risk of occurrence of an allergic reaction upon accidental ingestion. Modeling risk reduction as an outcome is an appropriate method to assessing clinical and economic impact of peanut allergy treatment.

Treatment duration and progressive desensitization: We encourage ICER to consider treatment responsiveness of at least a 3-year period, based on experience with subcutaneous immunotherapy, which is widely accepted for the treatment of venom and environmental allergies, having been demonstrated to result in progressive desensitization over a 3 to 5-year period⁴. Similarly, ICER should consider long-term Viaskin Peanut Phase II clinical trial data.

The VIPES and OLFUS-VIPES study evaluated Viaskin Peanut in patients that were studied for up to 3 years. These studies demonstrated a progressive desensitization to peanut protein over 3 years in patients ages 4-11⁵.

Approach to QALYs: Considering the recency of investigational therapies for peanut allergy, the lack of mature QoL and Health State Utility (HSU) data for any investigational treatment limits the effectiveness and the reliability of a quality adjusted life years (QALY) based cost effectiveness analysis. If ICER applies QALYs in its assessment, we recommend food allergy as the closest analog disease state for deriving HSU. In addition, we recommend consideration of health state disutilities associated with treatment adverse events (e.g. moderate to severe anaphylaxis, epinephrine use, moderate to severe gastrointestinal distress, nausea, etc.), using analogs where appropriate.

Population: In its draft scope, ICER indicates that it will evaluate Viaskin Peanut for peanut allergy patients between the ages of 4 to 17. In the Phase III PEPITES study, Viaskin Peanut was evaluated in patients in 4 to 11 years old¹. Accordingly, we recommend ICER model Viaskin Peanut treatment consistent with the Phase III population.

Oral allergy immunotherapy is associated with adverse events that frequently lead to discontinuation and interruption of treatment⁶. ICER must fully account for patients intending to be treated for peanut allergy by assessing intent to treat trial populations. Without real world data, the intent to treat population from clinical trials may be the best representation for projecting patient and provider behaviors in clinical practice and account for treatment

discontinuations and/or dropouts in both the desensitization and maintenance stages of treatment, where appropriate.

Treatment Setting: We support ICER's plan to include treatment setting and associated resource utilization and costs in its assessment. To minimize safety risks, the administration of all experimental oral immunotherapy for peanut allergy depends on well-coordinated patient treatment within a physician's office. Viaskin Peanut is an epicutaneous patch that is designed for outpatient administration, thereby minimizing the need for frequent office visits that increase the complexity and cost of care.

Societal Burden of Disease: DBV Technologies encourages ICER to incorporate societal burden, and specifically the costs to caregivers, in its base case.

Total direct medical costs due to food allergy in the US have been estimated at \$4.3 billion⁷. Non-medical costs including out of pocket treatment costs, caregiver absenteeism and opportunity costs related to employment are estimated at almost 5 times the direct costs at \$20.5 billion⁷. The societal and financial burden of food allergy are significant and need to be comprehensively considered in any cost effectiveness evaluations of novel treatment options in peanut allergy.

The ICER framework specifically disadvantages innovation in conditions where caregivers must make therapeutic decisions and bear both opportunity and out of pocket costs of treatment. By excluding caregiver burden in its base case, ICER assigns lower value to treatments in conditions where caregivers are essential contributors than it does when it assigns value to treatments directed at patients capable of self-care.

Caregivers of pediatric food allergy patients suffer significant financial and psychosocial burden⁷. Improvements in patients' health and outcomes resulting from new therapies may substantially offset caregiver burden including out of pocket costs, lost productivity and job opportunity cost.

DBV Technologies appreciates the opportunity to share our comments on ICER's draft scope. Please feel free to contact us should you wish to discuss in further detail.

Sincerely,



Emmanuel M. Mahlis, MD
Senior Vice President, Global Medical Affairs

References

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To whom it may concern:

I am James R Baker Jr., MD, the director of the Mary H Weiser Food Allergy Center at the University of Michigan, the former CEO of Food Allergy Research and Education (FARE) and an allergist for over 30 years. I am well known in the food allergy community for trying to achieve useful and cost-effective therapies for food allergy patients. I have taken a national leadership stance on the affordability of medicine for allergy patients, especially epinephrine auto-injectors. Given this background, I felt it was important for me to provide public comment on the Institute for Clinical Economic Review (ICER's) proposed review of peanut allergy therapies.

