FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
Allergenic Products Advisory Committee (APAC)
30th Meeting

This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

OPEN PUBLIC MEETING

FDA White Oak Campus
Great Room Salon B&C
Silver Spring, MD 20903

September 13, 2019
# PARTICIPANTS

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paul A. Greenberger, M.D.</td>
<td>Northwestern University</td>
</tr>
<tr>
<td>Serina A. Hunter-Thomas, M.S.A., R.N.</td>
<td>Food and Drug Administration (FDA)</td>
</tr>
<tr>
<td>Andrea Apter, M.D., MSc, MA</td>
<td>Hospital of the University of Pennsylvania</td>
</tr>
<tr>
<td>Erica Brittain, PhD</td>
<td>National Institute of Health (NIH)</td>
</tr>
<tr>
<td>Mark Dykewicz, M.D.</td>
<td>Saint Louis University School of Medicine</td>
</tr>
<tr>
<td>Ira Finegold, M.D., MS</td>
<td>Icahn School of Medicine</td>
</tr>
<tr>
<td>Randy Hawkins, M.D.</td>
<td>Charles Drew University</td>
</tr>
<tr>
<td>John Kelso</td>
<td>Scripps Clinic</td>
</tr>
<tr>
<td>Soheila Maleki, PhD, FAAAAAI</td>
<td>U.S. Department of Agriculture</td>
</tr>
<tr>
<td>Gailen Marshall, M.D., PhD, FACP</td>
<td>UMMC</td>
</tr>
<tr>
<td>Hendrik Nolte, M.D., PhD</td>
<td>ALK, Inc.</td>
</tr>
<tr>
<td>Daniel Adelman, M.D.</td>
<td>Aimmune Therapeutics</td>
</tr>
<tr>
<td>James Baker, M.D.</td>
<td>Mary H. Weiser Food Allergy Center</td>
</tr>
<tr>
<td>A. Wesley Burks, M.D.</td>
<td>UNC Health Care</td>
</tr>
<tr>
<td>Sofia Chaudhry, M.D.</td>
<td>CBER</td>
</tr>
<tr>
<td>Stephen Dilly, MBBS, PhD</td>
<td>Aimmune Therapeutics</td>
</tr>
<tr>
<td>Marion Gruber, PhD</td>
<td>CBER</td>
</tr>
<tr>
<td>Pamela A. Guerrero, M.D., PhD</td>
<td>National Institute of Health (NIH)</td>
</tr>
<tr>
<td>Kathleen S. Hise, M.D.</td>
<td>CBER</td>
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<tr>
<td>Taruna Khurana, PhD</td>
<td>CBER</td>
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<td>Louise Peacock</td>
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CALL TO ORDER/OPENING REMARKS/INTRODUCTIONS

DR. PAUL GREENBERGER: Welcome to the Allergenic Products Advisory Committee. I'm Dr. Paul Greenberger, Northwestern University, Chicago, Illinois. The committee will meet today to discuss and make recommendations on the safety and efficacy of peanut allergen powder manufactured by Aimmune Therapeutics Incorporated. Indicated as an oral immunotherapy to reduce the incidence and severity of allergic reactions, including anaphylaxis after accidental exposure to peanut in patients ages 4 to 17 years of age with a confirmed diagnosis of peanut allergy.

At the beginning, I would like each person at the table here to identify themselves, give their institutional expertise and interests. And I'm going to start with Dr. Nolte, please.

DR. HENDRIK NOLTE: Good morning. My name is Hendrik Nolte. I’m the industry representative. I’m currently employed by ALK. I’m a pulmonologist also trained in allergy.
DR. RANDY HAWKINS: Good morning, Dr. Randy Hawkins, internist and pulmonologist in private practice in Los Angeles, California, consumer representative.

DR. PAUL GREENBERGER: Thank you. Dr. Maleki.

DR. SOHEILA MALEKI: Good morning. My name is Soheila Maleki. I work with the U.S. Department of Agriculture, and I specialize in biochemistry and immunology of allergens.


DR. GAILEN MARSHALL: Gailen Marshall, University of Mississippi Medical Center, and I specialize in allergy and immunology.

DR. PAUL GREENBERGER: Thank you. Dr. Kelso.

DR. JOHN KELSO: I am John Kelso from Scripps Clinic in San Diego, and I'm an allergist.

DR. ANDREA APTER: I am Andrea Apter from the University of Pennsylvania. I'm an allergist and
immunologist and an epidemiologist, and my research focuses on asthma in underserved populations.

DR. PAUL GREENBERGER: Thank you. Dr. Brittain.

DR. ERICA BRITTAIN: I'm Erica Brittain. I'm a statistician at the National Institute of Allergy and Infectious Diseases.

DR. PAUL GREENBERGER: Thank you. Dr. Dykewicz.

DR. MARK DYKEWICZ: Mark Dykewicz, allergy and immunology at St. Louis University School of Medicine.

DR. PAUL GREENBERGER: Dr. Gruber.

DR. MARION GRUBER: My name is Marion Gruber. I am the Director of the Office of Vaccines Research and Review at CBER. And this office regulates not only preventive vaccines, but other related biological products including allergenic products.

DR. PAUL GREENBERGER: Thanks you. Dr. Chaudhry.
DR. SOFIA CHAUDHRY: Sofia Chaudhry. I am a clinical team leader in the Office of Vaccines Research and Review as well.

DR. PAUL GREENBERGER: Thank you, and I want to make these comments to those of you giving presentations for the open public hearing, which we value very much. We do ask that you make sure your remarks are limited to the four minutes because we have many speakers today. Thank you. And, I am going to ask Captain Hunter-Thomas to take over.

CAPT. SERINA HUNTER-THOMAS: Thank you, Dr. Greenberger. Good morning everyone. My name is Captain Serina Hunter-Thomas and it is my pleasure to serve as the Designated Federal Officer for the 30th APAC Meeting. The committee management specialists for this meeting are Ms. Angelica Jones and Ms. Monique Hill. The committee management officer for this meeting is Ms. Casey Stewart. And our director is also in the room, Dr. Prabhakara Atreya. On behalf of the FDA, the Center for Biologics Evaluation and Research
and APAC, we would like to welcome everyone to this meeting.

Today's session has one topic that is open to the public in its entirety. The meeting topic is described in the Federal Register notice that was published on June 24th, with a follow-up notice update that was published on July 11th. The FDA CBER press media representative for today's meeting is Megan McSeveney. Ms. McSeveney, if you are here, please stand up so that members of the press can identify and reach out to you as needed. Thank you. And the transcriptionist for the meeting today is Ms. Devin Shiple. Did I say that right?

I would like to remind everyone to please check your pagers and cell phones and please make sure that they are either turned off or in silent mode. Also, when making your comments, please first state your name and speak loudly and clearly so that your comments are accurately recorded for transcription. Please keep in mind that there is a committee member
who is joining us remotely. Ira, would you like to introduce yourself?

DR. IRA FINEGOLD: Yes. I am Dr. Ira Finegold, Chief of Allergy at Mount Sinai, Weston, New York. And I am principally in private practice as an allergist/immunologist.

CONFLICT OF INTEREST STATEMENT

CAPT. SERINA HUNTER-THOMAS: Thank you. So that everyone can be heard for the benefit of everyone attending in the room, and also joining us remotely, I will now proceed to read the Conflict of Interest Statement for this meeting.

The Food and Drug Administration is convening today, September 13, 2019, for the 30th Meeting of the Allergenic Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. This meeting is held in open session in its entirety. Today, the Committee will discuss and make recommendations on the safety and efficacy of Peanut
Allergen Powder manufactured by Aimmune Therapeutics, Incorporated, indicated for treatment to reduce the risk of anaphylaxis after accidental exposure to peanuts in patients age 4 to 17 years with a confirmed diagnosis of a peanut allergy.

This topic is determined to be a particular matter involving specific parties. With the exception of the industry representative, all participants of the committee are special government employees or regular federal government employees from other agencies and are subject to the Federal Conflict of Interest laws and regulations.

The following information on the status of this advisory committee's compliance with Federal Ethics and Conflict of Interest laws, including but not limited to 18 U.S.C. Section 208 is being provided to participants at this meeting and to the public. This Conflict of Interest Statement will be available for public viewing at the registration table.

Related to the discussions at this meeting, all members and consultants of this committee have been
screened for potential conflicts of interest of their own as well as those imputed to them, including those of their spouse or minor children; and for the purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts/grants/CRADAs, teaching/speaking/writing, patents and royalties and primary employment.

FDA has determined that all members of this Advisory Committee are in compliance with Federal Ethics and Conflict of Interest laws. Under 18 U.S.C. Section 208, Congress has authorized the FDA to grant waivers to Special Government Employees and regular government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential conflict of interest.

Based on today's agenda, no conflict of interest waivers were issued to any members or consultants under 18 U.S.C. Section 208.
Dr. Hendrik Nolte is currently serving as the industry representative to this Committee. He is employed by ALK, Incorporated. Industry representatives act on behalf of all related industry and bring general industry perspective to the Committee. Industry representatives are non-voting members of the Committee and are not appointed as Special Government Employees; hence, industry representatives are not screened and do not participate in the closed sessions and do not have voting privileges.

Dr. Randy Hawkins is serving as a temporary consumer representative for this Committee. Consumer representatives are appointed Special Government Employees and are screened and cleared prior to their participation in the meeting. They are voting members of the Committee and hence, do have voting privileges; and they do participate in the closed sessions if they are held.

Dr. Pamela Guerrerio is serving as a speaker. She is the Chief of the Food Allergy Research Unit in
NIAID's Division of Intramural Research. She is screened for her financial conflict of interest and cleared to participate. At this meeting, there may be regulated industry speakers and other outside organization speakers making presentations. These participates may have financial interests associated with their employer and with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflict of interest.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms, its products and, if known, its direct competitors. We would like to remind members, consultants and participates that if the discussion involves any other products or firms not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participants needs to inform the DFO and exclude
themselves from such involvement; and their exclusion will be noted for the record.

This concludes my reading of the Conflict of Interest Statement for the public record. And at this time, I would like to hand the meeting over to Dr. Paul Greenberger. Thank you.

DR. PAUL GREENBERGER: Thank you. Our first speaker, Dr. Taruna Khurana, is speaking on the subject Introduction from the FDA and Presentation of Questions.

FDA - PEANUT (ARACHIS HYPOGAEA) ALLERGEN

POWDER: PALFORZIA

DR. TARUNA KHURANA: Thank you, Dr. Greenberger, and thank you, Serina. Good morning everyone.

UNIDENTIFIED MALE: Cannot hear you.

DR. TARUNA KHURANA: Hope you can hear now. Sorry. I welcome you all again to this Allergenic Products Advisory Committee meeting. My name is Taruna Khurana. I am with the Office of Vaccines Research and
Review within CBER/FDA, and I am chair for the BLA Review Committee.

Today, in this Allergenic Products Advisory Committee meeting, we will be discussing peanut allergen powder, also known as Palforzia. The Biologics License Application for Palforzia was submitted by Aimmune Therapeutics to FDA for review. This is an overview of the agenda today.

I will give a very brief introduction, and I will introduce the product and the clinical package of Palforzia. And I will conclude my presentation with presenting questions to the Committee for discussion and voting. I will be followed by Dr. Pam Guerrerio from NIAID/NIH. She will be presenting on the current state of treatment for food allergy. Aimmune presentations will follow right after that.

We will break for lunch, and after lunch we will reconvene for open public hearing. The open public hearing will be followed by FDA presentation, Dr. Kathleen Hise. She is a clinical reviewer assigned to this BLA, and she will present the clinical and
safety data from the studies conducted with Palforzia. Right after FDA presentations, the Committee will be asked to discuss and vote on the questions and the meeting will adjourn.

Let me talk about the peanut allergy. The peanut allergy affects more than six million children in the United States, and only 20 percent of the children outgrow peanut allergy. The quality of life for peanut allergy individuals and their caregivers is adversely affected, mostly due to the fear and anxiety of accidental exposures.

To prevent systemic allergic reactions that include anaphylaxis, these individuals must maintain strict avoidance. But despite the avoidance measures, the accidental exposures do happen. And, in that condition, the antihistamines and epinephrine are the only options that can be used to treat systemic allergic reactions. I would like to add here that no immunotherapy is licensed for peanut allergy.
Palforzia, the product that is the topic of discussion here in this Advisory Committee, contains the active component that is 12 percent defatted peanut powder. The product is supplied in pull-apart, color-coded capsules and foil-laminated sachet. The product is emptied from capsules or sachet before mixing with semisolid food for oral administration.

This slide shows a table which is pretty much formulary composition of the drug product of Palforzia. As I just mentioned, the drug substance or the active component of Palforzia is light-roasted 12 percent defatted peanut powder. There are four excipients: maize powder, which acts as a diluent; microcrystalline cellulose acts as diluent; colloidal silicone dioxide is a glidant; and magnesium stearate is a lubricant in the product.

This is the dosing regimen of Palforzia. Palforzia dosing regimen includes three phases: initial dose escalation phase, up-dosing phase, and the daily maintenance phase. The initial dose escalation phase is conducted in a single day and consists of five dose
levels, starting from 0.5 mg to 6.0 mg. Each dose is administered at 20 to 30-minute intervals under the supervision of a qualified healthcare professional.

The initial dose phase escalation is followed by an up-dosing phase that begins at 3 milligram and continues as tolerated, with up-dosing every two weeks, reaching to 300 milligram daily maintenance treatment.

I would like to emphasize here that the first dose of each new level in the up-dosing phase is administered under medical supervision, followed by at-home daily dose at the same level for the next two weeks. After completing all the dose levels of up-dosing, the maintenance dose stops. The first 300 milligram of the maintenance dose is administered in clinic, very similar to the previous up-dosing levels. If tolerated, the patient continues taking the daily maintenance dose at home.

This slide shows the packaging configuration for all the dosing regimens. Panel A is the initial dose escalation card. All the five doses starting from 0.5 to 6.0 milligram are packaged in a single card,
which is the initial dose escalation card. Panel B is an up-dosing folio card. Here is just one example of a two-week supply where the first dose is taken in clinic, and the patient can take at home for the next two weeks. Panel C is the daily maintenance dose, which is a 300-milligram sachet, not the capsule.

Aimmune reports the following indications for Palforzia. Palforzia is indicated to reduce the incidence and severity of allergic reactions, including anaphylaxis after accidental exposure to peanuts in patients age 4 through 17 years with a confirmed diagnosis of peanut allergy. Palforzia is not intended for the immediate relief of allergic symptoms and is to be used in conjunction with a peanut avoidant diet.

This slide shows the clinical package submitted for Palforzia. The clinical package included safety and efficacy data from four Phase 3 studies. ARC003 is Phase 3 randomized double-blind, placebo-controlled study for safety and efficacy in subjects 4 to 55 with a treatment duration of 12 months.
ARC007 is a Phase 3 safety study. It is also a randomized double-blind, placebo-controlled study in subjects 4 to 17, and the treatment duration for ARC007 was six months.

ARC004 is a Phase 3 open label follow on study for ARC003, again for safety in subjects 4 to 55; and the treatment duration for this ongoing study is up to three years.

ARC011 is a Phase 3 open-label uncontrolled study, a follow on for ARC007 safety in subjects 4 to 17 years, and the treatment duration for this study is six months.

Right after the FDA presentation today this afternoon, the Committee will be asked to discuss and vote on the following questions:

Question 1: Are the available efficacy data adequate to support the use of Palforzia as a treatment to reduce the incidence and severity of allergic reactions, including anaphylaxis, after accidental exposure to peanuts in patients age 4 to 17 years with
a confirmed diagnosis of peanut allergy. Please vote yes or no.

As a part of risk evaluation and mitigation strategy, the Agency will require to follow the risks of systemic allergic reactions, including anaphylaxis, due to Palforzia:

A. Documentation that any patient prescribed Palforzia has a valid prescription for injectable epinephrine.

B. Caregivers and patients must attest to carrying injectable epinephrine while on Palforzia.

C. Initial dose escalation and the first dose of each up-dosing level must be administered in a certified facility capable of treating systemic allergic reactions.

The Committee would like to vote on these questions:

Question 2. Are the available safety data in conjunction with these additional safeguards adequate
to support the use of Palforzia in patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy. And, with that, I conclude my presentation.

DR. PAUL GREENBERGER: Thank you. Our next speaker is Dr Pamela Guerrerio. And her topic, The Current State of Treatment for Food Allergy.

GUEST PRESENTATION: THE CURRENT STATE OF TREATMENT FOR FOOD ALLERGY

DR. PAMELA GUERRERIO: Good morning everyone. First of all, I would like to say thank you to the Committee for the opportunity to speak this morning. Over the last few decades, food allergy has emerged as a major public health issue affecting up to 10 percent of people in westernized countries, although the prevalence is rapidly growing in underdeveloped nations as well. Overall, it is estimated that about 3 percent of the world's population is affected, which equates to about 240 million people.
Here in the United States, food allergy affects 32 million Americans, including one in 13 children. Perhaps not surprisingly, given how pervasive food is in our daily lives, food allergy has a tremendous negative impact on quality of life and also creates a significant financial burden. Food allergy costs American families about 25 billion dollars each year.

Some children with food allergy will naturally outgrow their disease, and the likelihood of this depends on a number of factors, including the food. About half the children allergic to milk, egg, wheat and soy will outgrow their allergy by about age 10. Although allergy to peanut and tree nuts tends to be more persistent, with these being lifelong allergies for most patients.

Children who have had severe reactions in the past, or who have reacted to very small doses of the food, are generally more likely to have persistent disease. The presence of other allergic disorders, such as asthma and eczema, or a larger skin-prick test
response or IgE levels for the food, can also make it less likely for a child to outgrow their allergy. Our current treatment for food allergy is strict avoidance with ready access to rescue medications, including an epinephrine auto-injector.

A recent study in the United States that looked at 900 adults, adolescents and children, found that the majority of patients fill their prescriptions for epinephrine, just under 90 percent. With costs and lack of a reaction history being the primary reason cited why patients did not. However, only 44 percent of people in this study admitted to carrying their epinephrine all the time. And half of the adults and 30 percent of the children reported that they had had at least one severe reaction, where epinephrine would likely have been beneficial, but was not used.

The question of how often children with food allergy experience allergic reactions was addressed in a prospective observational study that included 500 preschool age children with milk and egg allergies. In this study, the children experienced about one reaction
per year, with milk being the most common trigger, followed by egg and peanut. The majority of these reactions were the result of accidental exposures, either due to unintentional ingestion, errors reading labels, or cross-contact. And 11 percent were the result, however, of purposeful exposure to the food. Interestingly, over half the reactions were attributed to food that was not provided by the parent, so either relatives or teachers.

The authors found that children who had a higher number of food allergies or higher IgE levels for the food were more likely to have reactions. And 11 percent of the reactions were considered severe, yet less than one-third of these were appropriately treated with epinephrine. And the primary reasons given were that the reaction was just not perceive as severe, epinephrine was simply not available, or the caretakers were not comfortable administering the drug.

Allergic reactions also appeared to be quite common in adolescence. A population-based study from Australia looked at over 500 children 10 to 14 years of
age with possible food allergy. They found that 44 percent of the children had at least one reaction to food in the last year, and 34 percent had more than one. Similar to the study in infants, about 10 percent of these reactions were consistent with anaphylaxis, yet again, less than half of these reactions were treated with epinephrine.

In this study, peanuts and tree nuts were identified as the most common trigger for reactions, which were overall more common in females, children who had two or more food allergies, and those with a history of asthma. Multiple studies have shown that food is the most common cause of anaphylaxis in both children and young adults. However, fortunately, the number of cases of fatal food-induced anaphylaxis were relatively low, with the likelihood this being less than the likelihood of death due to accident, murder or fire. There is some geographic variation in the rate of fatal anaphylaxis, ranging from 0.04 per million person years here in the United States to 0.12 in the
United Kingdom, although these numbers do vary with different studies.

There has been a lot of interest in trying to identify which children are at higher risk for having a severe reaction. Most studies have found that peanut and tree nuts are the most common trigger for food-induced anaphylaxis, although milk is more common in infants and young children. Interestingly, egg allergy is very common and can induce anaphylaxis, but has only rarely been associated with life-threatening reactions. Asthma, and particularly poorly controlled asthma, is another important risk factor.

Most cases of fatal food-induced anaphylaxis have occurred in children who were known to be allergic to the food and had a history of anaphylactic reactions in the past. Although the rates of food-induced anaphylaxis are highest in young children, most fatal cases have occurred in adolescence and young adults. And several studies have found that a delay in administering epinephrine is associated with severe
reactions. There are, at this point, no laboratory
tests that can reliably predict reaction severity.

There have been a couple of studies suggesting
that greater reactivity to peanut and the basophil
activation test might indicate which subjects are more
likely to have severe reactions to peanuts during an
oral food challenge. A number of studies have found
that food and component IgE levels are associated with
a likelihood of having an allergic reaction. But these
tests have not reliably predicted reactions severity in
most studies.