ICER proposes to compare three different approaches to address type I hypersensitivity to peanuts ("peanut allergy"). These include the Viaskin® peanut patch (DBV Technologies), AR101 (Aimmune Therapeutics) oral desensitization therapy and what ICER identifies as "non-commercialized oral immunotherapy"(1). This review is markedly different from anything else ICER has attempted in the past because it is being undertaken before FDA review and approval of the approaches under consideration. Because of this, the review cannot define the specific patient population or duration of use that will be approved for each therapy. In addition, the pricing of these therapies is not yet defined and the exact peanut allergy population to be addressed has not been characterized. This latter problem awaits better biomarkers to define the disease, since many individuals with immunologic evidence of peanut sensitization do not react on peanut challenge (2-6).

Let me comment on three different aspects of the ICER proposal to explain why this initiative, while well intentioned, is in fact premature and why the proposed analysis is likely to result in a flawed conclusion.

Patient Population Concerns

First, ICER needs to have a much better understanding of the peanut-allergic patient population and the economic impact of this disease. ICER's statements seem to indicate that they believe that they can identify a "population of interest" but they then default (in their Figure 1.1) to ages "4-17 years." This is different from the age groups for which these therapies are seeking approval (let alone what they may be approved for) and certainly there are physicians using "non-commercialized oral immunotherapy" in younger and older individuals. ICER also does not address how patients on these therapies will be treated once they are beyond this age group. The ICER review also seems to suggest they are targeting "patients at risk," yet there is also no definitive way to stratify peanut allergic patients at definitive risk for anaphylaxis in the scientific literature (2, 7).

In addition, the description of the economic impact of food allergy seems vague. It is particularly disconcerting that ICER does not reference the most comprehensive review of the commercial impact of food allergy on medical economics, which was conducted and published in 2017 by FAIR Health (8), the prominent independent nonprofit that analyzes healthcare costs and insurance information. Fair Health's report is drawn from a review of its database of over 24 billion privately billed healthcare procedures, and shows a financial and social impact of food allergy far greater than that alluded to in ICER's comments. It also shows a markedly increasing impact of food-induced anaphylaxis on adults ages 20-40 years old; a population ICER ignores in its proposed analysis. Without critical information like this and a

better understanding of the patient and economic impact, any assessment of the utility of these potential therapies is premature and will present an inaccurate assessment.

Analysis of “Outcomes” Before Therapies are Approved

More disconcerting is the fact that the exact clinical outcomes of peanut allergy therapies ICER is proposing to analyze are not completely defined. DBV's Viaskin patch has not had its Phase III clinical trial data fully presented in the peer-reviewed literature and while the AR101 Phase III data has been published (9), the package for clinical approval of this therapy has not yet been submitted to the FDA. Since the FDA data on either approach will not be publicly available until approved by the agency, it is impossible to anticipate the role for these therapies since the FDA may restrict use, require monitoring or place other requirements that would limit the patients eligible for either of these approaches. In fact, there is the possibility that the FDA will not approve one or both of the therapies, which would make ICER's entire effort irrelevant. It seems unrealistic to attempt to assess the economic benefit of a new therapeutic *before* it is: defined as a commercial product, has suggested pricing, plus expected length and approach to therapy (which would come from clinical approval).

The Assessment of “Non-Commercialized Oral Immunotherapy”

The inclusion of “non-commercialized oral immunotherapy” (ICER's terminology) in ICER's proposed analysis creates an unusual dynamic in this assessment. This treatment approach involves feeding peanut in increasing amounts to patients in an attempt to “desensitize” reducing allergic reactions to the food (10). While this desensitization approach has been successful and very helpful in a subgroup of patients, the exact outcomes and adverse reactions associated with this therapy are not defined. The protocols, dosing schedules and sources of peanut are unique to each allergist's office, although recent attempts have tried to standardize these variables (11, 12). This approach also has not been approved by professional societies and is viewed by most insurers and even those practicing the technique as experimental (13, 14). Unfortunately, the patient population and outcomes from “non-commercialized oral immunotherapy” studies cannot be compared to the other therapies ICER is reviewing as a significant proportion of the patients have not undergone food challenge before entering into treatment (11, 12).

The exact economic costs and benefits of this approach are difficult to assess. While this therapy is “non-commercial,” it is almost always done for some charge, often without insurance coverage. The economic analyses of this approach tend to ignore many factors including variations in practice patterns and medical costs across the United States. Of interest, the most prominent analysis of “non-commercialized oral immunotherapy” included the use of “probiotics” with the oral immunotherapy (15). This proposed treatment protocol was based on a single study from Australia that only examined children up to age 10 and lacked appropriate controls (16). Therefore, extending these results to the general, U.S. population is totally inappropriate. Finally, ICER makes no mention of the potential disparities in care that result from a therapy that, for the most part, is not available to individuals who have Medicaid. I can find no other situation where ICER has reviewed a non-approved therapeutic approach that is not covered by most insurance plans, and it is not clear to me the outcome ICER expects from this analysis.

A More Useful Approach to Peanut Allergy Therapy

If ICER truly wants to help peanut allergic individuals, I believe that the best course of action is to step back and do several things before an assessment of these diverse approaches is performed. First, ICER must do a much better job of identifying and stratifying the peanut-allergic population, including

assessing who would be treated with these therapies, and it should use commercial sources to better define the economic impact of food allergy on both the health system and the individual. Secondly, it should wait until the DBV and Aimmune drugs are approved and their actual use and economic cost can be accurately determined. With this information in hand, I believe it would then be of greater value to do an individual assessment of each of the approaches to peanut allergy rather than comparing therapies given their vast differences in approach and treatment population. Finally, any assessment of “non-commercialized oral immunotherapy” should first involve some definition of the purpose and expected outcome of this review given the variability in the application of this technique and the issues surrounding insurance coverage that limit its availability.

Sincerely,

A handwritten signature in blue ink, reading "J.R. Baker, Jr., MD.", enclosed in a thin blue rectangular border.

James R. Baker, Jr., MD
Ruth Dow Doan Professor
Director, Mary H. Weiser Food Allergy Center

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December 5, 2018

Steven D. Pearson, MD, MSc
Institute for Clinical and Economic Review Two Liberty Square, 9th floor
Boston, MA 02109

Dear Dr. Pearson:

On behalf of the >60 Million Americans living with allergies, asthma and related conditions, we submit the following letter to the Institute for Clinical and Economic Review (ICER) and the opportunity to comment on the draft scope for ICER's review of peanut allergy treatments.

Burden

According to recent estimates approximately 1.4-4.5% of children suffer from peanut allergy. In addition, peanut allergy is the leading cause of death from anaphylaxis due to food, particularly in teenagers.

Food allergy reactions can range from mild cutaneous symptoms, such as nausea, vomiting, and diarrhea, on to the more severe angioedema and anaphylaxis. The allergy usually begins early in life and only a minority of patients outgrow their food allergy. Furthermore, approximately one- third of patients with peanut allergy suffer from additional food allergies. 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. 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 up to 39% of those with peanut allergy may experience an accidental exposure and reaction each year.

It is with these patients in mind, that we provide the following recommendations to ensure a more patient-driven approach to assessing value. We have categorized our recommendations into the following core themes:

I. Disease Impact

Given the burden and impact stated above, we recommend ICER consider cost-effective analyses to capture both healthcare payer and the societal perspectives. We also urge ICER to include patient community representatives as appraisal committee members with full voting rights. No one understands the burden and impact of peanut allergy better than patients and patient advocates who have dedicated their lives to addressing this condition.

II. Disease Complexity

The scoping document does not address the patient population that has been defined by FDA and most updated clinical guidelines. We believe ICER should consider the following key factors in assessing the complexity of



disease: disease impact as defined by patients (impact on activities of daily living, fear, anxiety and depression, quality of life burden, absenteeism, presenteeism, lost opportunity costs, ER visits/hospitalizations, etc.); heterogeneity & variability of disease (onset of disease, length of time since diagnosis, length of time since last severe reaction, life expectancy, adherence & compliance differences, phenotype, etc.)

III. Lack of HEOR Data & Variability of Clinical Data

The scoping document does not explain how ICER will account for the lack of HEOR data and the variability in clinical trial inclusions & exclusion criteria based on previous medication history, reaction history, different mechanisms of action, placebo rates, biomarkers used to identify patients, long-term vs short-term safety and efficacy, etc. Furthermore, ICER suggests Other OIT Peanut Products as an intervention; however, there is little, to no, published data on this practice.