There has also been a lot of interest in
trying to define the minimum quantity of a food that is
necessary to elicit an allergic reaction. This
question was addressed in an international study of
over 1,600 children who underwent an oral food
challenge to peanut. And 32 percent of these children
failed their challenge. And the authors used this
information to calculate the eliciting dose 10, or
ED10, which is the dose of peanut where 10 percent of
peanut-allergic individuals would be expected to have an allergic reaction. They calculated this value to be 20 milligram of whole peanut. The ED50, where half of patients would react, was about 300 milligram of whole peanut, which is the equivalent of about half of a peanut kernel. The authors reported that ten percent of the children who failed challenges in this study failed anaphylaxis. This was three times more common in teenagers than in younger children, particularly when the participant reacted at a lower dose of peanut. Overall, anaphylaxis was more common in all age groups with increasing amounts of peanut consumed during the challenge.

Two additional studies from Europe tried to define the ED5 for peanut using double blind placebo-controlled food challenges. They identified this value to be 1.56 milligram of peanut protein in one study, and 1.95 milligram in the second. They tried to validate this level in the Peanut Allergen Threshold
Study. This was an international study that included 378 children with peanut allergy. All of these children were challenged with a single dose of 1.5 milligram of peanut protein in the form of a cookie, which is about 1/100 of a peanut kernel. Importantly, children were included regardless of how severe their reactions to peanut were in the past.

In this study, 65 percent of the participants had no reaction at all; 18 percent had subjective symptoms only with no objective findings; 15 percent had mild transient symptoms, such as a few hives that resolved in a few minutes; and two percent had objective symptoms. Of these eight children, four were treated with an oral antihistamine, and the other four did not require treatment at all. None of the children required epinephrine.

The authors also found that food allergy related quality of life did improve one month after the challenge, regardless of the challenge outcome. It turns out, however, that an individual's threshold dose
may not be static, and can vary day to day, depending on a number of factors.

In a recent study from the UK, peanut-allergic individuals underwent three peanut oral food challenges in a random order; one where they exercised after each dose, one where they were sleep-deprived before undergoing the challenge, and one with no intervention. They found that the mean threshold dose of peanut that elicited an allergic reaction with no intervention was 214 milligram of peanut protein. And this was reduced by 45 percent by both exercise and sleep deprivation.

They calculated the ED1, where one percent of people would react, to be 1.5 milligram of peanut protein in the no intervention. This was reduced to 0.5 milligram after sleep deprivation and 0.3 milligram with exercise. So, this study shows that exercise and sleep deprivation may make it more likely for people to experience allergic reactions.

Certainly, much of the burden of having a food allergy comes from the psychosocial impact of this disease. Several studies have found that quality of
Life of children with food allergy is more significantly impacted than children who have rheumatologic disease or Type 1 diabetes; in part because this disease affects nearly every aspect of their daily lives and also creates a burden for their parents.

Forty percent of parents believe that their child has a very great chance of dying from their food allergy. Over 40 percent of parents report that they are not comfortable going on a vacation where they may need to stay away from home; 30 percent of parents report that they visit their child's school at least once a month to discuss their child's food allergy; and 35 percent of both children and adults report that they have been bullied because of their food allergy.

Strategies that can reduce any degree of the uncertainty surrounding food allergic reactions have been shown to improve quality of life. Oral food challenges significantly improve health-related quality of life for both patient and the parents, and this
benefit was seen regardless of whether the child passed
or failed the challenge.

Another study found that access to 24-hour
expert guidance regarding how to treat an allergic
reaction improved quality of life, regardless of
whether the family ever called the help line or not.

So, these studies suggest that strategies that
can provide any clarity regarding the severity of an
allergy, how to treat a reaction, or that can confirm
that diagnosis with certainty, may all improve quality
of life without directly affecting the natural history
of the disease.

The rapidly growing prevalence of food allergy
does necessitate a viable treatment for this disease;
and the goals of such a treatment may vary from patient
to patient, with some patients prioritizing protection
against accidental exposures and severe reactions,
while some patient report that they want to be able to
eat the food in limited quantities. Certainly, given
the psychosocial impact of this disease, an improvement
of quality of life is also a worthy goal.
Immunotherapy has been used for over a century now as a treatment for allergic disorders, but it has really only been in the last couple of decades that this has been systematically studied for food allergy. The different forms of immunotherapy vary in the mechanism in which the allergen is delivered.

With oral immunotherapy, patients directly ingest the allergen in a food vehicle that is given in gradually increasing quantities. With sublingual immunotherapy are split. Patients dispense a premeasured amount of an allergen-containing solution under their tongue and then hold it there for a few minutes before swallowing. With epicutaneous immunotherapy, the allergen is delivered through the skin via a patch which is applied on the upper arm or back, and then changed every 24 hours.

Before I discuss the different immunotherapy approaches for food allergy, I first want to review a few food allergy definitions that are often used when describing the results of these studies. Oral tolerance is defined as the normal response to food.
This is characterized by a complete lack of clinical activity and does not require regular exposure to the food. Desensitization refers to the increase in the amount of food that a patient can tolerate while on treatment, and this requires that the patient be continuously exposed to the food. Sustained unresponsiveness, or remission for the purposes of this presentation, refers to a lack of clinical reactivity to the food that persists, even when treatment has discontinued. And this, too, may require some level of continued exposure.

Although immunotherapy has been around for decades, we still do not have a complete understanding of the mechanisms responsible for its clinical benefits. Several immunotherapy studies have shown that specific IgE levels do decrease over the course of treatment, usually following an initial bump early in the course of treatment. Specific IgG levels also increase, particularly IgG4 which is known to have IgE blocking activity; and IgE levels also generally rise, particularly with OIT and SLIT. Both basophil and MAST
cell activity responses are suppressed with immunotherapy, as indicated by reduced skin prick test responses and basophil CD63 expression. Peripheral blood mononuclear cells from patients undergoing immunotherapy often show reduced expression of pro-allergic TH2 cytokines following allergen stimulation, and there is often a concomitant increase in IL-10 and TGF Beta which can have pro-allergenic effects. Finally, some studies have shown an increase in T-regulatory cells that can suppress the effector response to allergen.

Oral immunotherapy or OIT has been best studied in food allergies for peanut, egg and milk. This is usually conducted over four phases. Most patients undergo a screening or a baseline oral food challenge to determine their pre-treatment level of reactivity to the food. This is followed by an initial dose escalation day where patients generally aim to reach about 10-25 mg of the food protein. Next, is the dose build-up phase, where patients ingest gradually increasing quantities of the food, usually increased
every 1-2 weeks in the clinic; and, at the end of that is the maintenance phase where patients ingest between 500-4,000 mg of the food daily over the course of months to years.

At the end of maintenance dosing, patients usually undergo a second oral food challenge to assess desensitization; and in some studies, patients are taken off treatment for a period of time to assess sustained unresponsiveness.

Although there has been a great deal of heterogeneity across OIT trials for food allergy, most of the data would suggest that this treatment is extraordinarily effective at inducing desensitization for patients, with 60-80 percent achieving this outcome.

The rates of sustained unresponsiveness have been more variable, ranging from 30-70 percent, depending on the study, how old the patients were who were treated, the food that was given, how long patients continued on dosing, and how low they were
taken off dosing before treatment, and then sustained unresponsiveness was assessed.

There have been a few studies that have looked at quality of life following immunotherapy, and these have generally shown an increase in parent-reported outcomes, although patient-reported outcomes have not been consistently assessed.

The clinical benefits of OIT are counterbalanced by its relatively high rate of allergic reactions. These are most common during the dose escalation and build-up phase, although can occur during maintenance, and, in some cases, can occur unpredictably in response to previously tolerated doses. The majority of these reactions are mild, usually mouth itching or a few hives, and often resolve spontaneously without treatment, or, in some cases, with oral antihistamines. However, in cross-OIT trials about 10-20 percent of participants do withdraw from study because of an unacceptably high rate of side effects, usually chronic abdominal pain. A recent meta-analysis found that just under three percent of
subjects receiving OIT develop a condition called eosinophilic esophagitis or EoE, which is a condition characterized by an excessive accumulation of eosinophils in the esophagus. Now whether this represents new cases of EoE that were caused by OIT or whether this is a masking of previously undiagnosed disease remains to be seen.

Pulled safety data from three pediatric peanut OIT trials revealed that about 80 percent of subjects did experience an adverse event, the majority of which occurred at home, 90 percent. Forty-two percent of these reactions were considered systemic. Just under half of patients had GI complaints. Overall, across the three studies, 20 percent of participants dropped out, most commonly because of GI side effects. Over 60 percent required some form of treatment for an adverse event, most commonly antihistamines, although 12 percent were treated with epinephrine. The authors did note that there were an additional nearly 100 adverse events where epinephrine was likely indicated but was not given. They further showed that the patients with
allergic rhinitis, asthma and higher skin prick test responses to peanut generally had a higher overall rate of adverse events.

Another meta-analysis published recently looked at 12 randomized controlled OIT trials to assess the safety and efficacy of this treatment. Compared to subjects who were practicing strict avoidance or received placebo, those who received OIT were much more likely to pass an oral food challenge to peanut, again attesting to the ability of OIT to effectively induce desensitization. However, those subjects who received OIT were also more likely to experience anaphylaxis, a higher frequency of anaphylaxis, a greater need to use epinephrine, and an overall increased rate of serious adverse events, as well as non-anaphylactic reaction, such as vomiting, angioedema, and upper and lower respiratory reactions.

How OIT might translate to the real world was recently addressed in a study published this year where five practices reported their experiences with 270 pediatric patients. Here, just under 80 percent of
patients were able to complete the escalation and reach maintenance dosing. Those who were younger and had lower peanut-specific IgE levels were more likely to have success. The authors did not systematically assess adverse events in this study; but just under a quarter of the patients did require epinephrine for an OIT related reaction and 37% developed GI symptoms.

A number of factors have been identified that may increase the risk of adverse events during OIT, and there are a number of measures that can be taken to mitigate this risk. Some groups recommend that the dose be taken at a consistent time each day and following a meal or snack since there is some evidence that taking the dose on an empty stomach might increase the risk of a reaction. I talked earlier how exercise can lower the reaction threshold, so it is often recommended that patients restrict physical activity for 1-2 hours after they take the dose. Febrile illnesses and other viral gastroenteritis have been associated with a higher rate of reaction. So, dosing is often suspended in those situations. Depending on
how long dosing is suspended, it may be necessary to either reduce the dose or give the next dose in the clinic once treatment is resumed.

Optimal control of allergic diseases, such as asthma and allergic rhinitis, can also reduce the rate of allergic reactions. Finally, patients are also asked to continue having an allergy action plan available and to carry an epinephrine auto-injector with them at all times.

There has been a lot of interest in identifying bio-markers that might predict which patients might respond best to OIT. Specific IgG4 levels do increase with treatment, but the magnitude of this increase or the absolute levels have no reliably predicted response to treatment for any individual patient. Several studies have found that lower IgE levels to the food and skin prick test reactivity pre-treatment, as well as well-controlled asthma, might be associated with better outcomes. The longer that patients undergo OIT, the more likely they are to achieve desensitization as well as sustained
unresponsiveness. Finally, there is some evidence that OIT may be more effective in younger children. Vickery and colleagues performed early OIT on 40 children 9-36 months of age. The children were randomized to either 300 or 3,000 mg of peanut flour for their maintenance, and they continued treatment for up to three years. In this study, just under 80 percent of the subjects achieved sustained unresponsiveness, which is much higher than the 20-30 percent that has been reported in many other OIT trials for peanut. Importantly, there was no difference in the likelihood of achieving sustained unresponsiveness whether the child received the higher or lower dose of maintenance. Overall, the children treated with early OIT were 19 times more likely to tolerate peanut than their age-matched controls who did not receive OIT.

I mentioned that there are other forms of immunotherapy being investigated for food allergy, including SLIT. This has been best studied for peanut, milk, hazelnut and fresh fruit. Because of limitations in extract concentrations and the volume of fluid that
patients can practically hold under their tongue,
typical maintenance doses with SLIT are lower than
those used for OIT, generally in the 1-10 mg range.
SLIT has been associated with moderate clinical
desensitization and immunologic changes; but it is
uncommon for patients to achieve sustained
unresponsiveness.

Typical maintenance doses with epicutaneous
immunotherapy are generally in the 200-500 mcg range.
EPIT has been best studied for peanut and milk allergy,
where it has been shown to induce modest
desensitization and immunologic changes. EPIT may have
the most benefit in younger children, although that may
be true for all forms of immunotherapy. Because
allergen is not thought to reach the systemic
circulation with epicutaneous immunotherapy, this
treatment has been associated with a very low rate of
systemic adverse events.

The European Academy of Clinical Immunology
recently performed a systematic review and meta-
analysis of immunotherapy for food allergy that
included 25 OIT trials, five split trials, and one EPIT trial. Most of these studies were performed in children. The review found that there was a significant benefit from immunotherapy in terms of inducing desensitization. The benefit was also suggested for sustained unresponsiveness, but this did not reach statistical significance.

Each of the different forms of immunotherapy have a number of advantages and disadvantages. OIT has been associated with the highest rates of desensitization and sustained unresponsiveness, although this is counterbalanced by a relatively high rate and severity of reactions. Overall, about 10-20 percent of children are unable to complete treatment because of side effects.

SLIT induces moderate desensitization and minimal sustained unresponsiveness. The rate of adverse events during SLIT is generally lower than OIT, primarily restricted to mouth itching that often does not require treatment. Systemic reactions are rare,
and there have been no cases that EoE reported associated with SLIT for food allergy.

Epicutaneous immunotherapy induces modest desensitization, but adverse are generally very minimal, usually limited to irritation at the patch site. Systemic reactions and GI side effects are overall quite rare, and, in general, this treatment is well tolerated with few study drop-outs.

Products for OIT and EPIT for peanut are furthest along in development; and, if these products are approved, the decision about which one to use for a given patient will require careful assessment of both the patient's and the family's goals for treatment.

Oral immunotherapy is likely to offer the greatest chance for tolerating larger amounts of the food; however, families must be comfortable treating allergic reactions, including possibly using epinephrine. OIT does require some time commitment with frequent clinic visits, generally during the escalation phase.

Compliance is an issue since some patients have lost or regained reactivity after just one week of avoidance;
and taste aversion is another consideration since patients will be needing to adjust the dose on a daily basis.

With epicutaneous immunotherapy it may require a longer time on treatment to achieve a similar level of protection. However, EPIT has a very low rate of side effects and may require fewer clinical resources.

There are a number of limitations of the current trials for food allergy that are worth mentioning. Many of the studies have included a relatively small number of participants with limited racial and ethnic diversity. There also has been significant heterogeneity, both in how the trials were designed and the outcomes that were assessed; and that can make it difficult to compare across studies. Many of the studies have only included patients who reacted below the 100-300 mg of food protein during their baseline oral food challenge, and we know that many patients react about that threshold. Patients who have life-threatening anaphylaxis or severe asthma are often excluded from these trials; but these may be the
patients in greatest need of a treatment; and finally, few studies have incorporated health-related quality of life, either before, during or following completion of the trial; and this will be an important outcome to assess in the future.

There are a number of variations in immunotherapy strategies that have been tested in pilot studies. About 30 percent of people with food allergy are allergic to more than one food; and these children may be more likely to have persistent disease. A recent Phase 1 study found that the rate of adverse events among children undergoing OIT for multiple foods, in this case peanuts and up to four other foods, was similar to the rate of adverse events of children undergoing OIT alone.

There has also been some interesting combination immunotherapy where patients begin treatment with either epicutaneous or sublingual immunotherapy, and then transition to OIT to try and reduce adverse events and improve safety.
In summary then, food allergy has become a major public health issue affecting millions of people across the globe. Much of the morbidity from food allergy really lies in its psychosocial impact, with a poor quality of life being reported in many patients. Despite strict avoidance, accidental exposures and reactions are common in all age groups; and finally, oral sublingual and epicutaneous immunotherapy are promising potential treatments for food allergy, each with their own set of advantages and disadvantages.

Thank you.

**DR. PAUL GREENBERGER:** Thank you very much, Dr. Guerrerio. I would like you to stay at the lectern so that the Committee can ask any questions they may have or make comments appropriate. Dr. Brittain.

**DR. ERICA BRITTAIN:** Hi. In the real world where people are using OIT, what happens after they are done with their maintenance phase?

**DR. PAMELA GUERRERIO:** That, I think, depends on the study. Some patients will continue on treatment, but that has varied from study to study.
DR. ERICA BRITTAINE: So, I don't know. I think there is some real-world OIT practice going on, right?

DR. PAMELA GUERRERIO: Most of those patients, I think, continue on therapy indefinitely.

DR. PAUL GREENBERGER: Dr. Maleki is next.

DR. SOHEILA MALEKI: Go ahead.

DR. PAUL GREENBERGER: Okay, your red is on. Dr. Hawkins.

DR. RANDY HAWKINS: I just want information about ethnicity and susceptibility to food allergy, racial backgrounds, African Americans, Asians, and Latinos. We saw some information in the presenters about the number of participants in each group. Do you have any information about that information?

DR. PAMELA GUERRERIO: About the diversity of the patients included in the studies?

DR. RANDY HAWKINS: The occurrence in the real world?

DR. PAMELA GUERRERIO: In the real world for the prevalence of allergy? Yeah. So there is some
evidence that children of African American descent and others may be at higher risk for having higher IgE level. Now, whether that always translates to a higher rate of food allergy remains to be debated, since some children will have positive IgE testing to foods, but not be clinically reactive.

**DR. RANDY HAWKINS:** I have a question. Could you comment on the drop-outs of the research subjects, like the timing? In other words, is it early on in the initial phase, or is it later on, after escalation has occurred and they have reached maintenance?

**DR. PAMELA GUERRERIO:** I mean certainly, the rate of adverse reactions is highest during that escalation phase. So, I think it can happen really at any point along treatment, but I think most of the adverse events are occurring during the escalation.

**DR. PAUL GREENBERGER:** Dr. Kelso.

**DR. JOHN KELSO:** I just wanted to reiterate a couple of points that you made to kind of put the problem in perspective. One was that most patients with peanut allergy on average have one reaction per
year to an accidental ingestion, and that about 10 percent of those would be labeled as severe. And that the fatality rate, if you ask most people, there has been a figure that has been floating around for a year that 100-200 people a year die from food allergy-induced anaphylaxis. But that's an extrapolated number. The number that you gave of a rate of 0.04 per million correlates more closely with actual CDC data that, in one year when it was evaluated, suggested that there were 11 fatalities in a given year from food allergy.

And then the third point that I think is important to just again kind of put the whole thing in perspective that you mentioned was that the ED50, the amount of peanut protein that a patient with peanut allergy would ingest that would cause some reaction -- not a severe reaction, just any reaction in 50 percent -- the ED50 is 300 milligram, which is one peanut kernel. So, half of patients with peanut allergy could eat a peanut kernel and not have a reaction.
So, I think those, just in putting in terms of perspective, the rate of reactions, the rarity of fatal reactions, and the kind of clinical level of tolerance of most patients, I think it's important the points that you made to put it in perspective.

DR. PAUL GREENBERGER: Dr. Maleki.

DR. SOHEILA MALEKI: Yeah. You alluded to the fact that there were patients that have potentially, like with viral or bacterial infections, that that might make their reactivity increase. And I was wondering if there is much known about that on people that have been through oral immunotherapy?

DR. PAMELA GUERRERIO: Yeah. I mean the reasons that people think that might happen is that the stress response from the infection might increase gut permeability and absorption of the allergen. But, I don't think we have a full understanding of why illnesses like that might increase the rate of reaction. It's more been an observation.

DR. SOHEILA MALEKI: Are there like recommendations for how the treatment-- would it alter
the treatment if somebody's, for example, in the process of it, or --

DR. PAMELA GUERRERIO: Yeah.

DR. SOHEILA MALEKI: Or is that known?

Dr. PAMELA GUERRERIO: So, I think, depending on how long treatment is suspended, you know, it is recommended that it may be necessary to give the next dose under observation in case the patient would react and have regained reactivity during that period of avoidance. Or even to go down to a lower dose when they reinitiate treatment.

DR. SOHEILA MALEKI: Thank you.

DR. PAUL GREENBERGER: For the audience, this issue will come up, I imagine, with the industry presentation and the discussions during the rest of the day. Dr. Apter.

DR. ANDREA APTER: A very nice presentation.

How much data is there, that you are aware of, of patients who have completed OIT and are on maintenance? How many persists for how many years? How many drop out? What sort of reactions do they have?
DR. PAMELA GUERRERIO: Once on maintenance?

DR. ANDREA APTER: Yes.

DR. PAMELA GUERRERIO: I don't have that data off the top of my head what the rate of reactions is specifically during the maintenance dose. I am sorry I don't know that.

DR. ANDREA APTER: I think it may be an important gap that nobody has.