IV. Health Related Quality of Life

The scoping document does not account for other validated quality of life measurements that have been utilized in the literature in peanut allergy. We urge ICER to truly consider what matters most to patients and look beyond one single QOL tool to determine impact.

Allergy & Asthma Network stands ready to partner with ICER to support the value assessment & ensure cost-effectiveness of these treatment solutions. We implore the evaluators to consider patient-reported outcomes rather than simply QALY's. We advocate for appropriate use of these innovative treatments and believe that when the right treatment is selected for the right patient at the right time it inevitably saves the system and individual patient.

It is truly a promising time for those in the peanut allergy community. Significant scientific advancements in diagnosis, phenotyping and treatment are exciting. We look forward to the opportunity to provide additional insights and/or patient testimonies. Please do not hesitate to contact me should you have any questions.

All my best,

A handwritten signature in black ink that reads "Tonya A. Winders". The signature is written in a cursive, flowing style.

Tonya A. Winders
President & CEO



December 12, 2018

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109
Submitted electronically to publiccomments@icer-review.org

To Whom It May Concern:

The Asthma and Allergy Foundation of America (AAFA) appreciates the opportunity to provide the Institute for Clinical and Economic Review (ICER) with the perspective of patients with food allergies as ICER begins reviewing the evidence surrounding the treatment of peanut allergies with Viaskin® Peanut and AR101. We thank ICER for acknowledging the importance of stakeholder participation and engagement in evaluating the value of preventive treatments for food allergies. As the leading patient organization for people with allergies and asthma and an active online community, AAFA is well positioned to provide ICER with meaningful insight into the experiences of patients with food allergies, particularly peanut allergies.

Patient and Family Impact of Peanut Allergy

Peanut and other food allergies have an enormous impact on the lives of patients and their families.

The proximate impact of exposure to the allergen can range from mild to catastrophic, with a severity that cannot be predicted from one reaction to the next. Exposure to trigger foods, including peanuts, for those with food allergies can symptoms ranging from hives, nausea, vomiting, or diarrhea to the more serious symptoms like angioedema, anaphylaxis, and possible death.

Food labeling helps people with peanut allergy attempt to avoid exposure. However, as ICER noted, up to 39% of those with peanut allergy may still experience accidental exposure and reactions.^{1,2,3}

In addition, many children and adults with peanut allergy are also managing other food allergies. ICER noted a 1998 study showing that approximately one-third of individuals with peanut allergy also suffer from additional food allergies.⁴ In fact, today this rate may be even higher; in a more recent, internal survey of our food allergy community (unreleased), AAFA found that close to two-thirds of individuals with peanut allergies suffer from other food allergies. People with peanut allergy also

¹ Gupta R.S., Springston E.E., Warrier M.R., et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128(1):e9-17.

² Panel N.I.-S.E., Boyce J.A., Assa'ad A., et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(6 Suppl):S1-58.

³ Green T.D., LaBelle V.S., Steele P.H., et al. Clinical characteristics of peanut-allergic children: recent changes. *Pediatrics*. 2007;120(6):1304-1310.

⁴ Sicherer S.H., Burks A.W., Sampson H.A.. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics*. 1998;102(1):e6.



have high rates of comorbidities such as asthma, eczema, and rhinitis, all of which can be exacerbated by allergen exposure, further compounding the effect of the allergy.^{5,6,7}

Children with food allergies and their caregivers have lower quality of life scores compared to the general population. Negative impacts include fear of being exposed to allergens in daily activities including school, family events, camp, and at restaurants, along with the subsequent social isolation.^{8,9,10} Anxiety and fear surrounding potential exposure can be compounded by bullying and further social isolation.^{11,12,13,14,15,16} Children with food allergies experience an alarming level of bullying based on the allergies.^{17,18} Though the long-term impacts of allergy-related bullying are unknown, in general, bullying leads to increased risks of suicide, increased risks of teenage pregnancy, higher risk-taking in social situations among adolescents, and higher rates of mood and anxiety

⁵ Sicherer S.H., Noone S.A., Muñoz-Furlong A. The impact of childhood food allergy on quality of life. *Annals of allergy, asthma & immunology*. 2001;87(6):461-4.

⁶ Bollinger M.E., Dahlquist L.M., Mudd K., Sonntag C., Dillinger L., McKenna K.. The impact of food allergy on the daily activities of children and their families. *Annals of Allergy, Asthma & Immunology*. 2006;96(3):415-21.

⁷ Lagercrantz B., Persson Å., Kull I. "Healthcare seems to vary a lot": A focus group study among parents of children with severe allergy. *Journal of Asthma*. 2017;54(7):672-8.

⁸ Bollinger M.E., Dahlquist L.M., Mudd K., Sonntag C., Dillinger L., McKenna K.. The impact of food allergy on the daily activities of children and their families. *Annals of Allergy, Asthma & Immunology*. 2006;96(3):415-21.

⁹ Sampson M.A., Muñoz-Furlong A., Sicherer S.H.. Risk-taking and coping strategies of adolescents and young adults with food allergy. *Journal of Allergy and Clinical Immunology*. 2006;117(6):1440-5.

¹⁰ Lagercrantz B., Persson Å., Kull I. "Healthcare seems to vary a lot": A focus group study among parents of children with severe allergy. *Journal of Asthma*. 2017;54(7):672-8.

¹¹ Annunziato R.A., Rubes M., Ambrose M.A., Mullarkey C., Shemesh E., Sicherer S.H.. Longitudinal evaluation of food allergy-related bullying. *The Journal of Allergy and Clinical Immunology: In Practice*. 2014;2(5):639-41.

¹² Sicherer S.H., Noone S.A., Muñoz-Furlong A. The impact of childhood food allergy on quality of life. *Annals of allergy, asthma & immunology*. 2001;87(6):461-4.

¹³ Shemesh E., Annunziato R.A., Ambrose M.A., Ravid N.L., Mullarkey C., Rubes M., Chuang K., Sicherer M., Sicherer S.H.. Child and parental reports of bullying in a consecutive sample of children with food allergy. *Pediatrics*. 2013;131(1):e10-7.

¹⁴ Lieberman J.A., Weiss C., Furlong T.J., Sicherer M., Sicherer S.H. Bullying among pediatric patients with food allergy. *Annals of Allergy, Asthma & Immunology*. 2010;105(4):282-6.

¹⁵ Bollinger M.E., Dahlquist L.M., Mudd K., Sonntag C., Dillinger L., McKenna K.. The impact of food allergy on the daily activities of children and their families. *Annals of Allergy, Asthma & Immunology*. 2006;96(3):415-21.

¹⁶ Fong A.T., Katelaris C.H., Wainstein B. Bullying and quality of life in children and adolescents with food allergy. *Journal of paediatrics and child health*. 2017;53(7):630-5.

¹⁷ Shemesh E., Annunziato R.A., Ambrose M.A., Ravid N.L., Mullarkey C., Rubes M., Chuang K., Sicherer M., Sicherer S.H.. Child and parental reports of bullying in a consecutive sample of children with food allergy. *Pediatrics*. 2013;131(1):e10-7.

¹⁸ Sicherer S.H., Noone S.A., Muñoz-Furlong A. The impact of childhood food allergy on quality of life. *Annals of allergy, asthma & immunology*. 2001;87(6):461-4.



disorders,^{19,20,21,22} all of which can increase long-term healthcare costs. Protective measures taken by parents, like intentional isolation from events where allergens or bullying may be present, can lead to loss of self-esteem, which can lead to diminished academic achievement and long-term socioeconomic issues.^{23,24,25}

Scope of Clinical Evidence Review

AAFA believes ICER’s proposed scope of clinical studies to include in this assessment is appropriate. Focusing on trials targeting children between the ages of 4 and 17 with peanut allergy will ideally reveal early interventions to induce immune tolerance that result in healthier, less allergic children and, eventually, healthier and less allergic adults. We recommend focusing on randomized controlled trials while using high-quality systematic reviews and high-quality comparative cohort studies to supplement the evidence review.

We suspect that ICER may encounter difficulty identifying many long-term outcome cohort studies for Viaskin® Peanut and AR101. Unlike non-commercialized oral immunotherapy, which has a longer history of use, Viaskin® Peanut and AR101 are newer peanut allergy treatments that largely lack evidence for long-term outcomes. We still think it is worthwhile to review the available evidence surrounding long-term outcomes for non-commercialized oral immunotherapy and short- to medium-term outcomes for Viaskin® Peanut and AR101. It may be worthwhile to plan to review the evidence on long-term outcomes for Viaskin® Peanut and AR101 again at some point in the future.