DR. PAUL GREENBERGER: I am going to take the liberty of making one more comment, and this is regarding your part of the information about the right patient and circumstances about the patient. I would like to comment that there should be information regarding the office of doing the supervision and, to me at least, there should be dedicated people, healthcare professionals that would be available to help manage some of these issues that might come up like a sickness of some sort.

DR. IRA FINEGOLD: Can I ask a question? Because nobody could see my hand is raised.
DR. PAUL GREENBERGER: Sorry. Go ahead.

DR. IRA FINEGOLD: Okay. What I wanted to know in any of the methods to reduce reactions, are there any data about the use of antihistamines or antileukotrienes?

DR. PAMELA GUERRERIO: I don't know of any data off the top of my head that specifically looks at that. Certainly, some patients will take an antihistamine to try and reduce reactions during OIT, and they are commonly used to treat reactions after that happens in OIT. But, how effective they are preventing reactions, I do not know that data.

DR. IRA FINEGOLD: Thank you.

DR. PAUL GREENBERGER: That's a very good question and thank you. I think we could look at practice parameters, allergy/immunology practice parameters. And there is very little to no evidence that antihistamines alone would be protective against major anaphylactic reactions.

DR. PAMELA GUERRERIO: Against systemic reactions, yes.
DR. PAUL GREENBERGER: Okay. Dr. Dykewicz.

DR. MARK DYKEWICZ: It may not pertain specifically to your presentation, but, in terms of the FDA proposal for product labeling for risk evaluation and mitigation strategy, it says, "Initial dose escalation in the first dose of each up-dosing level must be administered in a certified facility capable of treating systemic allergic reactions." Does the Agency have a position of what would constitute a certified facility?

Dr. SOFIA CHAUDHRY: Sofia Chaudhry, FDA. I will take that question. So we are still working with Aimmune on how we would implement any REMS that are coming out of this application package. However, there are legal standards as well as specialists within the FDA that do deal with the REMS procedures in terms of what constitutes the certification. We do have the authority and the ability to outline what elements we would look for in those facilities. However, before we get wrapped up in the specifics, we need to take a step back and understand
what, as an Agency, we would be looking for. And I
don't think it is anything out of the realm, or
anything abnormal compared to what we would expect for
any practice that is administering any immunotherapy to
have.

In terms of where this dose would be
administered, we are looking for the providers and the
facility to have epinephrine to treat the patients
accordingly, to be able to follow blood pressures and
heart rates, and oxygen saturations, if needed, to
start an IV if needed. But again, the details of that
would be worked out with the company.

**DR. PAUL GREENBERGER:** Dr. Marshall.

**DR. GAILEN MARSHALL:** And forgive me for
speaking away from you, I don't know how to put my face
to the microphone and look at you at the same time. I
am interested in that a moment ago someone used the
term anaphylaxis, and then you said systemic. What I
need to know is if, either for you or for the FDA in
general, are you separating those two? Because most of
us around the room that take care of these would argue
that someone who has nasal congestion and urticaria simultaneously, both of which are pretty innocuous in themselves, are experiencing an anaphylactic reaction that has potentially life-threatening consequences. As opposed to what many people think of as anaphylaxis is when your blood pressure goes away or your trachea collapses. And I am just asking for your opinion. Are you parsing those two out, or do you consider them the same thing?

DR. PAMELA GUERRERIO: No. I consider two systems involved as anaphylaxis.

DR. GALEN MARSHALL: Thank you.

DR. PAMELA GUERRERIO: I don't know about the FDA.

DR. PAUL GREENBERGER: I wonder if Dr Chaundhry could comment on this?

DR. SOHEILA CHAUDHRY: Soheila Chaudhry, FDA. So, anaphylaxis in the realm of drug development, and specifically with immunotherapy, is a very difficult term to use. The Agency is well aware that this are differences in opinion in terms of the terminology. I
think the allergy and immunology community has one, or actually several definitions, that are used.

When we look at safety data across all drug development programs though, we tend to take a very conservative view. There is a general understanding that when you have a systemic allergic reaction, the practice in the community, appropriately so, is for epinephrine to be administered early and often. So, we would look at all ranges of severity with a critical eye. We are not discounting mild reactions, I guess, would be the takeaway.

DR. GAILEN MARSHALL: With a follow-up. So, if this is not the appropriate time to ask, just say so. But, would that then extend that any sort of educational information associated with a product, not unlike, as you point out, other forms of immunotherapy would take a more conservative definition of anaphylaxis for those who are not, shall we say, experts in dealing with this on a regular basis? The argument being that a safety concern as a spectrum,
going back to the early question about what a certified facility is.

This is something we have dealt with in plain old subcutaneous immunotherapy for decades. What constitutes a certified facility? What level of training will allergists support when it is given somewhere else versus those who support at home, et cetera. I am very comforted to hear that it is a conservative approach, but specifically, would there be language that would help the interested person or persons to be able to define what that means?

DR. SOFIA CHAUDHRY: Sofia Chaudhry, FDA. I want to make sure that I understand your question correctly, and I may be getting too technical. Are you looking for language in the product label in terms of how the Agency handles systemic reactions versus anaphylaxis? Are you looking for materials for the patient?

DR. GAILEN MARSHALL: I am thinking more of, I guess, the term would be an educational program to make certain that people understand the spectrum of...
anaphylaxis and that mild symptoms do not portend that, "Okay, I'll swallow an antihistamine and it will all be okay." As opposed to no one would argue that if the blood pressure drop by 50 percent that epinephrine would be immediately administered. I am thinking in terms of helping people understand the value of a conservative approach when a safety concern emerges.

DR. SOFIA CHAUDHRY: We certainly are looking forward to working with the Company as they do develop their educational materials. I think that's all we can say at this point.

DR. PAUL GREENBERGER: This is an important comment that has come up. The way I interpreted the briefing materials was that if there is an allergic-type reaction, it is called a systemic allergic reaction, of which anaphylaxis is a subtype of that. Is that correct?

DR. SOFIA CHAUDHRY: So, this is something that I think the field has struggled with for a very long time. A lot of differences in how the terminology is reported is actually right or wrong based off of how
the terminology is defined in the protocol and how the adverse events are collected. However, when the reviewers are looking at the data -- again, you know I have been doing this just under ten years -- we do take a very conservative approach when we're looking at systemic reactions.

**DR. PAUL GREENBERGER:** Dr. Kelso.

**DR. JOHN KELSO:** We were talking about -- it was mentioned, I think Dr Dykewicz had mentioned these risk mitigation strategies that are actually part of the question that we are ultimately going to be voting on. One of which, for example, that the caregiver or the patient has to carry self-injectable epinephrine.

Will those kinds of risk mitigation strategies also include specific instructions regarding some of the things that were mentioned in the presentation that also increase the risk of adverse reaction? For example, will it say that the patient has to be under observation for two hours after each dose, or can't exercise, or can't take a shower, and can't be tired?
DR. SOFIA CHAUDHRY: So again, to reiterate, we are still in a work in progress. With regards to the specific elements that would be included under the REMS. However, prescribing information is also a work in progress. However, I do know that those types of recommendations would be included in the product information as well.

But, I think it's important to take a step back and to recognize that a lot of this -- this is a very difficult therapy -- and a lot of those decisions need to be made on a case by case basis between the physician and the patient. So, we need to be very careful in what we mandate through either a REMS or through the prescribing information to insure that we are not inadvertently making it more difficult for a physician to care for their patient.

DR. PAUL GREENBERGER: The Committee will be able to make comments on this this afternoon and recommendations. There are more areas where more information is needed. Dr. Feingold, any questions?

DR. IRA FINEGOLD: None at the moment.
DR. PAUL GREENBERGER: Because I cannot see when you have a red light. Thank you. Dr. Guerrerio thank you very much. Now you can leave. We're going to take the break now for about how long, say 15-minute break, so we will come back at 9:50. Thank you.

[BREAK]

SPONSOR - AR101 (PALFORZIA) FOR PATIENTS WITH PEANUT ALLERGY

DR. PAUL GREENBERGER: This begins the sponsor’s presentation. And I turn it over to the Louise Peacock.

MS. LOUISE PEACOCK: Good morning, Mr. Chairman, members of the Advisory Committee and members of the Food and Drug Administration. My name is Louise Peacock and I'm Vice President of Global Regulatory Affairs at Aimmune Therapeutics. We're pleased to be here today to present the results from our clinical development program that support the use of AR101 an
oral immunotherapy for patients with peanut allergy.
The proposed trade name for the product is Palforzia, although we’ll refer to it as AR101 throughout this presentation.

Oral immunotherapy for peanut allergy has been of interest for many years. An increasing number of practices in the U.S. currently offer oral immunotherapy using food as the allergen, with products typically formulated in physician’s offices and using non-standardized treatment protocols. Currently, no approved oral immunotherapy exists for any food allergy; and there's a need to make a scalable regulated product available to peanut-allergic patients.

With this in mind, FDA guidance was to develop a drug product, according to current good manufacturing practices, and evaluate these products in a rigorous clinical development program. FDA also required the use of a double-blind, placebo-controlled food challenge as the standard for both study entry and primary efficacy assessment.
As discussed at the Allergenic Products Advisory Committee meeting in 2016, a clinically relevant goal of immunotherapy, for use in food allergy, would be the development of a product that could diminish the risk of life-threatening allergy with accidental exposure.

Peanut allergy is a common lifelong condition, usually starting in childhood. For many patients, the risks associated with accidental exposure, such as anaphylaxis, can be life threatening and are unpredictable. There are no approved prophylactic treatment options available; and patients are instructed to practice strict peanut avoidance and are provided epinephrine auto injectors for symptomatic management following accidental exposure.

Patients need a regulated treatment to reduce the risk of severe allergic reactions, which can occur at exposures of less than one peanut or about 300 milligrams of peanut protein.

The paradigm of desensitization immunotherapy is important to discuss as it's unlike other
therapeutic intervention. With allergy immunotherapy, the very protein to which a patient is allergic is administered, in a carefully regimented dose escalation, to desensitize the patient over time.

On the path to desensitization, patients can experience treatment-related adverse events, and some patients may even discontinue treatment. This is an expected part of the journey in immunotherapy.

With continued immunotherapy, the tolerated dose increases and reactions to therapeutic doses become increasingly less common, even though patients continue to receive the allergen. This results in patients being better able to tolerate accidental exposures to allergenic proteins. And adverse events associated with treatment decline as the level of desensitization improves over time.

AR101 is formulated under current GMP, which provides the regulatory requirements to ensure that consistent and well-controlled pharmaceuticals are produced according to quality standards. AR101 is naturally derived and contains key allergens found in
peanuts. Analytical testing is conducted to ensure lot-to-lot consistency in allergen content and potency. The excipients in AR101 are generally recognized as safe by FDA.

The data supports that AR101 provides a clinically meaningful level of desensitization to exposures to peanuts that should reduce the incidence and severity of allergic reactions; and thereby provides patients with a sense of security from the unpredictable risk that they try to navigate on a daily basis.

With AR101, as with other immunotherapies, predictable and manageable allergic events occur during the desensitization process, as patients progress towards the objective of reducing the risk of unpredictable, potentially life-threatening reactions on accidental exposures. This positive benefit/risk profile has been demonstrated in a non-pretreated, highly allergic population; a population potentially most in need of treatment.
Therefore, with the patient scholar therapy in mind, we're here today to present data supporting the proposed indication for AR101. To reduce the incidence and severity of allergic reactions, including anaphylaxis after accidental exposure to peanut in patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy.

I particularly like to note that with this indication, we're recommending AR101 is used in conjunction with the peanut avoidant diet, and the patients continue to carry epinephrine auto injectors. We also recommend that patients are permitted to continue therapy when they reach their 18th birthday, as peanut allergy is a lifelong condition.

Here now is the agenda for the remainder of our presentation. Dr. James Baker will present the current unmet medical need. Dr. Stephen Dilly will describe the efficacy, the patients age 4 to 17 years. And Dr. Daniel Adelman will present the safety data for this population. Finally, Dr. Wesley Burks will conclude with his clinical perspective. We also have
additional experts with us today. All outside experts have been compensated for their time and travel to today's meeting.

Thank you. I'll now turn the lectern over to Dr. Baker.

UNMET MEDICAL NEED IN PEANUT ALLERGY

DR. JAMES BAKER: Thank you. I am James Baker, Director of the Mary H. Weiser Food Allergy Center at the University of Michigan. For almost five years I was also the CEO and CMO of FARE, the leading national in food allergy foundation.

During this time I've had thousands of encounters with food allergy patients and their families. This has given me a real understanding of their desires for medical therapy for this disease. And I've come to believe that some type of therapy for food allergy and for peanut allergy in particular, is one of the most important unmet needs in medical care.

Peanut allergy is the most common food allergy in the United States, particularly in children. You
can see from this slide that approximately 2.2 percent of children suffer from peanut allergy, which is more than other food allergies such as milk, egg or tree nuts.

Until I became a patient advocate, I really didn't understand the devastating impact of this lifelong disease on patients and their families. Patients are especially frustrated because there is no therapy to prevent allergic attacks. The only current approved approach to mandating peanut allergy is avoidance, and unfortunately it's often ineffective. This can result in systemic allergic reactions in anaphylaxis. Peanut is found in many different foods and labeling is inconsistent and confusing. This makes avoidance especially difficult.

Reactions are also triggered by small amounts of peanut, even contamination. And reactivity to peanut can be magnified by factors such as exercise or upper respiratory infections. Patients are seeking a therapy that will provide them a means to actively address their disease.
When we look at who is having these anaphylactic reactions to peanuts, they are disproportionately observed in children, adolescents and young adults. As shown here, 88 percent of these anaphylaxis reactions occur in patients from zero to 18 years of age. This, therefore, is the target group for prophylactic treatment.

In addition, you can also see that 6 percent of the claims occur in patients age 19 to 30. This group is also at higher risk for reactions as these patients transition into adulthood. Anaphylactic reactions, like the ones shown here, are the things that scare patients and families the most.

The risk of accidental peanut exposure resulting in allergic reactions is truly a rational concern for patients. Several different measures definitively show this. Over half of peanut-allergic children experience one or more allergic reactions in the six years after they're diagnosed. Peanut allergic reactions remain unpredictable in timing and severity.
and are also the most common cause of anaphylaxis from food.

Families are concerned not just because of the rare reports of deaths, but because many have seen their own children go into anaphylaxis and spend hours in the doctor's office or emergency room receiving treatment. Families spend incredible efforts, often altering their entire lifestyle to practice avoidance. However, they know there is no guarantee that this will prevent future reactions.

Desensitization enhances avoidance alone by reducing the severity of reactions when an accidental exposure occurs. This would be a tremendous advance for patients. And as for physicians, it's important that we recognize this need.

Peanut anaphylactic reactions have been increasing over the past few years. If you look at the anaphylactic reactions to peanuts, they are now a quarter of all anaphylactic reactions diagnosed in the United States. Even compared to other food allergy reactions, shown here in orange, reactions to peanut
have increased more dramatically. Therefore, peanut protein allergy is an important and particularly unique problem.

If we are trying to prevent reactions from accidental exposure, it's important to understand how much peanut protein is actually causing these reactions, and what type of intervention would be meaningful to our patients.

The best data available on accidental exposure is from the MIRABEL study. They evaluated 785 patients with real-world reactions; and found that these reactions came from the ingestion of a median of 125 milligrams of protein. And this is different from the 300 milligrams that was quoted earlier, which is whole peanut as compared to the allergenic protein. Therefore, logic would suggest that if a patient ingest 300 milligrams of peanut protein a day and can pass a food challenge with 600 milligrams of peanut protein, then the risk associated for most accidental peanut exposures in the real world should be reduce.
OIT using food has been identified as a potential treatment for patients with food allergy. Despite being an experimental therapy, the demand for OIT from patients is very high. In response, more allergists are currently offering OIT; however, it remains unregulated with most of these allergist using commercial food for the treatment. Even with this, only around 200 of the 5000 allergists in the U.S. are identified as providing OIT with food.

According to a study by Greenhawt and Vickery in 2015, Seventy four percent of allergist surveyed are waiting for an approved product before they will perform OIT. So without an approved therapy, patients are not being well served. The need for regulated OIT is also supported by these research studies.

As alluded to, by Dr. Guerrerio, these studies show overall good success and offer significant evidence that there is benefit. But the variations in up-dosing, maintenance dose and outcome are substantial. This variability in current management
has been reinforced by a recent paper by Michael Blaiss and colleagues, who reviewed OIT and current practice. For example, one of the things that's been observed is that the maintenance dose in these protocols vary from 500 to 400 milligrams. Patients and their families undergoing unregulated OIT have shared their frustration about these variances; and have even described how their child failed OIT because they were unable to tolerate a very high maintenance dose, despite otherwise successful desensitization.

As mentioned, the outcome from these treatment protocols are all different; so it's difficult to predict the benefit for patients. We need a defined therapy, so patients and physicians know what to expect in terms of outcomes and side effects from OIT.

In summary, patients are at significant risk for accidental exposure, which is a serious life-threatening problem. The quality of life for patients and their caregivers is adversely affected due to the fear and anxiety of accidental ingestion that can occur at unpredictable times. Also, the effort required with
avoidance is tremendous, and it alone doesn't provide absolute protection. However, there are no FDA-approved treatment options for these patients. As an allergist, I'm embarrassed and frustrated by that. There are clear benefits from having a regulated FDA-approved OIT. OIT has historically shown value. And while it's certainly not for everyone, data from consistent protocols and outcomes will inform who might really benefit from this study.

Physicians and patients truly want and need a well-studied, regulated product that has an established positive benefit/risk profile. And approval of this type of product would improve access for all patients and finally give them what they want, a means to actively address their disease.

Thank you and I will now turn the podium over to Dr. Dilly.

AR101 EFFICACY (4-17 YEARS)
DR. STEPHEN DILLY: Thank you, Dr. Baker.

Good morning. I'm Stephen Dilly from Aimmune Therapeutics. I’ve been working on this program since its inception. We're humbled and honored to be here to review the data with you today. Those data support that desensitization to peanut protein with AR101 will reduce the incidence and severity of allergic reactions associated with peanut exposure.

The clinical development programs supporting AR101 includes completed and ongoing efficacy and safety studies. Assessing safety and efficacy are inextricably linked. When studying peanut allergy, it's all about assessing reactions to peanut protein in allergic individuals. The program started with two Phase 2 studies.

ARC003 is our pivotal Phase 3 study, the details of which I'll review shortly. ARC004 is an open-label, follow-on study to evaluate longer term safety of AR101. Placebo patients crossed over and underwent up-dosing and continued to be followed.
ARC007 is a randomized, double-blind placebo-controlled safety study.

The study was specifically designed to assess the safety of AR101 during up-dosing in a population identified as they would be in routine clinical practice. So no entry food challenge was required. Rather, eligibility for enrollment was based on clinical history, corroborated by stringent criteria, peanut skin-prick test, wheal diameter and specific IgE levels at baseline. Upon completion of this study, patients on AR101 rolled over to an open-label follow-on study, ARC011.

The AC007 placebo crossovers were up-dosed in ARC008 and continued to be followed. Now ARC008 is important because it will enable us to collect long-term, multi-year observational data, particularly safety, on a large group of patients receiving AR101. It’s intended that all patients completing other studies enter and remain in ARC008.

The primary evidence of efficacy comes from a pivotal Phase 3 study 003. ARC003 was a Phase 3,
randomized, double-blind placebo-controlled study in 555 patients, age four to 55 years old, with confirmed peanut allergy. The study was conducted across 66 sites in the U.S., Canada and Europe, and included 399 patients from 46 U.S. sites. Enrolled patients were randomized 3:1 to receive either AR101 or placebo.

Though we enrolled a population through 55 years, based on low adult enrollment and prior to unblinding, we agreed with the FDA that patients 4 to 17 years would be the primary analysis population. Key inclusion criteria included patients four to 55 years old with a clinical history of peanut allergy, confirmed by a serum peanut-specific IgE greater than or equal to 0.35 and/or by peanut skin-prick test wheal diameter greater than or equal to 3 millimeters larger than the negative control.

All eligible patients were required to have dose-limiting symptoms to a single dose of peanut protein of less than or equal to 100 milligrams during Entry Food Challenge. Patients were excluded from study if they presented with a history of severe or life-
threatening anaphylaxis or anaphylactic shock within 60 days of screening. However, patients with a past medical history of anaphylaxis were not excluded. Patients were also excluded if they had eosinophilic gastrointestinal disease, EoE, gastroesophageal reflux disease or GI symptoms of undiagnosed etiology, or uncontrolled asthma, or other chronic diseases.

Turning now to the Entry Food Challenge. All patients completed a double-blind, placebo-controlled food challenges screening to confirm that they reacted to less than or equal to 100 milligrams of peanut protein; or approximately one third of a peanut kernel, which would be indicative of a highly sensitive patient population.

The Entry Food Challenge consisted of five-dose levels ranging from one to 100 milligrams of peanut protein. Cumulative doses, shown in parentheses, ranged from one to 144 milligrams. Doses were administered every 20 minutes until a reactive dose level was identified.
A single highest-tolerated dose for each patient was also recorded. This was the highest dose given during the food challenge that elicited either no symptoms or symptoms that were not clearly indicative of an allergic reaction. And these assessments were made by an independent blinded assessor. All patients enrolled in ARC003 had a confirmed allergic reaction to 100 milligrams or less of peanut protein.

Following randomization, qualifying patients proceeded through a supervised initial dose escalation. On day one, AR101 and placebo were dosed from 0.5 milligrams to 6 milligrams. On day two, tolerability of the 3-milligram dose was confirmed. Of note, patients were not permitted to receive pretreatment with antihistamines or other symptomatic therapies, particularly prior to this IDE day or any in-office dosing, so as to not mask any potential adverse events.

After completion of the initial dose escalation, patients began the six-month up-dosing phase. Therapy was increased gradually, starting a daily dose of 3 milligrams, and advancing at two-week
intervals under physician supervision, up to 300 milligrams. Now desensitization is an ongoing process. And the up-dosing phase is designed so the target dose is achieved in a timely fashion, while staying below the individual patients tolerability threshold.

While the majority of patients completed the up-dosing phase within six months, physicians were permitted to extend the dose escalation phase based on individual patient circumstances. Following up-dosing, patients entered the six-month maintenance phase where they receive 300 milligrams of their randomized therapy per day. And the concept of maintenance dosing is that the level of desensitization continues to increase with prolonged regular exposure of the allergen.

All patients were reminded to continue a strict peanut-avoidant diet and to carry epinephrine. In keeping with routine clinical practice, many sites recommended the administration of epinephrine early in the course of an allergic reaction.

At study exit, after approximately a year of treatment, patients completed a double-blind, placebo-
controlled food challenge conducted by an independent blinded assessor to determine their highest tolerated dose. The food challenge provides insight into what can be expected in the event of peanut exposure after about a year of treatment.

Yet the exit food challenge consisted of dose levels ranging from the 3 to 1000 milligrams of peanut protein; and challenge doses were administered every 20 minutes. Patients who experienced dose-limiting symptoms did not advance to the next challenge dose level.

Patients who tolerated a single dose of at least 600 milligrams, with no more than mild symptoms, achieved the pre-specified primary endpoint. Patients who successfully tolerated 600 milligrams, then received the maximum challenge dose of 1000 milligrams of peanut protein.

The pre-specified primary endpoint was the proportion of AR101 treated patients, age 4 to 17, who tolerated a single highest dose of at least 600 milligrams of peanut protein with no more than mild symptoms.
symptoms; as determined by the independent blinded assessor at the exit food challenge, compared to placebo. This endpoint directly assesses the patient's goal of therapy, by demonstrating a meaningful level of desensitization well above what is likely to be encountered in an accidental exposure.

It was also important to demonstrate a clinically meaningful treatment effect. Therefore, in agreement with the FDA, success was achieved if the lower bound of the 95 percent confidence interval of the treatment difference was greater than 15 percentage points.

For the calculation of the pre-specified primary endpoint, all patients who discontinue therapy were considered non-responders. Hierarchically tested secondary endpoints were also included in the study. Three of four focused on the 4 to 17-year-old age group; the fourth endpoint assessed the proportion of patients who tolerated at least 600 milligrams of peanut protein, in patients aged 18 to 55 years.
Overall, 750 patients aged 4 to 17 years were screened, and 499 enrolled into the study. And 374 were randomized to AR101, and 125 to placebo. Now, 2 patients in the AR101 group, and 1 patient in placebo, did not receive their randomized therapy. And therefore as agreed with the FDA, the pre-specified Intention To Treat, or ITT population excluded these three patients, was comprised of 372 patients with AR101 and 124 patients treated with placebo.

At 12 months, 79 percent of AR101 patients and 92 percent of placebo patients completed the study. The majority of discontinuations in AR101 group were due to an adverse event or withdrawal of consent by the patient and occurred early in treatment. This profile was as expected and is consistent with other approved immunotherapies.

Moving to demographics: Baseline demographics in patients 4 to 17 years of age were balanced between groups and are in line with patients who commonly present with peanut allergy. Just over half the patients were male and 78 percent were white. The
The majority were less than 11 years of age and were enrolled in the U.S.

The study enrolled highly atopic patients with significant histories reflecting real-world allergic patients. The median wheal diameter following skin-prick test was 11 millimeters in the AR101 group, 12 in the placebo group. The median peanut specific IgE was 69 and 75 in the AR101 and placebo groups respectively. At baseline, patients median highest tolerated dose of peanut protein was 10 milligrams in both groups.

Almost three quarters of patients had a history of anaphylactic reactions due to accidental peanut ingestion, and approximately half had asthma. And the majority of patients had multiple food allergies, a history of a topic dermatitis and allergic rhinitis.

The primary efficacy endpoint was met; 67 percent of AR101 patient, shown in blue, compared to 4 percent of placebo patient, shown in white, were able to tolerate a single dose of at least 600 milligrams peanut protein with no more than mild symptoms during
the exit food challenge. The result was highly statistically significant. And the lower bound of the 95 percent confidence interval, between the AR101 and placebo, was 53 percentage points; well exceeding the pre-specified threshold of 15 percentage points.

All sensitivity analyses also support the primary results, including a worst-case scenario analysis that continued to demonstrate a robust treatment effect for AR101. For this analysis, all patients in the AR101 group without an exit food challenge were considered non responders; and patients in the placebo group without an exit food challenge were considered responders. Even with this conservative approach, the results remain highly statistically significant, favoring AR101, continuing to exceed the superiority margin of 15 percentage points.

Results for the first two hierarchal secondary endpoints were also highly statistically significant favoring AR101. On the left is the proportion of patients for the tolerated dose of at least 300
milligrams of peanut protein in the exit food challenge. And on the right, 1000 milligrams which represents the highest dose in the challenge.

These results of 1000 milligrams represent 100-fold higher median tolerated dose compared to study entry after one year of treatment. And recall, the cumulative exposure at this challenge was just over 2 grams.

The next hierarchical secondary endpoint evaluated the maximum severity of symptoms that patients experience at any dose during the exit food challenge. You can see more AR101 treated patients experience no events, at the exit challenge, compared to only 2 percent of placebo patients. And many more placebo patients experienced moderate to severe events compared to AR101.

These data did not take into account the specific challenge dose at which these maximum severities occurred. The last hierarchically tested secondary endpoint in study three evaluated adult patients. The endpoint did not meet statistical
significance, due to small sample size at a higher withdrawal rate in the AR101 group compared to younger patients. When looking at the adults who completed, 85 percent of AR101 treated patients met the primary endpoint, versus 15 percent in the control arm, suggesting those who stayed on treatment did quite well.

Now I’ll discuss the implications of these results in terms of clinical utility. Here again, you see the symptom severity of the exit food challenge, but now broken down by the doses that elicited the reactions.

This slide focuses on patients still on treatment at a year and entering each level of the food challenge. As a reminder, doses were administered every 20 minutes. Patients were first challenge with a 3-milligram dose. Reactions were graded by severity, with severe reactions shown in red, moderate in yellow, mild in blue and no reaction in green.

You can see here that the lowest challenge dose, placebo patients experiencing moderate reactions.
Patients who experienced dose-limiting symptoms did not advance to the next dose level. Others continued to the 10-milligram challenge.

Here we see the early emergence of severe reactions in the placebo group. Then the challenge continues to 30 milligrams, 100 milligrams; and by the time patients reached 300 milligrams, the groups are strikingly different. Patients then continued all the way up to 1000 milligrams. The number of patients reaching each dose is shown on the bottom of each column. You can also see that only five patients in the placebo group made it to 1000 milligram challenge does. This is consistent with the observation that life threatening reactions can occur after exposure to relatively small amounts of peanut as Dr. Baker noted. Accidental exposures usually occur at a median of around 125 milligrams of peanut.

The picture is quite different in the active group. The threshold at which patients first react is higher and the reaction tends to be milder. Additionally, 250 out of 296 completers were able to
progress to the 1000 milligram challenge dose. This should translate to reduce frequency and severity of reactions to the accidental exposures that will inevitably occur despite best efforts at avoidance.

Another measure meaningful to patients is epinephrine use. Less rescue epinephrine was used for AR101 treated patients at each challenge dose compared to placebo. At the 100 milligrams and 300 milligram doses, only one AR101 treated patient, or 0.3 percent, required epinephrine; 2 percent at the 600-milligram dose and 8 percent at the 1000 milligram dose. In contrast, many patients in the placebo group required epinephrine, even at low challenge doses.

During the first six months of the trial, we saw similar rates of accidental peanut exposure reported in active and placebo arms. Most were symptomatic and most of those required treatment.

During the second half of the trial, when AR101 patients would have achieved at least partial desensitization, we see about the same ratio of accidental exposures between groups. But the
proportion that was symptomatic or required treatment seems to diverge, favoring those treated with AR101.

To conclude: Patients 4 to 17 years of age, receiving AR101 as oral immunotherapy, tolerated higher doses and experienced fewer and less severe symptoms compared to placebo patients at the exit challenge.

The primary endpoint was met at the level that will be expected to reduce the incidence and severity reactions to exposure to peanut. And the available, albeit limited observational data, support that assertion.

Thank you. Dr. Adelman will now discuss the safety profile of AR101.

AR101 SAFETY (4-17 YEARS)

DR. DANIEL ADELMAN: Thank you. I'm Daniel Adelman, Chief Medical Officer at Aimmune. I will now present the AR101 safety data for patients 4 to 17. For completeness, we are including the adult safety data for areas of special interest.
Oral immunotherapy with AR101 has a well-characterized and manageable tolerability, and a safety profile in line with the paradigm of desensitization that my colleagues described earlier. Initially, treatment related to adverse allergic events result from exposure to peanut protein in allergic individuals.

For example, with all exposure we expect to see associated gastrointestinal adverse events in some patients, including mouth itch, abdominal pain, nausea, and vomiting. We expect to see associated allergic reactions that can range from mild to moderate, or severe, such as rhinitis, urticaria, wheezing and potentially even anaphylaxis. Importantly, with continued immunotherapy, we also expect the rate and severity of these adverse allergic events to decrease over time.

First, the safety and tolerability data from studies ARC003 and ARC007, both of which had a placebo-control group, represents our controlled population. This population includes 709 AR101 treated patients and
292 placebo patients. Since ARC007 only included an IDE and up-dosing phase, exposure in the maintenance phase is comprised of 310 AR101 patients and 118 placebo patients coming from ARC003 alone. These data allow us to draw some conclusions regarding the event likely related to AR101 exposure, and those more likely related to underlying disease.

We also looked at the larger integrated population that includes cumulative AR101 exposure across our controlled as well as our open-label studies ARC004 and ARC011. The results from these studies provide insight into the safety and tolerability profile of longer-term dosing with AR101.

Overall, 812 patients, 4 to 17 years of age, are included in the larger integrated safety population. And 794 patients proceeded to up-dosing and 662 to maintenance. Our safety database consists of 1050 patients exposed to at least one dose of AR101; and this includes earlier phase and follow up studies. We look at events of clinical interest in this larger, total exposed population.
Let's now look at the overall safety profile in the controlled population. The safety profile we observed was consistent with the expectations for immunotherapy. We present the safety profile irrespective of causality throughout this presentation. A high proportion of patients in both groups had at least one adverse event, although there were fewer during maintenance dosing than in the initial phases.

As expected, for AR101 patients, adverse events leading to discontinuation occurred more frequently than placebo, and more frequently early in treatment. Most adverse events were mild to moderate in severity. Severe events occurred during up-dosing in both arms, and the first six months of maintenance in the AR101 treatment group.

One patient developed acute lymphocytic leukemia that was noted as life threatening and was considered unrelated to AR101. A few serious adverse events occurred in either arm. One death was reported in a placebo treated patient. This patient sustained a cranial cerebral injury in a road traffic accident.
The most commonly reported adverse events, with at least five percentage points higher frequency compared to placebo, are presented in this slide. These events were as expected, allergic in nature and mostly associated with gastrointestinal and skin events. Again, events were reported more frequently during initial dose escalation and up-dosing compared to maintenance dosing. During maintenance, the rate of these adverse events fall to levels comparable to those seen in the placebo patients.

Now, I will move to a review of adverse events that led to discontinuations. A higher proportion of AR101 treated patients discontinued due to an adverse event. And the majority of adverse events, leading to discontinuation, were gastrointestinal in nature with abdominal pain being the most common. Discontinuation of study drug due to an adverse event became less frequent once patients reached maintenance, at about 1 percent during this phase.

This table shows severe adverse events which occurred in more than one patient. The preferred term
of anaphylactic reaction was reported in four AR101 patients during the initial does escalation and up-dosing, and in 1 patient during maintenance. I will discuss these events in further detail shortly. Again, GI events were some of the most commonly reported.

Turning to serious adverse events: Serious adverse events were defined using the standard regulatory definitions. Most events were reported in individual patients. Only anaphylactic reaction and asthma were reported by more than one patient in the AR101 group.

Now turning to adverse events of clinical interest: We prospectively designated specific events of clinical interest; systemic allergic reactions including anaphylaxis, use of epinephrine, and eosinophilic esophagitis and allergic reaction involving the esophagus. All of these events that have been reported in the context of oral immunotherapy.

For this section, I will present data from the controlled, integrated and total exposed populations.
Before getting into the data, let me briefly review how we define systemic allergic reactions.

To avoid potential underreporting, systemic allergic reactions were defined as allergic reactions of any severity that affected two or more body systems, or that included hypertension. All systemic allergic events were coded to the MedDRA preferred term anaphylactic reaction in our database. These two terms were used synonymously. Severity was graded according to the EAACI/Muraro criteria; and seriousness of all systemic allergic reactions was determined using standard regulatory definitions.

Here's a summary of the frequency of adverse events of clinical interest as they occurred in the controlled population. The percent of patients with one or more systemic allergic reactions, or anaphylaxis, occurred more frequently in patients on AR101 compared to placebo. Of note, during up-dosing and maintenance, 4 percent and 2 percent of placebo patients experienced systemic allergic reactions, which
may reflect the background rate in a highly atopic
group of patients.

Use of epinephrine during the initial dose
escalation and up-dosing was 10 percent for AR101
treated patients, compared to 5 percent of placebo
patients. During maintenance, 8 percent of AR101
treated patients and 3 percent of placebo patients had
an episode of epinephrine use. Three episodes of
eosinophilic esophagitis occurred during up-dosing in
AR101 patients.

Now, turning to the larger integrated dataset:

In the integrated safety population, the majority of
patients who had systemic allergic reactions reported a
single event. Most events were mild or moderate in
severity. Four patients or 0.5 percent, during up-
dosing, and 6 patients or 0.9 percent, during
maintenance, had severe systemic allergic reactions.
In totality, 10 cases.

Overall, few patients treated with AR101
discontinued due to systemic allergic reactions. Even
the majority of patients with severe reactions remained
on therapy. Epinephrine use was mostly outside of the clinic setting and associated with systemic allergic reactions.

Looking at the 10 severe systemic allergic reactions in more detail: These 10 cases represent the totality of severe cases reported in the 1050 patients exposed across the program. Four occurred during up-dosing, and six during maintenance. Seven of the 10 continued AR101 treatment without additional severe events.

Episodes were temporarily associated with the administration of the AR101 dose with 8 of 10 occurring within two hours of dose administration. Importantly, no severe systemic allergic reactions have been reported beyond 52 weeks of maintenance therapy as of August 2019.

Moving now to the use of epinephrine during treatment. Enrolled patients or their caregivers were required to have an epinephrine auto injector for emergency treatment. All were trained on the proper use of the device and encouraged to use it in the event
of a perceived allergic reaction. Of the 812 patients exposed to AR101 in the integrated population, 2 percent of patients were administered epinephrine during the initial dose escalation, and 10 percent each during up-dosing and maintenance.

Most of these episodes involved a single dose of epinephrine. Most adverse events associated with the use of epinephrine were mild or moderate. With AR101 treatment, we will recommend that patients continue to carry an epinephrine auto injector; so this picture may be a reasonable representation of what's likely to happen in clinical practice.

Eosinophilic esophagitis, or EoE, is another adverse event of clinical interest for our program. The data in this table are derived from all 1050 patients, age 4 to 55 years, who were exposed to any amount of AR101.

In the Phase 3 studies, patients with chronic or recurrent gastrointestinal events were followed closely for symptom resolution. Patients whose symptoms did not resolve, after drug discontinuation,
were to be referred to a gastroenterologist for evaluation and treatment. Overall, there have been 12 biopsy confirmed cases reported in the 1050 AR101 treated patients. No cases were considered serious adverse events.

The severity of EoE was considered mild in 3 patients, moderate in 7, and severe in 2. All patients discontinued AR101 treatment. Data in the last two columns are based on ongoing follow up as of August 2019. These data were not available at the time of the BLA submission.

Repeat biopsy reports are available for 8 patients, and 6 showed resolution and 2 showed improvement. Of note, the 2 severe cases resolved both histologically and systematically. Moreover, symptomatic improvement was reported for all 12 patients.

Turning to the safety profile in asthmatics: We also examined patients with asthma, as asthma is a recognized comorbidity in peanut allergic patients. In fact, just over 50 percent of patients in the
integrated population had a history of asthma at study entry. No meaningful differences in the incidence of adverse events were observed.

Patients with asthma were assessed for changes, and asthma controlled using spirometry, peak expiratory flow rate, and the asthma-control test questionnaire at baseline and various times throughout the study. There were no meaningful changes in these parameters over time when comparing AR101 to placebo.

Aimmune is committed to the long-term assessment of AR101. Long term safety data is being collected in a multicenter open-label study, ARC008, which will further inform patients and physicians.

Ninety six percent of patients, or 799, who completed earlier studies elected to enroll in study ARC008. The objective is to collect safety data on at least three years of cumulative daily maintenance treatment. This will include data on all adverse events of clinical interest and events of accidental food allergen exposure. The collection and analysis of
these long-term safety data will quantify long term safety dynamically over time.

Patient Safety has been central to Aimmune since the beginning of the development program. As such, we proactively proposed a comprehensive risk management plan in our BLA, and it is currently being discussed with FDA. Our proposal includes the requirement that the initial dose escalation, and the first dose of each up-dosing level, must be administered in a healthcare setting equipped to treat systemic allergic reactions. This is the same process of drug administration that was used in our clinical development program, and what we are recommending post approval.

Our proposal also includes the documentation that AR101 patients will have a valid epinephrine prescription prior to initiation of AR101 dosing. Distribution of the drug will be controlled through specialty pharmacies, and we have purposely designed packaging so that patients only receive their appropriate dose. We have also proposed additional
post approval activities, which include pharmacovigilance questionnaires, a medication guide, in addition to professional and patient-focused labeling and educational materials.

Aimmune and FDA are absolutely aligned in our focus on patient safety; and we believe we have proposed a risk management plan to support the safe use of our product.

To summarize, the safety profile AR101 is well characterized, and the reported events are as expected. Similar to other forms of approved immunotherapy, events were primarily allergic reactions. Overall, most adverse events were mild or moderate in severity, and consistent with the route of administration. The majority of allergic events were gastrointestinal in nature.

Importantly, the incidence of adverse events declined, and the severity diminished from up-dosing to maintenance and continue to decrease with prolonged dosing. Most systemic allergic reactions were also mild or moderate in severity, with a similar frequency
in up-dosing and maintenance in the first year and
occurred within two hours of dose administration.

Severe events occurred in 10 patients out of
more than 1000 patients exposed in the clinical
database. Seven of those patients continued therapy
and, as of August 2019, no additional severe systemic
allergic reactions have been reported beyond 52 weeks
of maintenance. Across the program, there have been 12
cases of biopsy confirmed EoE. All have shown
resolution or improvement following withdrawal of
AR101.

Additionally, the ongoing study, ARC008, will
further assess long-term safety for adverse events of
clinical interest. And we have proposed a
comprehensive risk management plan to support the safe
use of our product.

I'll now turn the podium over to Dr. Wesley
Burks to provide his clinical perspectives.

CLINICAL PERSPECTIVE
DR. WESLEY BURKS: Thank you. I'm Wesley Burks, Dean of UNC School of Medicine and CEO of UNC Health Care. Peanut allergy is a significant problem for both patients and families. There are no current treatments available. And although the possible outcome of a life-threatening allergic reaction is not frequent for any one patient, the severity of the consequences, when it does happen, make it important that we find a treatment.

Oral immunotherapy for peanut allergy has historically shown promise. Now we have the opportunity to make a regulated, consistent treatment a reality for our patients.