Potential Other Benefits and Contextual Considerations

AAFA strongly recommends inclusion of the “potential other benefits and contextual considerations” to generate a complete view of the benefits of Viaskin® Peanut, AR101, and other OIT. Many are of primary importance when it comes to assessing the true outcomes of any intervention targeting food allergies, and there is evidence to help characterize the scope of their impact. For instance, an “intervention [that] offers reduced complexity that...significantly improve[s] patient outcomes” would

¹⁹ Sampson M.A., Muñoz-Furlong A., Sicherer S.H.. Risk-taking and coping strategies of adolescents and young adults with food allergy. *Journal of Allergy and Clinical Immunology*. 2006;117(6):1440-5.

²⁰ Shemesh E., Annunziato R.A., Ambrose M.A., Ravid N.L., Mullarkey C., Rubes M., Chuang K., Sicherer M., Sicherer S.H.. Child and parental reports of bullying in a consecutive sample of children with food allergy. *Pediatrics*. 2013;131(1):e10-7.

²¹ Ravid N.L., Annunziato R.A., Ambrose M.A., Chuang K., Mullarkey C., Sicherer S.H., Shemesh E., Cox A.L.. Mental health and quality-of-life concerns related to the burden of food allergy. *Immunology and Allergy Clinics*. 2012;32(1):83-95.

²² *Id.*

²³ Von Kobyletzki L.B., Beckman L., Smeeth L., McKee M., Quint J.K., Abuabara K., Langan S. Association between childhood allergic diseases, educational attainment and occupational status in later life: systematic review protocol. *BMJ open*. 2017;7(10):e017245.

²⁴ Bollinger M.E., Dahlquist L.M., Mudd K., Sonntag C., Dillinger L., McKenna K.. The impact of food allergy on the daily activities of children and their families. *Annals of Allergy, Asthma & Immunology*. 2006;96(3):415-21.

²⁵ Aika S., Ito M., Yamamoto Y. Food allergy response capabilities of mothers and related factors. *Nursing & health sciences*. 2017 (3):340-50.



generate an enormous benefit to the almost 40% of individuals with peanut allergies who experience accidental exposure or reaction^{26,27,28} despite attempts to avoid exposure through food labeling.²⁹ Interventions that “significantly reduce caregiver or broader family burden” should also be among the primary benefits of any new intervention, considering the low quality of life scores the caregivers of those with food allergies report.^{30,31} Among the other potential contextual considerations, an intervention that is the “first to offer any improvement for patients with this condition” is particularly relevant to Viaskin® Peanut and AR101 which, along with other non-commercialized oral-immunotherapy, are some of the first interventions to offer actual relief from peanut and other food allergies.

Scope of Comparative Value Analyses

Like most health conditions, food allergy has impacts, economic and otherwise, that extend beyond the healthcare setting. Because food is such an integral component of daily life and must be managed by patients and their families across all settings, it is particularly important that ICER consider the non-healthcare costs of food allergy as central elements in its analysis.

AAFA therefore encourages ICER to develop a comprehensive health economic simulation model that includes societal impacts combined with a scenario sensitivity analysis as part of ICER’s *base case*. This will more accurately reflect real-world scenarios. The current plan suggests there will be a base case analysis that will take health care sector costs (i.e. direct medical costs) into perspective. Then productivity losses and other indirect costs will be considered in a separate societal perspective analysis. AAFA is eager to partner with ICER to conduct research within AAFA’s own community to help better inform ICER’s analysis. While we believe assessing the impact of these new therapies have on direct health care costs is essential, it is imperative that these costs are socially contextualized. As discussed above, food allergies have a profound impact on the lives of patients and their families in multiple ways. Building these indirect costs into the base analysis will provide stakeholders with a more complete understanding of the economic impact of Viaskin® Peanut, AR101, and non-commercialized oral-immunotherapy.

²⁶ Gupta R.S., Springston E.E., Warrier M.R., et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128(1):e9-17.

²⁷ Panel N.I.-S.E., Boyce J.A., Assa'ad A., et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(6 Suppl):S1-58.

²⁸ Green T.D., LaBelle V.S., Steele P.H., et al. Clinical characteristics of peanut-allergic children: recent changes. *Pediatrics*. 2007;120(6):1304-1310.