The concept of oral immunotherapy has been around for over 100 years. My colleagues and I started researching oral immunotherapy in Arkansas in 2001, and continued this work at Duke in 2003, and now at UNC. We were encouraged with initial outcomes. Yet nothing has moved the field forward to meet the needs of our patients.
Thought promising, the earlier studies had limitations. The quality of the data was not sufficient to warrant a recommendation of use in practice guidelines. The field needed studies of sufficient size and rigor, so that we can fully understand the benefit/risk of oral immunotherapy for peanut allergy. It's gratified and finally you see pivotal data that in many ways substantiate and expand our earlier findings. The AR101 program has generated the type of rigorous evidence that could change practice.

A desensitization treatment has the potential to lessen the burden of peanut allergy for our patients and provide them a way to actively address their disease. Having peanut allergy considerably impacts patients, families and caregivers. These are highly motivated patients. My experience with OIT, patients are very diligent about taking their therapy.

Avoidance is really our only preventive management tool; and with a high number of emergency room visits annually, you can see that it doesn't
always work. As a result, patients live in constant fear of exposure and allergic reactions. The need for a regulated, consistent product and protocol with a well understood benefit/risk profile has never been greater, as seen by the increasing number of practices currently using peanuts to treat patients.

The decision for treatment is always based on clinical equipoise for each patient and family. Currently, when meeting with patients and families with no approved therapies, allergists discuss peanut avoidance and how that affects their day to day lives. We review the risk associated with peanut exposure, and the use of epinephrine as a rescue medication.

Patients and families fear life-threatening and life-ending allergic reactions the most. These reactions are unpredictable and can occur all too easily. Children may try to avoid allergens but consume food without even knowing peanut is present. Parents are also concerned that their children will have these reactions away from them and result in more severe outcomes.
You've seen these data previously. It shows that the majority of AR101 treated patients achieve not only the primary endpoint, but 50 percent also tolerated up to 1000 milligrams of peanut protein. The data for those who completed this study further informs us on the magnitude of this effect.

So what does these statistically significant results mean to our patients? If a patient completes the first year of AR101 treatment, over 95 percent can be expected to be desensitized to at least the amount of peanut protein in a single peanut, over 80 percent to two peanuts and almost two thirds to three to four peanuts.

So what does these positive efficacy outcomes mean for our patients in real world terms? As you've heard, the average amount of peanut protein to induce an accidental reaction is about 125 milligrams. A 600-milligrams single highest tolerated dose, the equivalent of about two peanuts, should therefore provide a margin well above most real world exposures.
Not only is this beneficial, but it will lend comfort to our patients and their families. While we still recommend that patients treated with AR101 maintain a peanut avoidance diet, the clinical data indicate that patients will have fewer symptoms and less severe symptoms when accidental exposures occur. This represents truly clinically meaningful benefit.

Patients who enrolled in this study represent the types of patients allergists see. Additionally, the types of symptoms during a food challenge reflect those that often occur after an exposure, indicating that this is the best model we have to assess efficacy.

The safety profile of AR101 is what I'd expect from a desensitization immunotherapy. Initially, during the desensitization process, we expect temporally related and manageable risk. The common adverse events, mostly involving gastrointestinal events, are what we've seen with other oral immunotherapies. When giving the food allergic patient the very food that they're allergic to, you'd expect
some reaction to occur initially. What is reassuring, is that adverse events are reported less frequently during the maintenance compared to initial dose escalation and up-dosing.

The dosing schedule studied is broadly applicable to the majority of this population. Importantly, it also allows accommodation for tolerability and the realities of day to day life. Allergist understand how to tailor treatment for each patient; for example, slowing the up-dosing schedule as needed.

Study ARC003 was the first OIT study that allowed patients with a history of severe anaphylactic reaction to be enrolled; which allowed assessment of patients with the greatest unmet medical need. Investigators in this field usually recommend to their study participants and families, that epinephrine is to be given early during an allergic reaction. And as such, 92 percent of epinephrine use during the course of treatment was for mild or moderate reactions.
Severe systemic allergic events, specifically anaphylaxis, were uncommon.

Among the patients exposed, 10 experienced severe systemic allergic reactions; one of which was serious, and seven of these patients were able to continue treatment without further incidents. The important point to remember about these episodes is that they occurred temporarily associated with dosing, which makes the episode more predictable. What really concerns patients and families are accidental exposures to peanut occurring at unpredictable times, often away from home and despite their best effort at avoidance.

EoE is another event associated with oral immunotherapy. Therefore, Aimmune paid close attention to these events throughout their program as we do in clinical practice. While EoE can be significant, it too is manageable.

As you know, we have a close relationships with our patients. And if a patient were to go on AR101, we dose them initially in a controlled environment. We see them every two weeks during that
dosing, as well as see them regularly during maintenance. If they are having GI symptoms, we can reduce or withhold their dose; and if symptoms persist, discontinue therapy.

Based on our code understanding, if you remove the triggering allergen from the diet, the EoE goes away. Discontinuation is the first line management for EoE. And in my experience, and as observed in the AR101 program, symptoms generally resolved within a month after discontinuation.

For my review of the data, the benefits of a or AR101 outweigh the risk; and the positive benefit/risk profile clearly exceeds avoidance alone, which as we've discussed is often ineffective.

As with any treatment, this is not a drug for everyone. But for those patients who are able to obtain maintenance, AR101 offers an effective treatment to achieve desensitization. AR101 would be the first therapy from a large randomized control trial to treat a food allergy. The results were statistically
significant, and more importantly clinically meaningful.

The outcomes aligns with the goal of therapy to reduce the risk of life-threatening events associated with accidental exposures, the thing that our patients and families fear the most. Outcomes also align with the patient's goal as evidenced by the fact that similar to our clinical experience, 96 percent of patients continued into follow on study 008.

The safety profile is expected of a desensitization treatment. Most of the adverse events were mild to moderate; and most systemic allergic reactions occurred within two hours of dosing. This predictable nature allows the preparedness for our patients, unlike accidental exposures that are unpredictable.

Importantly, allergist and patients will be able to manage these potential risks. Epinephrine use can be an expected part of an early desensitization. And the clinical program aligns nicely with clinical
practice, where we’ll train and counsel our patients on appropriate use of epinephrine.

Perhaps most important to consider is that patients, families and physicians need and want a safe, effective and regulated treatment. Approval of AR101 would be the first step for meeting this unmet medical need. And it has the potential to change the field and change patient’s lives.

Thank you. Dr. Dilly will return to take your questions.

QUESTIONS - DISCUSSION

DR. PAUL GREENBERGER: I'm going to ask -- first, Dr. Finegold gets to go first, and I’m also going to come back to Ira at the end since we don't know if you have a question or not. But, do you want to start? All right. Okay, I'll start with Dr. Brittain here.

DR. ERICA BRITTAINE: Okay. So, I'd like to talk about slide CO-45. Obviously, you have a
fantastic result on your primary endpoint. But I want to dig down a little bit on the information you have about accidental exposures, which is really more what the indication would be.

I find this particular display, which I see here in a lot of the slides, a little hard to interpret. Because when we get into the 300 milligram per day, we’ve lost a lot of people in the active arm. And they're the most reactive -- presumably tend to be the most reactive people. So we don't really have -- we have a bit of an apples to oranges comparison at this point, where we're getting to the 300 milligrams per day.

My question in terms of the accidental exposure, for the people who stopped dosing, did you collect the information about their accidental exposures? Once they are no longer getting their dosing -- because then you could do an intent to treat comparison of the accidental exposures.

I mean, this is relevant in terms of -- I'm interested in this in terms of looking at the active
arm alone. But when you're comparing it to placebo, I'd want to see an intent to treat comparison.

**DR. STEPHEN DILLY:** So this comes back to the very big question that this panel actually thought about in 2016; which is, how do you measure efficacy for a product that is designed to reduce the severity reaction that having exposures? And at that time there was discussion around field trials versus the double-blind placebo-controlled food challenge. And it was determined that the most robust way forward -- and I believe this was in the briefing materials -- was the food challenge.

And what we're providing this with is to say, well, does the observational data, albeit limited, actually aligned with that? And the answer is, yes, it does. And the very reason you said there are more withdrawals in the active than the placebo group, is why I was not making anything of the difference in the overall rate of accidental exposures. Right.

The one thing that I think stood out from this slide was as patients moved into a period of
desensitization, the proportion of those accidental exposures that resulted in symptoms and required treatment seemed to go down, concordant with the primary endpoint result, and we wouldn't go any further than that.

**DR. ERICA BRITTAINE:** My other question was, do you have the data on accidental exposures on those patients who discontinued -- who had early reactions and stopped dosing? Again, then you can make a fair intent to treat comparison.

**DR. STEPHEN DILLY:** So we don't have that formal analysis. What we did with patients who discontinued the study, is we followed them for a period of time for resolution of any symptoms. Remember, there were a group of patients who withdrew from the study due to GI symptoms. We needed to make sure that all of those had resolved. And so, we followed them for a period of at least three months after they withdrew from the study; but we don't have data on accidental exposure.
DR. ERICA BRITTAIN: I guess I’ll just make a general comment that a lot of the slides you showed in the safety section did have that feature where we don't quite have comparable groups when you're getting to that second half of the study. Which I understand is the difficulty of the design?

DR. STEPHEN DILLY: It is. But we would also stress that -- if I could show slide CO-43. This is why we were looking at this particular group of the year; because we know whether a patient has withdrawn from therapy or not. And part of the equipoise that Dr. Burks was talking about was the conversation with the patient. To say, you know, there's a 20 percent chance that you will withdraw from therapy, probably due to an adverse event. But if you can get to a year, this is what it looks like. And that's always the equation.

DR. PAUL GREENBERGER: Dr. Dykewicz.

DR. MARK DYKEWICZ: I guess my question pertains to something that would have import on risk mitigation when patients would be self-administering
the product out of the clinic setting. I was also intrigued by the statement that -- you said that many sites recommended early administration of epinephrine. During the conduct of this study, what were patients informed in terms of precautions to take at home? Where they told, for instance, what sort of scenarios would require epinephrine. Where they told that if they had increased asthma, that they should withhold the dose?

Again, looking at what study conduct instructions to patients, that could be translated into patient instructions, that would be given with labeling.

**DR. STEPHEN DILLY:** Absolutely. I'm going to ask Dr. Vickery to comment particularly on that. But I'd like to just give a little bit of a perspective. Which is when we designed this study, we had the benefit of historical studies to look at. But all of those data were from small groups of patients.

There were some things we knew about, which were for instance that exercise seem to be associated
with an increased incidence of reactions; so we
counseled patients to avoid exercise. We also had
rules around if patients had concomitant illnesses
which might raise their core temperature and so on.
But the advice, specifically, you’re asking
for was what to do in the case a reaction does happen?
And in broad terms that was intervene early; if in
doubt, use the epinephrine and then call the center.
Don't wait and talk to the doctor first, use it.
Brian?

**DR. BRIAN VICKERY:** Yes. Brian Vickery, Emory
University. This is a very important discussion.
Because as you say, most of the exposure happens at
home. To answer your question, the protocol contained
within it specific dosing guidance to be conveyed to
the families around these issues about intercurrent
illness, exercise and so on. This was specifically
laid out in the protocol.

The protocol also required that every patient
have access to an epinephrine auto injector that was in
date. And then furthermore that each time the
participant returned to the research unit, which during the up-dosing phase is approximately every two weeks, the study procedures required the sites to, again, retrain the participant about the proper dose administration, instructions and the indications with which to use epinephrine.

DR. SOHEILA MALEKI: Do you know if any of the -- what the adverse events -- when they had accidental ingestion, what’s the dosage perhaps they received? Was it more than the maintenance dose? I would assume the ones that had adverse events in -- was any kind of an investigation done on what type of dosage they got? Because I think that'll be interesting to know.

DR. STEPHEN DILLY: I don't believe we have data on the specific milligram doses during the accidental exposures. One reason for that is -- if we could bring up slide CO-45 again please.

One reason for that was that, you know, they are unpredictable in nature and timing. They were captured by diary card and patient report. And it's always -- in this world it’s fraught with difficulty to
go back and find out exactly how much they were
reacting to.

But what we did see was this decreased
proportion of the reported events that was
asymptomatic. Which begs to question, so if they
hadn't had a reaction, how did they know they had an
event? And what was reported there was taste. They
realized they had eaten something that either tasted of
peanut or they later found contained peanut. And
that's what they were reporting on.

DR. SOHEILA MALEKI: That was my next
question.

DR. PAUL GREENBERGER: I want to check with
Dr. Feingold to see if he has any questions.

DR. IRA FINEGOLD: Yes. Can you hear me now?

DR. PAUL GREENBERGER: Yes.

DR. IRA FINEGOLD: Okay. Yes, I think I was
muted the first opportunity. I have three questions.
How long did it take to reach that six-month level with
various lapses? That was one. And were any of these
lapses either short or long term? And what did you do
for longer laps of a week or two, something like that?
And then, do you require this sites to observe the
patients for two hours or longer?

**DR. STEPHEN DILLY:** Thank you for all of
those, and I will try and answer all three. So here is
a Kaplan-Meier of the time it took in the active and
placebo groups to reach the target 300-milligram dose.
And as you remember, we were counseling physicians that
it should be based on patient circumstances.

Now actually the placebo in the AR101 groups
for the first 50 percent behaved quite similarly. They
have a similar median time to get to 300-milligram
dose, maybe a week or so different. And even the
placebo people tended not to get there in the shortest
possible time. And quite often, this was scheduling,
right?

So, part of the practical lesson that we've
learned is you need to have a flexible supply
arrangement. Such that if the kid is going away to
summer camp, or whatever, you're not trying to up-dose
them the day before they go away. And when we looked
at our database, the single most common reason for
delay was some form of scheduling issue.

Now, there was the other group which was due
to people who were not yet tolerating fully the current
dose level. So if the patient presents on 12
milligrams and they're still having tingling in the
mouth, you're not going to up-dose them. So some had
repeating of the same dose, and some had concurrent
illnesses where we actually withdrew therapy. And if I
could have slide DC-10.

These are the rules that we gave to the sites
on what to do if people had missed one or two days
versus longer durations. What we did was under
different circumstances -- there was clinical judgment
in this. And I'm going to ask Dr. Vickery to comment
on it. But we had these rules, which we fully intend
to translate into the labeling so that people know what
to do. Because going through desensitization, kids
will get colds, and we need to know what to do. Brian?

**DR. BRIAN VICKERY:** Yes. Brian Vickery, Emory
University. I've been involved with OIT studies now
for over a dozen years. And the early academic studies seem to observe that it wasn't required to take a dose every single day, that a missed dose here or there didn't seem to affect the course of desensitization too much. But then of course, obviously, the desensitization effect can wane with extended absence of dosing. And this most commonly occurs, again, in the course of say an intercurrent illness.

And so, this accumulated clinical evidence and observations were encoded into the protocol as the recommendations you saw on the previous slide. Which provided sort of a real-world guidance for the investigators to adjust doses accordingly when these either real life events occurred or an illness. And this is consistent with general allergy practice; the same things that we do for patients who are on, say, injection immunotherapy and may have an illness or may experience temporarily, you know, a delay between visits. Very similar.

DR. STEPHEN DILLY: And the final question that was asked was, are we going to observe patients,
or should patients be observed following each up-dosing? And the answer is, absolutely.

We're still discussing, with the FDA, exactly what duration that should be for. But it should be long enough to capture the event, and long enough to see that any event that does occur actually has resolved before the patient goes home, is this the intent?

DR. PAUL GREENBERGER: Dr. Hawkins?

DR. RANDY HAWKINS: Yes, so in Southern California, of course, there’s a substantial number of Hispanic patients. I'm an adult physician.

In your briefing document, Table 13, on demographics, under ratio for like white predominant, Asian, Black or African American, other. I was wondering if we had any information about responses to adverse events to others as related to Asians, Black or African Americans. Any breakdown of adverse events or other things?

DR. STEPHEN DILLY: We do have a breakdown of efficacy by group. And we've also looked at race and
ethnicity as predictors of adverse events. What you can see is the point estimate is pretty similar in terms of efficacy across the different groups.

But, you know, you're pointing to an important issue here. Which is that we had an overrepresentation of white patients in this study population. And other groups were relatively small. This is largely an artifact of the centers that patients are presenting to now.

And one of our intents, with AR101, is to get to the centers where those other groups of patients actually are. And we think it's very, very important -- while there is no a priori reason to expect a different profile in these patients -- that we actually follow up and acquire data so that we can be reassured that is truly the case.

But the first step is to actually get to the centers which would particularly -- for instance, in the city centers that would actually treat a broader group.

DR. PAUL GREENBERGER: Dr. Marshall.
DR. GAILEN MARSHALL: Again, Dr. Dilly,

forgive me for having my back to you; I just can't talk
and look at the same time.

First of all, I want to compliment -- the
commentary that was put into the presentation about the
philosophy, the company and the studies, and their
intent to suggest the use of epinephrine early, and by
extension, often. My concern, again, goes back to what
I think has the potential to be quite confusing
information for those who would administer this drug.

In Aimmune’s sponsor briefing document, on
Page 76, there’s a commentary here about investigator
reported systemic allergic reactions were recorded in
the clinical databases. The MedDRA preferred term
anaphylactic reaction, which I think is appropriate --
a hundred percent appropriate.

The next statement disturbs me. In agreement
with the FDA, the term “systemic allergic reaction” is
used for anaphylactic reaction events of any severity.
And the term “anaphylaxis” is used to distinguish the
subset of anaphylactic reactions that were severe, life
threatening or fatal. You got a problem.

By definition an anaphylactic reaction is
potentially life threatening. The intensity can
certainly be different, mild, moderate or severe. But
the approach to therapy of an established anaphylactic
reaction should be consistent -- consistently
presented. And I submit that the sponsor, in terms of
what they presented, took that definition
appropriately.

Maybe this is more to you guys than it is to
the sponsor. But I think as we go forward,
particularly when we're struggling with some of these
words -- and I understand the variability. I don't
mean to sound like I'm sitting on an ivory tower
somewhere, I understand there's concern.

But the issue is that the consistency of this
is that the delayed use of epinephrine is still the
number one identified cause for death from anaphylaxis
of all causes. There's no reason to assume that this
would be any different in them as the uptick. And so I
want to bring that point up as being an extremely important one that may or may not need to be discussed by the committee.

**DR. PAUL GREENBERGER:** Could people from the FDA comment on that?

**DR. SOFIA CHAUDHRY:** Sofia Chaudhry, FDA. You know, we certainly acknowledge the commentary. I was not involved with the Division when the protocol was being written, but I will state that this is a very common problem with all protocols when we're dealing with anaphylaxis.

I do want to reiterate what I had said earlier; which is that when we are looking at the reactions, we are not solely looking at the ones that code to the term anaphylaxis or even anaphylaxis reaction. We are looking at systemic allergic reactions. And we're using epinephrine use as a marker in terms of what the patients and the investigators are identifying on the ground. A lot of this may be an artifact and how the terms are coded within MedDRA.
DR. STEPHEN DILLY: Would it be helpful to look at the use of epinephrine across severities of all the potential systemic allergic reactions? We do have those data. So you can see that there was -- we are in violent agreement that patients should have epinephrine with them at all times. They should intervene early if in doubt. That's why we've said, intervene first, call the center later. What we need to get past is any haziness of the semantics and say, if you're having an evolving allergic reaction, you need to intervene quickly.

And also, we need to make sure patients are counseled appropriately to avoid that happening in the first place. And a lot of that is around the management of cofactors. So this contact and conversation between the physician and the patient is absolutely crucial.

DR. PAUL GREENBERGER: I have a question for you, Dr. Dilly, and probably for FDA. If a child, or adolescent, develops acute limited urticaria, let's say
on the chest, and then has itchy eyes and conjunctival
injection can be seen, how would that be labeled?

DR. STEPHEN DILLY: Dr. Adelman, would you
like to think about that?

DR. DANIEL ADELMAN: Daniel Adelman, Aimmune.
The question is really two body systems involved with
what appears to be an IgE-mediated allergic reaction,
that would be classified as an anaphylactic reaction
and coded through MedDRA in that way.

DR. PAUL GREENBERGER: Was that type of
reaction in the data that you presented to us?

DR. DANIEL ADELMAN: Yes.

DR. PAUL GREENBERGER: So there wouldn't be
too many research subjects who had like a localized
reaction that did not progress, as Dr. Marshall has
brought up?

DR. DANIEL ADELMAN: There were certainly
patients who had symptoms like that, who received
epinephrine. There were also patients with symptoms
similar to that, that did not, and did not progress.

DR. PAUL GREENBERGER: Dr. Apter.
DR. ANDREA APTER: Thank you. I believe study ARC003 was from years 4 to 55. And there was a decision made that was ad hoc, after the design, to exclude patients 18 and above? That's one part of the question. And then, could you tell us more about the reactions of people -- the 50 or so patients that were older, 18 years or older?

And finally, what are we going to do when the 17-year-olds turn 18, and for older people? I think the severity of the reactions even in the 4 to 17-year-olds, there was a severity increase with age. So, a whole bunch of concerns that allergic reactions to peanuts in older people might be more severe and become problematic here.

DR. STEPHEN DILLY: First of all, as with all of the -- if it's (inaudible) peanut allergy, that's the yin and the yang. Which is, are the patient who are reacting mostly the ones with the greatest unmet need? And that's why we think adults are very important.
Now, here's what happened in terms of the ARC003 study. We intended it to be a study of 4 to 55-year-olds; the lower age limit really defined by practicality, reliably taking that dose every day. And 55 because we were aware of how much epinephrine would be used during the study, and we wanted to limit potential cardiovascular risk. So 4 to 55 was a paradigm going in.

We then split into predefined groups. The 4 to 11, the 12 to 17 and the 18 to 55. Our intent was to enroll more adults. But what happened was, with a target enrollment of 500, by the time we'd already hit 550, we only had 55 adults. We'd hoped to have about 100 adults.

We had a conversation at that time -- and this is a year before unblinding -- with the Agency, who asked us how many patients have you got? And at that point we said we have 499 children, aged 4 to 17. And they said, Well, our advice to you is that that aligns with your breakthrough designation, that aligns with your power calculation, that should be your primary
endpoint. And let's treat that now underpowered small
group of adults as an exploratory analysis. Okay. So
that's what happened. All of that was defined a year
before the study was unblinded.

We then follow that group of patients. We
have our primary endpoint that’s hit in the 4 to 17-
year-olds. We had a near miss in the 18 to 55-year-
olds on the intent to treat. But we had the
interesting observation that those that completed seem
to achieve a higher level of -- the same level of
desensitization.

Now, why did we miss? We missed because more
patients dropped out in the adult group, and that's
really quite important. So if we could look at the
adult disposition slide please, to show you why they
dropped out. This is really quite -- that would be DS-
2. Thank you very much.

Here are the 92 adults screened, and 56 get
in, 42 are on AR101, 14 on placebo. Only 20 of those
42 completed. You remember the overall withdrawal rate
was 20 percent, in adults it was 50 percent -- plus -- 52 percent.

A lot of those adults withdrew consent. Now, there was -- the withdrawals due to adverse events was about the same between the two groups. But there was this signal, particularly in the 18 to 25-year-old group, of adults withdrawing consent. We captured adverse events in all of them, but we went back and said why were they withdrawing consent?

And if you go to the verbatim reason that they reported for doing that, you know, in a lot of cases it was the conflict of rigorous scheduled up-dosing, multiple visits to the doctor's office with the activities of life that happen in young adults. But in a lot of them -- some of them also -- there were also some persistent tolerability issues, no different to other patients. But the combination of the two seem to push them out.

So in this small group of patients we've got no a priori reason to believe the efficacy is
different. The safety seems similar. The ability to
stick-with-it-ness doesn't seem to be quite the same.

So we then said, okay, what do we do? Because
we could successfully treat a bunch of 4 to 17-year-
olds, and some of them are going to reach their 18th
birthday, what do we do? And if we look at -- and this
is why it’s patients who have already achieved
desensitization, who are already on maintenance dosing.

We had a tiny group that actually did turn 18
during the trial, and they seem to behave exactly the
same. And the group of patients we have who were up-
dosed beyond their 18th birthday seem to do the same.

So putting a rug over all that, our recommendation is,
in that particular group of patients, they should be
allowed to continue therapy. But absolutely that's a
conversation between the physician and the patient.

DR. ANDREA APTER: I would certainly urge more
information in older age groups beyond 18 to 25. It's
very important to understand the mechanism of the
reaction as well there.
DR. STEPHEN DILLY: We very completely agree. And extending the age range is important. Because also, some of Dr. Vickery’s work, in particular, has shown that catching children early, in the 1 to 3-year-old group, is equally important. In some cases, you may get a more definitive outcome in those patients. That study is ongoing. It's a bit like the ethnicity question. Our first step is to actually get to the centers that treat adults in sufficient numbers, that we can do something about it.

DR. PAUL GREENBERGER: Thank you. Dr.

DR. ERICA BRITTAIN: No, I just wanted to ask a question. You briefly showed this Kaplan-Meier curve during the question period, and I wanted to go back to that.

DR. STEPHEN DILLY: This is the up-dosing period. The Kaplan-Meier of up-dosing duration.

DR. ERICA BRITTAIN: Right. Right.

DR. STEPHEN DILLY: Sorry, we’re just finding it. There you go.
DR. ERICA BRITTAINE: Okay. I'm not really interested in the placebo here. Again, I'm interested in those people who dropped out. It looks like since at 40 weeks, everybody in the active arm is considered getting to 300, you must be censoring the people who are dropping out. And I think -- I mean, this is the answering question in completers, I suppose. But to get an idea of your whole group, you would want not to censor the patient.

I mean, to be consistent with your primary analysis, where people who don't make it are considered failures, I think to be consistent with that you can't censor them. So, I think this might be a bit misleading.

DR. STEPHEN DILLY: If I can essentially blow up the analysis. And this is the ITT population, the Kaplan-Meier time to discontinuation due to adverse event or treatment failure.

Now, there's a really important point of art here. I think I should ask one of my physicians -- Dr. Jones, would you be willing to stand up and talk about
the conversation around how fast you up-dose a patient?
Because we had a protocol defined trajectory. And in
our label will be essentially a speed limit of do not
up-dose more frequently than every two weeks. But yet
some patients do go slower than that.

DR. STACIE JONES: Yes. Stacie Jones,
University of Arkansas and Arkansas Children's
Hospital. Like Dr. Burks, I've been treating patients
in clinical trials with oral immunotherapy. This trial
in particular, as Dr. Dilly has mentioned, recommended
per protocol for up-dosing every two weeks.

However, it’s in this protocol, as in many
others that we have done, that we often find that there
are participants in these studies -- and therefore
translating that to what we would anticipate will
happen in the clinic. There are patients that actually
cannot do that for scheduling reasons. But also just
for normal life, atopic disease reasons.

They may have skin that's flared, their asthma
may have flared, or they had an asthma exacerbation.
Or have a concurrent illness when they come into the
clinic or proceeding the clinic visit. So there are reasons that we would not want to increase that particular patient in the clinic setting.

Also, there are certain AEs, in particular mild GI or skin events that we may want to dose longer. And extend that dosing period for another two weeks, for instance, and be able to see if those symptoms are going to resolve. We even had the option -- and we would do this in clinical practice as well -- to down dose. To go back down to a tolerated dose, give a longer period of time on that dose, before going back up and marching back up the schema toward 300 milligrams.

DR. PAUL GREENBERGER: Dr. Kelso.

DR. JOHN KELSO: I think it's important for us to consider the efficacy data and the safety data together, because in some respect I think they're the same thing. What we're being asked about is, is this treatment effective to prevent patients from having reactions to accidental exposures? But as it’s been
found in the study, and in real life, such accidental exposures are rare and rarely severe.

So we can't answer the question directly, does this treatment prevent reactions to accidental exposures, because there are so few such exposures. So we've substituted a surrogate. The surrogate is this observed oral food challenge. But unfortunately, the surrogate is imperfect.

The implication is that because the patient was able to tolerate 300 milligrams, or 600 milligrams, on the day of their exit food challenge, that they are here forever protected from any exposure less than that amount. But clearly, that's not the case. Because as we've seen, reactions occur unpredictably in response to previously tolerated doses. And the sort of proof of that, if you will, is how often the patients need epinephrine, which gets to the safety data and why it sort of merges with the efficacy data.

So, if one way to look at this is if the treatment is effective overall -- not just on the day of the challenge -- would be the ask how often do
patients end up needing their epinephrine? And
patients undergoing this treatment end up needing
epinephrine twice as often as the patients who are not
undergoing the treatment. So it is not clear to me
that this treatment is effective, even though the
surrogate that we're using for the accidental exposure,
they clearly increase their tolerance on that day.

But they're having a challenge every day.

They're undergoing a challenge every day because
they're taking a dose of peanut. And although most
days they will do just fine, some days they will not,
they will have reactions. And the rate of that
cumulative reaction, because they're exposed and having
a challenge every day, ends up with the final bottom
line of they are needing their epinephrine twice as
often as they would have had they not undergone the
treatment.

I would like to see if there is any comment
from the sponsor, if we sort of merged the safety and
efficacy data, to reach any other conclusion that
people are needing epinephrine twice as often when they undergo the treatment.

DR. STEPHEN DILLY: Absolutely. So remember, what we were showing you was the situation after a year of treatment and the journey to get there. That's the combination. We absolutely accept that when you're giving a patient an increasing dose of peanut protein over time, they will have adverse reactions, they will need management. And during that early phase we do expect to see an increased use of epinephrine, increased symptoms, all the rest of it.

Now, we have to ask ourselves several questions. And, yeah, this is really important; it comes to the central thing we're looking at today. The first one is, is it a stable situation or is there evidence that the adverse events associated with dosing decrease over time? And we've looked at that in a number of ways.

You saw in the course slide that during the first year, that in CO-56, the number of adverse events that patients were having in the active group started
off considerably higher than the placebo group. And then in terms of the common adverse events -- I actually did want that slide, please, CO-56, yeah -- actually did come down to approach the placebo levels.

Now, we've also looked at all adverse events over time -- if we could have LT-15 -- in a longer duration. And what you can see here is, starting with up-dosing and going out to more and more weeks at -- LT-15, please. Thank you. What you can see here is starting at up-dosing and going down over more and more weeks, until we're actually at nearly two years of follow on after the up-dosing -- so this is now 130 weeks of treatment -- the overall rate of adverse events decreases over time in this population.

We've also looked at this through another lens. Which is whether -- you know, patients who stayed on therapy -- whether there was any temporal pattern. And we can see here in this slide, these are the patients who didn't drop out that went all the way through that. Again, there’s a gentle downward trend over the entire distribution.
Then we asked the question, okay, let's not just look at all adverse events, let's look at what people are really worried about, which is the severe, even life-threatening events. And first of all we have to establish, to the best of our abilities, what's the expected rate in a peanut-allergic population. And if I could have slide UN-11.

This is the best we could do on that. These are four studies, looking at severe systemic allergic reactions in an observed cohort of children with peanut allergy over time, where the definition was close to our definition. You heard some of the definitional difficulties earlier. And what we see is a point estimate of between 1.5 and two events per hundred patient years of experience. So what's our rate? Let's go and look at our own database. And if I could have slide AN-50.

At the time we submitted those 1050 patients to the FDA in December 2018, we had a point estimate of our own rate of 1.05. Now, our confidence intervals overlap with the confidence intervals you saw in the
previous slide. We are explicitly not claiming a
decrease in severe systemic allergic reactions during
that time period.

But what we do see, which is quite reassuring,
is with an additional 250 patient years of experience –
- which is what we had at the update in that same 1050
patients -- the observed rate is now 0.82. So all of
that suggests overall, in common with every other type
of immunotherapy, the picture gets better over time.
And we're arguing that the investment of time effort,
use of epinephrine, whatever, during that first year,
is worth it to get to that level of desensitization.

Finally, what we did -- and sorry to take some
time, this is a very, very important question -- is we
did a number needed to treat/a number needed to harm
analysis, which is on slide ST-7. And we looked at
achieving the primary endpoint, which we believe is
meaningful. We had a very good number needed to treat,
about 1.6 patients to hit that primary endpoint.

And then we said, let's not just look at the
severe SARs, let's look at moderate or severe --
because you've heard all about some of those could evolve or whatever. And the chance of seeing one of those was 1 in 18. And so if you put those two numbers together, you get a number needed to treat, over a number needed to harm ratio of 11 to 1.

So given that and finally what I'd like to do is turn to Dr. Burks to talk about the implications of these observations in terms of the nature of the reactions. The moving from unpredictable to predictable and manageable. Dr. Burks.

**DR. WESLEY BURKS:** Wesley Burks, University of North Carolina. Reflecting on your comments, Dr. Kelso, and just having thought about it a long time, I think Stacie and I and others, that have been involved in this research for a couple of decades, at the beginning really wanted to think about a treatment that really changed the disease to make it go away. And quickly after designing protocols based on other types of immunotherapy, listening to patients and families and why they came to see us for those studies, is what they wanted was protection from accidental reactions.
To feel differently. They didn't care that it went away necessarily. They would like that, but they really wanted protection from an accidental reaction.

So as they enrolled in the studies and saw the challenges at the beginning and the challenges at the end, those that got there, that feeling of they are protected from that accidental reaction changed pretty significantly. And so the predictable nature of the adverse events, the use of epinephrine and the other events that happened after dosing were predictable. They occurred within a certain timeframe.

And with that, they still wanted to continue with treatment. In this study and our studies that completed the regimented time of treatment, 95 percent of them wanted to continue into the follow up studies because of how they felt. Their family, their child was different than before they started treatment, despite those predictable side effects that we're talking about.

DR. PAUL GREENBERGER: Dr. Brittain.
DR. ERICA BRITTAIN: Can we see slide LT-16 again? Okay, thank you. I like this slide a lot better than a slide you showed a few slides before this. Where you had a slide of -- again, I just don't like those comparisons between the people who made it to 300 versus those who were early. Because they're just different people. Here we have all the same people at every time point. I think this is a much more helpful slide. And I just wanted it up for a moment to make sure I understood it.

So events per patient year is -- so the maintenance period is -- that in terms of days?

DR. STEPHEN DILLY: It's weeks. So it's 0 to 13 weeks, it would be.

DR. ERICA BRITTAIN: Oh, I see. So, there are very few down at the end. Okay. All right. So, this is showing about -- but they're still having about 20 events --

DR. STEPHEN DILLY: Right.

DR. ERICA BRITTAIN: Even in maintenance? Am I reading it right? They'll be having about 20 --
DR. STEPHEN DILLY: What we’re saying -- the background. The challenge here is in those last out groupings -- 66 to 78 and 79 to 91 weeks we're getting a little -- or diminishing numbers there. Because this is patients who’ve completed their studies, but not all of them have gone far enough in 008 to do it.

This is an attempt to show that. And show the overall pattern that we've seen, which is that the adverse events, in this highly atopic population, they really never go to zero. But they don't go to zero in the placebo group that we observed in ARC003 either.

And we're getting very close, if not at the placebo noise at this stage. Because remember, these are kids with often three or four food allergies. They've got atopic dermatitis, they've got asthma, they've got allergic rhinitis.

DR. ERICA BRITTAI N: So this is any AE --

DR. STEPHEN DILLY: Any AE over time.

DR. ERICA BRITTAI N: Okay.

DR. STEPHEN DILLY: And so, what we're saying is there is clearly an excess early on, right? And the
real thing to look at here is, when you do the initial
dose escalation, quite a lot of them have adverse
events. It's a single day period so the number is very
high. Up-dosing, that period there, a lot of them have
adverse events as we know, that's very predictable.
And then they tend to go down towards an asymptote over
time, after about a year or so of therapy.

Comment that Dr. Adelman made, which I think
is quite important, is that in terms of the severe
systemic allergic reactions, we haven't seen any of
those out beyond 52 weeks of maintenance. And you can
see we've got quite a few patients out that far now.

DR. ERICA BRITTAINE: And the people who
actually passed the primary endpoint, you have followed
some of them past that time point, right?

DR. STEPHEN DILLY: Absolutely.

DR. ERICA BRITTAINE: Of the people who
actually passed the primary endpoint, do some of them
have accidental exposures after that -- that need
epinephrine or whatever?
DR. STEPHEN DILLY: We've got a slide of accidental exposures over time. Now, this is the -- remember we had the controlled population, integrated population, which is everyone. And this goes now all the way up. We've got the early maintenance, which is the first six months -- that's when they were in ARC003. And then you've got the continuation, and 430 patients we've got in this dataset continuing to follow.

And you can see the -- yeah, the exposures continue to be reassuringly low. The association with a treatment emergent adverse event is low. And by now -- now we're on more than six months of maintenance -- none of them required epinephrine or was associated with an SAR. So we think we are seeing, you know, a reassuring signal in there. But this is within the limitations of the data we have.

DR. PAUL GREENBERGER: I'm asking if Dr. Finegold has any questions for us from New York?

DR. IRA FINEGOLD: Yes, thank you. I was wondering if you are going to recommend, like we do
with any other form of immunotherapy, that patients or
caregivers sign an informed consent?

DR. STEPHEN DILLY: If I can broaden that
question a little bit. We think it's really, really
important that the conditions under which AR101 is used
-- and if you like the real world -- closely match the
safeguards we had in place during the study.

Now, the risk management plan that we are
actively discussing with the Agency, as you've heard,
is an element where we seem to be very closely aligned
on what's really important. A lot of that is around
supervision of the dosing. But also making sure that
the patient is properly briefed to expect, and how to
manage adverse events when they happen. That the
distribution controls are in there.

The exact details have not been finalized, but
we're absolutely committed to doing this in the most
effective way possible. And we think in that context -
- and this could be a very important therapy. But the
whole reason to bring this under regulation, this is
the whole reason to have it done under this setting, is
so that these things can be in place.

DR. PAUL GREENBERGER: Any more questions?

DR. IRA FINEGOLD: No. That didn’t answer the
question, but that’s okay.

DR. STEPHEN DILLY: I don't know exactly yet,
is my best answer to that. But we're talking about it.

DR. IRA FINEGOLD: Okay. Thank you.

DR. PAUL GREENBERGER: I have two logistical
questions from the clinical studies. And the first was
if the consent forms said anything about how long the
responsible adult with epinephrine has to be in the
presence of the child or adolescent?

DR. STEPHEN DILLY: Dr. Adelman, can you
remember that?

DR. DANIEL ADELMAN: Could you restate your
question? I’m not sure I --

DR. PAUL GREENBERGER: It breaks down to
whether the child can get the tablet or contents, eat
breakfast and jump on the school bus. So how long does
the child or adolescent have to be in the presence of
the adult with the epinephrine?

**DR. DANIEL ADELMAN:** Certainly. So our
recommendation in the clinical trial was that patients
be administered the drug late in the day, generally
with dinner. We did that for two reasons.

Number one was it's the at the end of the day.
If the child had had an anaphylactic reaction during
the day, we could withhold the dose in the evening.
But more importantly, generally activities were
somewhat less in the evening and the child would be at
home with the parents, or with the caregiver.

And so our recommendation was, in fact, to
keep the child under observation for at least an hour
and a half or two hours, or even up to three hours,
depending on the child.

**DR. PAUL GREENBERGER:** Can I ask -- I wasn't
privy to your consent forms and the clinical
investigators have done many of the studies. How was
that handled, and might you be able to draw any
conclusions for how to handle that practically on the epinephrine and the child?

DR. STEPHEN DILLY: I’ll ask Dr. Jones, who was an investigator, to comment on that.

DR. STACIE JONES: Stacie Jones, University of Arkansas. I think this is a really important question as we potentially move forward into the clinic. And it gets to patient selection and patient education, which I think is what you're going toward.

I don't want to use a large term like all of us did exactly the same thing. But I think in general the practice was to advise patients and families, parents, care providers, to be able to observe for at least two hours. So not to put that child to bed, not to send them to daycare or put them on the bus. I think that's going to translate very well into practice.

I think as allergist who are going to be the people that primarily will be giving this therapy, that's going to be fairly standard of care for all of us. So constant access to epinephrine. But also close
observation with these periods of time that we know
that had the predictable reactions that are possible.

**DR. PAUL GREENBERGER:** And I'm going to ask
you regarding sedentary behavior or not. I heard that
the research subjects are counseled not to be doing
whatever, running or exercising for one to two hours.
Do you have data on that and was that in your study?
Can an eight-year-old wrestle with the six-year-old, or
something like that?

**DR. STACIE JONES:** Yeah, that's a great
question. In all the studies that we've done, we have
certainly noticed the variability among patients.
There are patients that can take their dose and have no
trouble and are definitely on active therapy. There's
a very nice paper from 2009 -- combined paper from our
groups -- that really highlighted exercise as a key
factor, and really increase of core body temperature.
So, we know that that is an association.

Again, for me, it's back to patient selection.
If the family cannot accommodate and adapt to some of
those so-called rules of management, and rules of
engagement for dosing this as a drug, then they're really not going to be the right person. And we know that this therapy is not for everyone. And that would be a patient that I would encourage to either alter their behavior or would exclude from the therapy.

**DR. STEPHEN DILLY:** Could we have the co-factor slide, please? And thank you, Dr. Jones. One of the beautiful things about having a large database is at last we can take some of the art and put some data behind it.

And this is looking at the control population in all systemic allergic reactions, what happened. And reassuringly it does align with the wisdom. That you have two thirds there was an identifiable cofactor. The most identifiable cofactor was exercise, right. And then other stuff that you'd expect would raise the core temperature; you know, hot water exposure and all the rest of it.

Now remember, this is in a group of people that had been told to avoid exercise and all the rest of it. And so, it just reinforces that, you know,
people will get it wrong sometimes. And so, we have to counsel them what to expect, to have the epinephrine available. Dr. Adleman’s point about dosing in the evening is quite important. Because it is a time when children are slightly more controllable. But stuff will happen, and we have to be aware of it.