²⁹ Vierk K.A., Koehler K.M., Fein S.B., Street D.A. Prevalence of self-reported food allergy in American adults and use of food labels. *Journal of Allergy and Clinical Immunology*. 2007;119(6):1504-10.

³⁰ Shemesh E., Annunziato R.A., Ambrose M.A., Ravid N.L., Mullarkey C., Rubes M., Chuang K., Sicherer M., Sicherer S.H.. Child and parental reports of bullying in a consecutive sample of children with food allergy. *Pediatrics*. 2013;131(1):e10-7.

³¹ Sicherer S.H., Noone S.A., Muñoz-Furlong A. The impact of childhood food allergy on quality of life. *Annals of allergy, asthma & immunology*. 2001;87(6):461-4.



Conclusion

Thank you for providing us with the opportunity to share the perspective of the food allergy community. We look forward to working with ICER to ensure that the needs of patients with food allergies and their families are more accurately reflected in ICER's review process.

Should you have any questions, please contact Kenneth Mendez at 202-974-1231 or kmendez@aafa.org.

Sincerely,

A handwritten signature in blue ink that reads 'Kenneth Mendez'. The signature is fluid and cursive, with a large, stylized 'y' at the end.

Kenneth Mendez,
President and Chief Executive Officer
Asthma and Allergy Foundation of America



December 12, 2018

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: ICER Evidence Review of Peanut Allergy Treatments – Draft Scoping Document

Dear Dr. Pearson:

Food Allergy Research & Education (FARE) is the leading patient advocacy organization promoting life, health and hope for the 15 million Americans living with food allergies. FARE appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER) “Viaskin® Peanut and Oral Immunotherapy for Peanut Allergy: Effectiveness and Value” Draft Scoping Document released on November 20, 2018.

FARE commends ICER’s engagement with the peanut allergy patient community to inform its draft scope and we look forward to future dialogue as ICER proceeds with its evaluation. FARE’s goal is to ensure ICER adopts a patient-driven approach to assessing value. As the leading global patient advocacy group working on behalf of the food allergy community for more than 25 years, FARE is uniquely positioned, and respectfully submits, the following comments to the Draft Scoping document.

1. Burden of Disease and Standard of Care

Mild vs. severe reactions: The characterization of using epinephrine for severe reactions in the Background Section is misleading and an oversimplification of the patient burden. There is no current way to predict the severity of reactions and severity characteristics are poorly defined. As a result, out of precaution and based on their own clinical history and advice from their allergist, many patients use epinephrine at first onset of symptoms, regardless of severity.

Stigma and psychosocial: Patients with peanut allergy can experience life-long issues associated with perceived societal stigmas caused by their disease. Psychosocial issues in this population are significant, under-recognized, and under-treated. ICER should include the full breadth and impact from psychosocial concerns (including the costs for services) in its value evaluation.

Food labeling: Food allergy labeling can be highly inconsistent, unreliable and confusing to food allergy patients. The use of precautionary labeling is voluntary, contributing to the confusion for patients managing peanut allergy.

2. Characterization of evidence review

FARE strongly recommends that ICER rephrase all references of “tolerance induction” to “desensitization” throughout the Scoping Document and in all future communications. We believe the use of “tolerance” is misleading to patients, given the published efficacy data for the interventions being evaluated. However, FARE believes it appropriate to consider the potential to achieve a state of

“sustained unresponsiveness,” (defined as protection against reaction after stopping therapy) which may be a distinct sub-population of treated patients.

3. Clarifications of Analytical Approach

Definition of Clinical Benefits and Outcomes: FARE requests ICER further clarify the nature of benefits and outcomes being measured. Specific suggestions include: a) defining how specific endpoints will be measured (e.g., Which measures of Quality of Life will be used? What does “expanded activities” for child include?) b) rephrasing outcomes into perceived benefits (e.g., reduced frequency of anaphylaxis vs. anaphylaxis) c) clarifying what constitutes a Serious Adverse Reaction relative to an Adverse Reaction.

Clarifying accidental vs. iatrogenic (e.g., treatment induced) exposure: In general, the distinction between outcomes that are accidental (e.g., the “background” rate during avoidance) and iatrogenic (e.g., treatment induced) is not clear throughout the document. This clarification is required for the analytic framework and to properly estimate effectiveness. Also, ICER should account for differences in severity between accidental vs. iatrogenic exposure and explore how this may impact differences in patient preferences.