**DR. PAUL GREENBERGER:** Are there more questions from the committee? Dr. Hawkins.

**DR. RANDY HAWKINS:** Just one question. In this one aspect of access and availability, in your briefing document you discuss the product, of course. How difficult or easy is this product to manufacture and how available will it be? I know we talked about national -- it would be an international demand if it’s approved. Give a little bit of a feel about that.

**DR. STEPHEN DILLY:** We're ready with this. One of the differences from current practice of oral immunotherapy is to do that with high quality, it's quite onerous in terms of preparing the individual doses. Because you have to have accuracy both in the
What we've done, from the get-go, is we've identified a particular source of peanuts that are consistently harvested and process to produce the peanut flour, which is our starting stuff for the manufacturing. So, they're always roasted at the same temperature, they're always squeezed to the same fat content, same grind, all that kind of stuff.

Then it goes into the classic sort of good manufacturing practice facility that we've got that has very, very high capacity. So, at the moment we are ready to supply this. And that's one of the advantages is it is available; and the physician can focus on the management of the patient rather than the production of the drug substance itself.

DR. PAUL GREENBERGER: Dr. Finegold, any questions before lunch?

DR. IRA FINEGOLD: The only question that I have -- and I congratulate the company on all the work
they’ve done. Is there any idea of cost? Or shouldn’t I ask that?

DR. STEPHEN DILLY: We are absolutely determined that the ability to pay should not be a barrier on the outside. We will probably be launching with an assistance program. We do think that -- you know, the evidence is that the patients that presents currently to allergists, that are able to get OIT, are a subset of the ones that need it. And so, this is a very important question. Bear with us; a lot of these decisions haven't been made yet.

DR. IRA FINEGOLD: Thank you.

DR. PAUL GREENBERGER: Okay. Thank you, everyone. I appreciate that we're on time and have had a very productive morning. We have one announcement.

CAPT. SERINA HUNTER-THOMAS: We're going to break for lunch now. But I want everyone to keep in mind that we are going to start promptly at 1:00 for OPH. Because it is going to be approximately 90 minutes instead of the 60 minutes that is indicated on
the draft agenda. So, we're going to start promptly at 1:00. Thank you.

[LUNCH BREAK]

OPEN PUBLIC HEARING

DR. PAUL GREENBERGER: Good afternoon, everyone. Welcome to the Open Public Hearing session. Please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making.

To ensure such transparency at the Open Public Hearing session of the Advisory Committee, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of the of your written or oral statement to advise the committee of any financial relationship that you have with a sponsor, its product and if known its direct competitors. For example, this financial
information may include the sponsor’s payment of your travel, lodging or other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you have not had any such financial relationships. If you choose not to address this issue of financial relationships, at the beginning of your statement, it will not preclude you from speaking.

Thank you. Now we're going to begin.

CAPT. SERINA HUNTER-THOMAS: Thank you. Just a reminder that everyone has four minutes to speak and we're going to go in rapid succession, starting with Ms. Rachel Packer.

MS. RACHEL PACKER: Before I start I just want to let you know that I have absolutely no financial relationship.

Good afternoon. I'd like to first thank the advisory committee for providing this forum in order for us to share our experiences in managing our children's food allergies. My husband and I have been
food allergy parents for almost 13 years. Our son, Ari, was diagnosed with severe food allergies to peanuts, tree nuts and eggs when he was two and a half. Of course, this was a time when Internet information was not as expansive. Social media was in its infancy, and we did not have the benefit of widespread information, support or research. Food labeling was paltry at best, and the variety of allergy-free food was extremely limited. The research on food allergy therapies was only under investigation, with oral immunotherapy in its very early existence. This provided us with little hope with the daily challenge of feeding our family safely.

Day to day living with food allergies is not a linear path. It is a road paved with fear, anxiety and exhaustion on a daily basis. As our child gets older, the challenges continue to change. And despite our best educated and controlled efforts, to keep him safe, two years ago we experienced an event that no parent should ever have to witness.
We were celebrating my milestone 50th birthday on Thanksgiving with family in New York. After a month of phone calls regarding seafood, caterer, food labels and even cooking my own seafood to bring to the event, our son inadvertently ate an olive that unbeknownst to us contained an almond. The chain of events to follow are so clearly etched in my brain from the immediate swelling of his face to a point of such grotesqueness, and with the realization that it could be the last image I see of my son; to his staccato breathing, and the fear on his face as we rushed him to the hospital to be pumped full of epinephrine, prednisone, Benadryl, and Zantac.

Ironically, the next morning in the hospital, his breakfast consisted of a large glob, if not lethal, side of peanut butter. We are truly never safe. Even in a place that should just not ultimately understand the repercussions of such an egregious error but should take every calculated measure to prevent it from happening. We However, were the lucky ones. We had our son.
There have been so many heartbreaking fatalities in the allergy community recently. And our hearts are shattered every time a child dies of an anaphylactic reaction. Our children live in an anxious reality of school shootings and violence. But the allergy child, they have an added burden. For them, suffering from a severe anaphylaxis reaction from accidental exposure is more likely their reality.

EpiPens are neither cures nor guarantees. And while we are grateful for them, we are cognizant that there is a level of failure. Moreover, access to epinephrine has been challenging, whether there's a shortage, a monumental price hike, or both. The allergy community needs these therapies to prevent these occurrences. Twelve years ago, we never thought that this would ever come to fruition. But here we are with a breakthrough that could change the lives for so many.

Our son wants to be a pediatric doctor. And while he still can't pick up his dirty socks, I believe his food allergy experiences will shape him into the
compassionate man doctor he is destined to be. Something the world could use a lot more of.

But fear of food and repercussions can prevent him and others of reaching their potential or having an impact on our world. Our hope for him and the entire allergy community is that this therapy will change our lives. And when I say, change our lives, I simply mean live normally. Thank you.

**DR. PAUL GREENBERGER:** Thank you.

**CAPT. SERINA HUNTER-THOMAS:** Thank you. Dr. Steve Kagan, former congressman.

**DR. STEVEN KAGEN:** Thank you for allowing me four minutes. As a former congressman, that's four times as much time as I got on the House floor from time to time.

And thank you for serving all of the public. Not just the medical community, but also the public at large, for the members on this committee. It's a great sacrifice to be here away from your family, your practices, your research. And thank you for your dedication to helping to improve the quality of care
for all of our patients, and especially our allergy
patients.

I'm Dr. Steve Kagan, I'm from Appleton, Wisconsin. I am a former congressman. I'm one of the
co-authors of Obamacare, the section that says that no
citizen of the United States should suffer from
discrimination just because you have a preexisting
medical condition or are a woman. You shouldn't have
to pay more than a man.

I've taken care of over 60,000 allergy
patients, many of them with peanut allergy and others
alike. I've had a research laboratory. I have
developed diagnostic tests in the 1980s. I worked with
my colleagues to develop the first test yourself kit
for AIDS. And then I was chairman of the Allergen
Standardization Committee for the American Academy of
Allergy and Immunology. And along with my friend and
colleague, Tom Platts-Mills, we work to standardize
dust allergens.

It may come as a surprise to some of you, but
four decades ago an allergist would collect your vacuum
bag, extract out whatever is in there, filter it and sterilize it and inject into you, hoping that somehow that would make you feel better. In fact, in March of 1923, I believe it was -- 24 -- the FDA approved the whole-body extract injections of house dust and ground up frozen carcasses of stinging insects. Hoping that the eyeball, the body parts and the legs wouldn't interfere with your immune system.

Well, we've come a long way in standardizing what we're doing, how we diagnose and treat the allergy patient. I'm here to support the application of Aimmune's product. I believe it's a great advance because now as an allergist I'll have a standardized product to test and potentially treat my patients.

I'll remind everybody -- and my colleagues in allergy are already aware of this -- that each and every allergy patient is unique. They're unique in terms of what they're allergic to, how their immune system works, and also how their autonomic nervous system, or the part of your brain you can't control works. So in our field of allergy, it's very important
that we identify the best patient and the best
treatment for that individual patient.

But again, I would encourage the committee and
the FDA to approve this standardized product which will
greatly improve the diagnosis and treatment of the
peanut allergic patient. Thank you for almost giving
me -- I took three minutes, so go for it.

DR. PAUL GREENBERGER: Thank you.

CAPT. SERINA HUNTER-THOMAS: Thank you, sir.

Next is Charmayne Anderson.

MS. CHARMAYNE ANDERSON: Good afternoon. Yes.

My name is Charmayne Anderson. I am the Director of
Advocacy for Allergy and Asthma Network. I do not have
any personal disclosures; however, the network does
receive resources for unrestricted education and
awareness from Aimmune and DBV.

Our organization is a national nonprofit,
dedicated to ending needless death and suffering due to
asthma, allergies and related conditions. Since 1985,
care teams throughout the U.S. to serve the 60 million Americans living with these conditions.

Today, however, I'm here specifically on behalf of the 3 to 4 million Americans living with peanut allergy. The prevalence and burden is growing, and these patients live in constant fear of accidental exposure. It is this segment that accounts for the majority of the $25 billion per year in direct and indirect cost based on the literature.

But these aren’t nameless, faceless statistics. These are real people with families, hopes, dreams and fears. I'm here to tell their story, amongst many others in the room, to bring forth a true societal perspective.

First, there's Allie from Philadelphia who's a 34-year-old young professional who lives with multiple food allergies, including peanut. She has taught elementary school abroad and stateside. She writes a blog about her challenges living with life-threatening allergies for the past 10 years. Yet every day at every meal she must remain hypervigilant to avoid a
life-threatening reaction, and take significant steps
to ensure her safety. Including skipping meals when
dining out and translating chef cards in many different
languages. And even so, each year she averages two to
three accidental exposures resulting in a reaction.

Next, there's Thomas in New York. Thomas is a
hard-working father of two. He suffered every parent's
nightmare in 2014, when his three-year-old son, Elijah,
died from a severe life-threatening allergy while at
preschool. Even though Thomas and his wife took great
strides in making sure his childcare providers were
aware of his food allergy, and prepared to administer
epinephrine, an accidental exposure occurred. And
within minutes, this man's world was turned upside
down. His family will never be the same. Avoidance
alone is simply not enough.

Finally, there's the story of Carson. From
the outside looking in, Carson is a vibrant 14-year-old
starting high school as a volleyball player. The truth
is she lives in constant fear and anxiety. Fear the
next bite of pizza may be the one that lands her in the
ER. Anxiety that her friends may have to administer epinephrine simply to save her life.

You see, Carson is the daughter of Tonya Winders, President and CEO of the Allergy and Asthma Network. And she is one of the many reasons our organization is represented here today. Allergy and Asthma Network believes patients deserve better options. Avoidance only is simply not enough.

Significant scientific advancements in peanut allergy diagnosis and treatment are promising so patients like these can depend on this innovation. Now is the time for FDA to act, along with many other stakeholders. Thank you.

DR. PAUL GREENBERGER: Thank you.

CAPT. SERINA HUNTER-THOMAS: Thank you. Next is Dr. Robert Wood.

DR. ROBERT WOOD: Thank you very much. I do have conflicts to declare; receiving a research report from Aimmune and all the other companies investigating treatments for food allergy.
I am here today as an individual. Although I am the Immediate Past President of the American Academy of Allergy, Asthma, and Immunology. I'm also the Principal Investigator of CoFAR, the Consortium of Food Allergy Research. As an individual, a pediatric allergist, in practice for over 30 years, I currently have over 1000 patients with peanut allergy in my practice. And over the course of my career, I'm sure I've cared for more than 10,000 patients. I also have a lifelong peanut allergy, so all of this is very real to me.

I'm going to go on here with questions and my own answers to those questions. Number one, is this a perfect therapy? Of course not. Absolutely not. Is it something that is an advance in the field? Absolutely. Are the benefits worth the risk? And as Dr. Burks presented, this is where the equipoise comes into play. And for one family the answer may be absolutely; and for another it may be absolutely not. And that's where this needs to be a shared decision, if
we're lucky enough to have this product, between us as providers and our patients.

How does this treatment compare to our currently available options? And the first option, obviously, is avoidance. And I'm not such a naysayer on avoidance; it actually works extremely well for most patients. And most of my families are not plagued by anxiety. They're doing quite nicely, leading normal lives; progressing from preschool to school, to high school to college very successfully in spite of their peanut allergy.

The other option out there is OIT purchased from the grocery store. And compared to that option, this is a tremendous leap forward. And I have been probably the most outspoken opponent of the OIT that's being provided, by practitioners, with products purchased in the grocery store, which really calls for the need for a well-standardized product as AR101 is.

The last questions are, if approved, would I provide this -- prescribe it for my patients? The answer is absolutely. If approved, would I recommend
it to my patients? The answer is absolutely not. And
the difference there is that it would be unfair for me
to recommend a treatment that has significant risk if a
family is quite satisfied with avoidance.

We've also not discussed today the burden of
this treatment. We've not discussed that it is all
likely a lifetime treatment. So this is where it would
be a shared decision where the treatment would be
offered, but not recommended. Thank you.

DR. PAUL GREENBERGER: Thank you.

CAPT. SERINA HUNTER-THOMAS: Thank you, Dr.
Wood. The next person is Alicia Ortego. Ms. Ortega,
can you press the green light to start your time when
you're ready. Thanks.

MS. ALICIA ORTEGO: We have no financial
relationship.

MS. JULIANA ORTEGO: My name is Juliana and at
dfour years old I became Children's National first
PALISADE patient. When diagnosed, we are told to
strictly avoid peanuts. And up until now that was our
only option.
But just avoiding peanuts isn't as easy as you think. It means sitting at a separate lunch table away from my class. It means only getting two friends at lunch instead of 20. It means never getting to eat cake at my friends parties and watching others enjoy it while I eat my safe snack. It's a big deal to a little kid.

It means being the outsider when worrying if they are going to touch me with peanut hands. It means feeling different all the time. Kids aren’t always accepting of people who are different. It's a world of, no, you can't have that, it's not safe. While everyone else around you can have it. It’s frustrating and divides my world into two groups, me and everyone else.

Avoiding peanuts doesn't just mean food. It means makeup, shampoo, lotions, chap stick. It means I can't plant a Mother’s Day flower because -- you guessed it -- potting soil has peanuts. It means having everyone look at you weird when your mom wipes down the movie theater seats with Clorox wipes. It
means worrying if one day I'll get attacked with peanut butter.

Everything is limited, even love. Family, you would think, would be safe to a kid. But to a kid like me, we can't run up and hug or kiss them. We have to ask did you eat peanuts today?

I wish I didn't have an allergy. But now after my medicine, I get a chance to make more friendships at lunch. I can get donuts and eat them with my class. I can hug my GiGi without asking her questions first. I can fly in an airplane and stay at hotels. And we don't need to be the weird family with Clorox wipes.

I will always be different. I will always need to be careful. But now I have freedoms I didn't have before. I get to feel a little more normal. And that lets me be a little more normal and stand out just a little bit less. My hope is that other allergic kids can experience this medicine too, because we all deserve those freedoms. Thank you.
MS. ALICIA ORTEGO:  My name is Alicia, and I am Juliana's mother. Even though she has previously tested negative for food allergies, at the age of two Juliana ate a peanut butter cracker and she went into immediate anaphylactic shock.

At the follow up appointment we were told that only 20 percent of kids will outgrow this allergy. And that the next year when they draw blood, if the numbers decrease, that we could have hope that our little girl would be that kid. Juliana is not that kid. In fact, her numbers quadrupled the next year. It was then that we knew that this was going to be a lifelong condition for her.

Her father and I felt an urgency to try to get her some form of treatment. And that is when we got wind of the PALISADE trial and we knew we had to get her into the study. But I want to be very clear about this, we knew that this program was never going to cure her. We were never looking for a cure. We had fully come to terms that she was a severe case, and that this trial may not even work for her.
Spoiler alert, she did not pass the final food challenge. So technically, we are not a story of success like others that you may hear today. Our story is a little different. But even still we accomplished our goal. Our goal of this study was to live more normally. We wanted her world to open up. We wanted it her to travel safer. I was worried about her being bullied, which is a very real and prominent thing.

Juliana has had several anaphylactic reactions. Once she had an anaphylactic reaction at her preschool, hours after lunchtime, when her peanut butter eating friends shared a kazoo for just one blow.

Traveling for us is too risky, the Metro, school buses, hotel rooms. There's no telling how often they clean or how much residue is lingering around. Flights are -- do I continue?

**CAPT. SERINA HUNTER-THOMAS:** Go ahead.

**MS. ALICIA ORTEGO:** Thank you. Flights and cruises are too far away from the hospital. For our vacations, we are limited to families houses or family-owned RVs that we know that would be safe.
This trial was not easy for Juliana. We frequently had GI symptoms while up-dosing. There were a few times that we had to down-dose for a few weeks and then bump back up. Other times we needed more time at a particular milligram level. We even had anaphylactic reactions. But we powered through.

We passed all the challenges until the last one. We were so hoping to pass that one so we could switch over to something more real life. Juliana, than age seven, received three EpiPen shots and a nebulizer treatment before even feeling relief. It was a very memorable day for everybody in the room. Clearly we have failed. Since then, we have been in a holding pattern of just taking the dose daily.

So how can I stand here and say that we have had victory? I measure our success by our goal, a new life. We accomplish goals by having more friends in elementary school, by sitting at the normal table. Because more friends means less likely to be bullied and less likely attacked by her allergen.
Our goal for travel. Even though we take
precautions, Juliana has flown on an airplane now and
has even taken a cruise. We can stay at hotels and
take public transportations, all because cross
contamination is not an intense risk anymore.

How do I know that she's being protected?
Because I have seen it with my own eyes. Her dad had
started bringing home donuts Friday morning since our
world has opened up. And we wake up to a special order
of donuts; Fridays are just glorious.

This summer, Juliana ate a donut and I noticed
soon after that her eyes started to puff up and itch.
And I instantly knew that she had eaten her peanut
allergen. I immediately called the store and found out
that their current specialty donuts contain peanuts.
But no other symptoms progress. So I gave her a
Claritin, and in surprise to my eyes things went back
to normal and that reaction ended.

Without this study, without AR101, Juliana
would have had zero desensitization. It would have
made our glorious Friday morning a fatal one. And I
don't say that as a hyperbole, this is a reality of our life. So many people are asking about this trial, about the worth of the risks, the risks of needing Epi or the risk of it not working.

Juliana represents that question so clearly, because she is that girl. She is the super rare kid that didn't pass the food challenge, but we are so blessed to be here with this opportunity.

Our worst-case scenario was that the meds would not work, there would be no desensitization and we would have to end up giving our little girl an EpiPen. Even as parents, it wouldn't be a total loss because at least we could say that we had tried everything for our little girl. The worst case never happened for us. She has levels of desensitization --

CAPT. SERINA HUNTER-THOMAS: Ms. Ortego?

Time.

MS. ALICIA ORTEGO: Thank you.

CAPT. SERINA HUNTER-THOMAS: Yes, ma'am.

DR. PAUL GREENBERGER: Thank you very much to both of you.
CAPT. SERINA HUNTER-THOMAS: The next person is Cathy Heald.

MS. CATHY HEALD: Good afternoon. My name is Kathy Heald and I'm here from Dallas. This is my 12-year-old son, Charlie, and my 15-year-old daughter, Ellie. Aimmune supported our travel here, but we are speaking on our own behalf. We felt it was important to take time away from school and work to be here today. We learned Charlie was allergic to peanuts before his first birthday. As a mother, it seems inherent that we will worry. But when faced with the food allergy, a heavier weight of constant worry enters.

We have learned how to avoid peanuts, but what about accidents out of our control? What if he forgets to ask the ingredients of a snack at a friend's house? What if someone incorrectly tells him something is nut free? What if his nut allergy gets lost in translation when he travels? These are constant and real fears, with extreme consequences, as our children become independent.
And as he ages, it's likely he will make some impulsive decisions. Did I mention he's a 12-year-old boy? As much as we prepare our kids, we know there may be some unintentional mistakes or missteps along the way.

As a three-year participant in this trial, we now have a new level of comfort. Charlie was on placebo the first year, but he has been committed to see this process through. While he still must avoid his allergen, we have seen proof of his tolerance. Working closely with his doctor, not only has he learned so much about his allergy and the symptoms, but we have seen him ingest the equivalent of about a dozen peanuts without a reaction.

We have confidently let him travel independently to Europe the past two summers; knowing that he will be okay on the long fight over, and once he's there in a foreign country, because we have seen proof of his tolerance. The peace of mind this treatment brings is invaluable.
In the recent past years, our family has considered relocation to two major U.S. cities. This treatment was not available in either city. We would have been left without the safety net that the treatment has provided him. We need more access so others can benefit.

In summary, we are grateful for the confidence that this has brought Charlie. We truly hope others can benefit from the peace of mind we have received.

MR. CHARLIE HEALD: I've had a food allergy all my life. So all I've ever known is don't eat peanuts. I felt tormented by my allergy. Whenever I pick up food, I must always look at the labels. Whenever there's food out, I must always ask someone if it has peanuts. I have to be very cautious about food. Even when a label says may contain peanuts, I would have to pass on eating that food.