4. Importance of Other Benefits and Contextual Considerations

Only treatment options available: ICER should appropriately weigh the positive impact a first-ever FDA approved therapy for peanut allergy will have on patients. These interventions are a breakthrough for food allergy and will be the only treatment options for peanut allergy. The standard of care – avoidance followed by epinephrine and going to the ER in the event of an exposure – is not a treatment. Avoidance is difficult, not effective and results in 1 in 4 children visiting an ER each year.

Emphasis in increased access: FARE commends ICER’s acknowledgement that another key benefit is the potential for “reducing the important health disparities across racial, ethnic, gender, socio-economic, or regional categories.” We strongly urge ICER to incorporate this consideration into its comparative analysis.

5. Inclusion of “OIT with other peanut products” as an intervention

Accepted intervention: FARE agrees that it is reasonable to include OIT with other peanut products as an intervention. However, we have significant concerns that should be addressed:

Concerns with available data sources and study biases: FARE requests ICER address the following issues related to including OIT with other peanut products as an intervention in its evaluation: a) not widely accessible by all peanut allergy patients and available in select clinics only b) available published studies tend to reflect non-randomized, non-controlled, usually retrospective case series which are subject to bias, make comparisons difficult, and are of poor quality c) estimating the true cost is challenging when taking into account differences in total fees charged to patients, reimbursed medical costs, non-reimbursed medical costs, etc.

6. Creation of *de novo* economic simulation model for comparative analysis

De novo model creation: FARE commends ICER’s efforts to create a *de novo* health economic simulation model for peanut allergy. However, given the substantial challenges in creating a *de novo* model, FARE suggests the following: a) expand the reference models used and explore analogous models used in other disease areas b) ensure that true lifetime cost benefit is measured and benefits realized past the age of 17 are included in the analysis (e.g., ability to avoid travel restrictions for

employment) c) reconsider the appropriate time period evaluated including pre-treatment, post-treatment and years of follow-up.

Direct medical costs may underestimate impact: ICER's proposed base case model will focus on direct medical costs only. FARE believes this approach has the potential to grossly underestimate the true impact of treatment. We believe the issues lie in the inherent difficulty of accurately measuring the costs and benefits of providing a patient with a lifetime of reduced daily burden and anxiety from living with peanut allergy. FARE recommend ICER modify the base case to account for this consideration and/or give greater weight to a societal perspective analysis in its final evaluation.

Key medical outcomes to measure: FARE believes it is imperative that ICER include a comparison of the number of allergic reactions, the incremental cost of each allergic reaction, and estimate of the number of allergic reactions prevented to truly model real-world effectiveness.

Clarification of patient states used: FARE requests further clarification on the patient states (e.g., well without peanut tolerance) being used in the model and how they will be applied. We assume being "well but having an allergic reaction" is based on accidental (vs. iatrogenic) exposure, but clarification is needed. FARE would also like to understand sources to estimate probabilities for transitioning through states over a patient's lifetime, and how that may vary by sub-group.

Patient heterogeneity: FARE strongly urges ICER to consider patient variability through sub-group analysis. Patients may vary greatly in terms of the following: goals in treatment, treatment response, tolerance for Adverse Events, age, onset of disease, preferences in route of administration and degree of desensitization. Other critical aspects may affect key model assumptions, such as weights used in QALY analysis.

7. Data sources and gaps

Concerns with availability of high quality data: FARE has an overall concern with the insufficient amount of high quality data needed to inform ICER's evaluation. Specific areas of concern include: a) nature of available data for 'OIT using other peanut' 2) lack of long-term outcomes 3) lack of rate of reactions and ED visits 4) poor patient quality of life measures 5) significant variability in clinical data across interventions (making comparisons difficult) and 6) poor understanding of meaningful sub-groups and needed differences in model weights and assumptions. FARE implores ICER evaluators to collaborate with FARE and other stakeholders to ensure the most accurate and comprehensive sources of data are used for ICER's evaluation.

FARE advocates for appropriate use of these innovative treatments and believes that patients with peanut allergy deserve choices to meet their diverse needs. FARE welcomes the opportunity to partner with ICER to support the value assessment and ensure cost-effectiveness of these treatment solutions. By working together, we believe we can ensure that we can create a new paradigm where people with peanut allergy really will be safe where they live, work, and play.

Thank you.

Best regards,

Lisa Gable
Chief Executive Officer