But now with this treatment, I can eat some of those things. I feel more confident now because I know what would happen if I reacted. I know now what a
reaction feels like and how to respond. I'm lucky to have learned that.

Two summers ago, when I was on the active drug, I was chosen for an international education program. I traveled without my family to Sweden for a month. Then this past summer, I participated again and lived with a family in Italy.

While I still have to be cautious about what I eat, it was great knowing if I missed something in translation I would have tolerance. I was able to enjoy so many new things in these foreign countries. It was nice not to miss out on these amazing experiences because of a peanut allergy. I don't want a food allergy to limit the cultures I can learn about.

This drug has helped me in many ways. But more importantly, I know how many other people this could help.

MS. ELLIE HEALD: For the first three years of my life peanut butter was a staple of my diet. I ate it at least once a day, every day. And then my brother came along and he was allergic to my main source of
protein. My diet was severely impacted. And it was hard for me to eat peanut butter around him, because I was so scared and anxious that I might forget and accidentally touch him.

This became an everyday worry for me, and I didn't eat peanut butter as much because of it. But now that he can take this treatment, I feel relief. We have seen that he can tolerate some peanuts, so I feel more comfortable slowly working peanut butter back into my life. It's nice to have this weight of responsibility lifted from me. And I feel more safe eating around my brother and I really hope one day he can enjoy the foods that I like too. Thank you for your time.

**DR. PAUL GREENBERGER:** Thank you to all three of you.

**CAPT. SERINA HUNTER-THOMAS:** Thank you. The next person is Amy Applegate.

**MS. AMY APPLEGATE:** Good afternoon. We are the Applegate family. And we were brought here and do
have a financial obligation with Aimmune. And our son, Rylan, was in the PALISADE trial.

May 20, 2012, reaction day. There isn't much that can really prepare you for seeing your child in anaphylaxis. You feel helpless. His reaction started immediately with coughing and irritability. My instincts told me that something wasn't right. On our way to the hospital, things progressed quickly.

Seeing your two-year-old wheezing, vomiting, lethargic, bloodshot eyes, and hives that looked like a fire against his skin. And him being hooked up to IVs and people being all over a trauma room is something you don't ever truly forget. And then we later experienced a biphasic reaction.

Fast forward to one year later, we'd become more educated as parents and we asked our allergist about OIT. His reply was, no way, not ever, don't ever consider that for your child; it's not ever going to be a possibility. I left that appointment in tears and felt defeated. To say the least, we found a new allergist.
As a food allergy parent, your anxiety is taken to a whole other level. You never stop worrying. You worry about every little cough. You worry about when your child will start dating. Will his teacher in school keep him safe? And is his emotional wellbeing okay? The list goes on and on. And it is just so hard knowing that the one thing your child needs to sustain life, food, can cause life altering events.

When our new allergist informed us about the PALISADE trial, we knew we had to be a part of it. The entrance challenges were petrifying, but our site provided us with so much care and reassurance. Rylan reacted at 30 milligrams and earned his spot. Each up-dosing visit brought back those first fears. But those quickly subsided as we saw the magic of this drug working. Or was it those amazing gift cards we received at each appointment? And I think we now own half of Lego.

Dosing at home has always been very manageable, you just plan ahead. And we work around the protocols. Besides, who doesn't like eating
cookies with vanilla icing every day. It feels like a miracle. We feel so truly blessed. Our peanut allergy kiddo can tolerate 4043 milligrams of peanut powder, and also two peanut M&Ms with no symptoms.

Today our fears have lessened, and our anxiety has lifted. You, Aimmune, have made this possible. You've given us a lifelong freedom. You've given our kiddo an amazing opportunity to make history. You've changed our lives and have made the power to change so many more. We are truly grateful and pray others will get the same opportunity. Our family cannot wait to pay it forward. Thank you.

DR. PAUL GREENBERGER: Thank you.

CAPT. SERINA HUNTER-THOMAS: Thank you. Next is Lisa Gable.

MS. LISA GABLE: Thank you. My name is Lisa Gable. I am the CEO of FARE, Food Allergy Research and Education, which is the largest private funder of food allergy research. We do not have a current relationship with the Aimimmune, although Aimimmune and the
other drug companies have provided us with funds for education and our patient registry.

I speak on behalf of the food allergy community in favor of breakthrough therapies and solutions. At FARE, our mission is to improve the quality of life and health of individuals with food allergies, and to provide them with hope through the promise of new treatments.

FARE's leadership and working to accelerate therapies, like AR101, is a major part of our mission and something we work towards every single day. In 2011, we recognized the need for a standardized oral immunotherapy product and protocol. The FDA review of AR101 has been many years in the making. And FARE has been involved since the beginning. We can't overstate the positive impact that this treatment will have on our community. I know from constant communication within our community that this therapy would fundamentally change the food allergy landscape. So there are two points we want to leave you with today.
Point number one, many patients, as heard today, are willing to accept some risk with new treatments. That decision should lie with them. Patients and doctors need the opportunity to make informed decisions on treatments that are based on scientific evidence. It is important that the development of therapies emphasize the patient experience and reflect the risks which patients are willing to take for life-changing treatments.

Previous assessment of AR101 have been failing to recognize the daily burden that life-threatening food allergies place on patients and their families. There's an important distinction between an anticipated reaction in a controlled environment, as with OIT, and then unanticipated allergic reaction resulting from accidental exposure. The difference between these two scenarios is pivotal for the food allergy patient.

And our second point. The current standard of care for individuals living with potentially life-threatening peanut allergy is unacceptable. It is unacceptable that the only care option available to 32
million Americans with food allergies is avoidance; and in the case of accidental exposure, an administration of epinephrine and a quick trip to the emergency room. Food allergy patients and their families live in constant fear of accidental exposure and have been calling for new and more comprehensive treatment options for far too long. It's time we answer that call with a potential solution.

The FDA approval of AR101 would represent an important first step in changing the standard of care for food allergy patients and pave the way for additional treatments for this unacceptable reality. Patients deserve choices. And when it comes to treating food allergies, this is the time to now give them this choice.

As we've heard today from the children who presented and their families, the people in this room, they need that choice and they want their friends to have that choice also. We thank you for your time.

DR. PAUL GREENBERGER: Thank you.

CAPT. SERINA HUNTER-THOMAS: Nina Zeldes.
MS. NINA ZELDES: Good afternoon. My name is Nina Zeldes, and I'm a senior fellow at the National Center for Health Research. Our research center analyzes scientific and medical data and provides objective health information to patients, providers and policymakers. We do not accept funding from drug and medical device companies, so I have no conflicts of interests.

CAPT. SERINA HUNTER-THOMAS: Can you talk into the microphone? We’re having --

MS. NINA ZELDES: Sorry. Sorry.

CAPT. SERINA HUNTER-THOMAS: Thank you.

MS. NINA ZELDES: Thank you. Did you hear what I was saying?

CAPT. SERINA HUNTER-THOMAS: Not really.

MS. NINA ZELDES: Sorry. Okay. My name is Nina Zeldes, and I’m a senior fellow at the National Center for Health Research. Our Center analyzes scientific and medical data and provides objective health information to patients, providers and policymakers. We do not accept funding from drug
companies and medical device companies, so I have no
conflicts of interests. Thank you for the opportunity
to speak here today.

As we have heard, peanut allergy is a common
and at time life-threatening condition that can
substantially impact patient’s quality of life. We all
agree that a treatment to reduce the incidence and
severity of allergic reactions is needed. Our goal
today is to determine if this allergen powder has
benefits that are critically meaningful to patients and
is proven to be safe.

The study results of this drug look promising,
but there are unanswered questions that are very
important to patients with a peanut allergy and their
parents. There is only one study focusing on the
efficacy of the drug and its increased tolerance to low
levels of peanut exposure. This would be clinically
meaningful because children would have less fear to
exposure to tiny amounts of peanuts that can be in many
foods.
However, replication is the key to scientific evidence. Independent clinical trials could have a smaller or larger effect due to differences in the demographics or comorbidities of patients or other factors. This is of particular importance because of the high rate of adverse events and a large number of participants who did not tolerate the treatment. Additionally, there was a lack of diversity. The children were predominantly white. As a result, we do not know if this treatment is safe and effective for all children who might consider taking it. To ensure that the benefits of this drug outweigh the risks, we have some questions that we hope you'll ask.

Drug patients developed EoE. Are there solid data to clearly explain the risks of this condition on the label in terms of incidence and severity? If not, can parents make an informed choice about whether or not to have their children use this medication? Are there any data on how many doses can be skipped before a reduction of incidences and severity of allergic reactions are affected? A daily regiment
is a challenge for many parents of young children, and
children might not always follow directions. It is
essential to know how important it is to have the
children take the exact correct dose every day.

What are the potential long-term consequences
of exposure to this drug, especially for those children
for whom treatment failed? Can the treatment increase
the reactivity to peanuts in the real world?

This is the first treatment for peanut
allergies; and if this drug is approved, despite the
unanswered questions, it will set a precedent for
future drugs to treat food allergies. It is especially
important that new classes of products provide strong
evidence of safety and efficacy before approval,
because it will be difficult, if not impossible, to
obtain it afterwards. Thank you for your time.

DR. PAUL GREENBERGER: Thank you.

CAPT. SERINA HUNTER-THOMAS: Christy

Eckenrode.

MS. CHRISTY ECKENRODE: Hi. My name is
Christy Eckenrode and this is my son, William
Eckenrode. I'm going to have him speak first because he's nervous. And then I will speak after him.

**MR. WILLIAM ECKENRODE:** Thank you to the peanut study and everybody who made it possible for me. Before I was in the study I felt like I couldn't do anything because it all included peanuts. I felt like I couldn't be around other kids because they all ate peanuts. I felt trapped in safe places because there weren't many and I couldn't do most -- oh, yeah.

Now I have confident, I feel safer. I can travel and I can also go to new schools. I can eat out and I can go to camps. I can go to church. I had to switch churches before because my first church had peanuts. I can sit with other kids that I couldn't sit with before. I believe that other kids that are allergic to peanuts should be able to do this so they can experience the same freedom that I’ve experienced.

Thank you.

**DR. PAUL GREENBERGER:** Thank you.

**MS. CHRISTY ECKENRODE:** My name is Christy Eckenrode. William was a patient in the PALISADE
study. He’s been a patient in this study for three years. And we do have financial ties with Aimmune. They paid for our travel today, and we speak on our own behalf.

Before this study -- we found out he was allergic when he was a baby. And we are probably the laxer version of a peanut allergy family. In fact, in speaking to some of the other families today, I realized that I'm probably the lax mom.

I can address that you can miss three days of doses successfully and pick up on that fourth day. And we've done that many times because I am so laxed. However, having a pre-measured dose has made the difference for us. We would not do OIT in private practice because we know we are laxed. And we know we forget things, and we know we make mistakes. The pre-measured dose made it a possibility for our crazy household -- with boys and a dad and a mom -- to feel confident and safe trying this.

The first year Will was on placebo. And on our entry he reacted to one two hundredth of a peanut.
One two hundredth of a peanut means if you touched the
wall or the carpet, or a pencil or a crayon, or
anything else that somebody has touched, after they
have eaten a peanut butter sandwich and they have not
washed their hands, you will react, and you will go
into anaphylaxis. Think about that for a 5-year-old
child.

Will was 5 when he started the study. At 5
years old he entered kindergarten and he had four
anaphylactic reactions at school while trying to avoid
peanuts. We got lawyers, the school got lawyers, we
got a 504 plan. No one could believe that he was
reacting to such small amounts of peanut, and yet he
was. Every reaction got worse. (timer sounds) May I
continue please?

CAPT. SERINA HUNTER-THOMAS: Go ahead.

MS. CHRISTY ECKENRODE: Every reaction got
worse. Every reaction his sensitivity got worse.
Avoiding did not work for us. Today, we are doing
things we were told we never could do by our doctors.
We flew on a plane for the first time coming here. We were told that would never be a possibility.

William can eat in a restaurant. Before the study, he could eat at the McDonalds in our small town in Minnesota. Where I had gone and talked to the owner and they had set up a specific safety protocol just for my son. Before this study, William had to stay in our home or go to school only. Those were the two safe spaces in the entire world for him.

If he left those two safe spaces, he had to have a nurse, or a parent, or a grandparent that knew all the safety protocols. Wiping things down with baby wipes before he sat. Making sure his hands were being washed frequently. Making sure he did not touch other children and they did not touch him. Making sure they did not share toys. Now I know William was an extreme example of what a peanut allergy can be.

**DR. PAUL GREENBERGER:** Okay. I’m going to asked you to summarize and finished please.

**MS. CHRISTY ECKENRODE:** All right. Thank you.

But, he is an example of what happens when you try to
avoid and it doesn't work. Each reaction gets worse.
This dose has made him a normal kid. He gets to be a
normal kid for the first time in his life.

And we feel very, very strongly that the three
hours of rest period a day are worth it. We've had two
reactions during this study, but they were at the time
of dosing, and they were due to our negligence. We
didn't pay attention to the fact that he had his asthma
exasperated, and we dosed him anyway. And we learned
from those. He's not reacting during those daily doses
anymore. But even with that, we had a medical team
supporting us.

DR. PAUL GREENBERGER: Okay, I’m going to have
to have you -- I thank you very much. We do have to
move on.

MS. CHRISTY ECKENRODE: Thank you for your
time today.

CAPT. SERINA HUNTER-THOMAS: David Anmuth.

DR. DAVID ANMUTH: Good afternoon. I have no
financial disclosures. I’m speaking on my own behalf.
So my name is David Anmuth. I am an allergist
immunologist based out of Fairfax, Virginia. I'm pediatric trained and I recently relocated here from Houston, Texas where I practiced for the past 10 years.

I'm here today not to give any statistics or discuss the efficacy of AR101; but rather to give you a perspective from a private allergist who's on the front lines of food allergy every day. As a doctor, my goal is to provide patients with the treatment to help fix whatever problem they present with.

Unfortunately, until this time, you've heard many times today, the only treatment that we currently have is epinephrine, which is to treat the only other treatment that we have, which is avoidance. This has been unacceptable to me. But until now there was nothing I could truly do.

As a private allergist, it's difficult to adopt non-FDA approved treatments for multiple reasons. I'm here today to ask you that you strongly consider this product for approval. Not for me, but for all the patients and the parents that you see here today. This may not be a perfect solution, but this is the first
solution, which I'm sure will eventually lead to many others.

Parents come to me each day and ask if there’s something else besides avoidance and epinephrine. While in Houston, I had many patients who would travel north to Dallas to see a doctor who was getting wonderful results with off-label desensitization protocols. Their smiling faces when they would return to see me were always so priceless. But I was always frustrated that I could not provide this treatment for my patients.

Having an FDA product that's available, not just to those who have the means but to those within reach of any board-certified allergist, will change the treatment of peanut allergy forever. It will increase our current knowledge and empower our patients and our families all at the same time.

As you've learned, parents know that these are not perfect solutions. And they understand the risks that come with these protocols. But most are willing to take their chances in a controlled environment.
versus taking their chances blindly each day. They would rather know that their child is protected from accidental exposure and acute reactions when they're not able to be with them.

I think unless you're personally affected, as you've learned today, you cannot realize the quality of life that this impacts to these families. The fear and anxiety from both parents and patients that they feel each day. All aspects of life seems to come into play.

Whether it's social, being potlucks at the pool, dinners at friends and families, religious community events, sports, there's many and there's all aspects of life. This may not be a cure but by restoring confidence and reducing fear, quality of life will certainly be greatly increased.

Please do consider my experiences and of those around me today when deciding today on AR101. Not every family will choose to do this therapy. But at least it'll be their choice. At least they can decide for themselves that avoidance may not be the answer.

Thank you for your time.
DR. PAUL GREENBERGER: Thank you.

CAPT. SERINA HUNTER-THOMAS: Next is Gwen Smith.

MS. GWEN SMITH: Hi. My name is Gwen Smith and I'm the Co-owner and Editor of Allergic Living, which is a national website and magazine. I don't have any financial disclosure. Our publishing firm does accept sponsorship, but I have no current relationship with Aimmune or DBV.

I am here today, however, because I represent an audience of almost 2 million Americans with food allergies. Plus I speak as someone who has severe food allergies. Now, I've seen news reports describe Aimmune's AR101 as not a cure for peanut allergy, but simply a desensitization therapy. Let's consider desensitization, what that means to the food allergy community and why there is no "simply" about it.

Severe anaphylaxis feels like -- well it feels like drowning without water. You can't get your breath, it's terrifying. That's the symptom that stands out the most. I know this firsthand.
To the parents I deal with, the very idea that
your child could be protected against that, that's
huge. Desensitization means being freed from having to
think that any tiny wrong bite could potentially kill —
life changing. A whole family can breathe again.

The AR101 protocol shouldn't be judged against
the cure, which is elusive, but rather against the
status quo of allergen avoidance. Consider this: In a
2018 paper, Mount Sinai allergist, Sicherer and Sampson
wrote “the emotional effect —

DR. PAUL GREENBERGER: Please speak better
into the microphone.

MS. GWEN SMITH: Sorry, I'm not in the mic?
Okay. Sorry. Sampson and Sicherer wrote, “that the
emotional effect of living with food allergies cannot
be underestimated. This is the avoidance status quo.”
A recent survey from the Asthma and Allergy Foundation
of America found 75 percent of this community consumed
by food allergy anxiety.

So widespread is food allergy anxiety that
psychologists now specializes in this as an area. I
have reported on those who've suffered PTSD following their children severe peanut reactions. Such as the mother who told me she burst into tears at the sound of sirens for over a year. And yet a psychologist told me, “I hear stories like hers all the time.”

The big fear, of course, is that anaphylaxis could be fatal. Now, the better news there is, is that tragedies are fortunately not common. However, severe reactions are common. A 2017 analysis of health insurance claims found emergency treatment of anaphylaxis spiked 377 percent in a decade. And the biggest individual food trigger, peanut.

I hear it regularly, “OIT improves quality of life.” So it's not surprising that a new follow up study from the Aimmune trial shows exactly this. Think of our food allergy families; for years they've been told, “OIT is not ready. Wait for the double-blind studies to see if a protocol can be effective and safe.”

There was a 2/3 success rate in the AR101 clinical trial, and many families now want this therapy
to protect their children. It's not perfect, there are adverse effects in the build-up phase. But many families are prepared, as you've heard today, for some symptoms for the longer-term peace of mind.

If the FDA approves AR101, many allergists would like to offer the therapy. They'd like to offer more than just avoidance. When I reported on a study that favored allergen avoidance over OIT, many parents were shocked by this. In their view, avoidance alone is no longer enough. The demand for food allergy treatment is here and anxiety plague community grows tired of waiting. (timer sounds) Can I just finish? Okay.

So my hope is that if FDA approves AR101, this will just be the start of emerging treatments for food allergy. It would be wonderful to see much improved quality of life for this community. Thank you for letting me speak on behalf of my community.

DR. PAUL GREENBERGER: Thank you.

CAPT. SERINA HUNTER-THOMAS: Tessa Grosso.
MS. TESSA GROSSO: I have no financial conflicts. Can you hear me?

Hello. Thank you for allowing me to speak and share my perspective on behalf of the thousands of other patients who can't be here today. My name is Tessa Grosso. I am 16 and one of the first to go through OIT. It has been the most valuable, empowering and defining experience of my life. And I'm the proof of longevity.

I would like to share a perspective that I believe you should consider while assessing the value of this food allergy treatment. After I was diagnosed with food allergies at six months old, our family was thrown into a life of fear and anxiety. One that was analogous to navigating a minefield. Avoiding allergens is much harder than it may seem. Accidental exposure is inevitable no matter how careful you are, and it is truly traumatizing.

When I was 18 months old, a drop of allergen touched my skin and I was sent into anaphylactic shock, which was nearly fatal. When I was seven, an
undeclared trace amount of allergen in a piece of bread caused my throat to close. I needed two shots of epinephrine and an ambulance ride to the ER to keep me alive. I will spare you more terrifying details. But these are just a few of the near-death experiences I suffered at the hands of my allergies.

Not only did my reactions lead to PTSD, but the fear lead to severe anxiety. The isolation caused by my inability to participate in a regular childhood left me with depression. Food allergies have an impact on the entire family. My parents, my sister's, my grandparents, their lives revolved around keeping me safe.

The impact of food allergies goes well beyond a restricted diet. So it is so frustrating to be told that avoidance is the only option when treatments exist. As I've said before, kids like me don't care about eating a PB&J, but we do want to sit at the table with our friends.

When I was six, after more trauma than any child should experience, my mom decided she would no
longer accept a life of avoidance and fear. She found Dr. Kari Nadeau, at Stanford, who was willing to fight for a solution. I was the first person to complete multi-allergen OIT, at Stanford, and my life changed forever. Seven years later, my allergies don't even cross my mind. I am a normal kid. I eat peanut butter every single morning.

This is not to say that eating food has been the best outcome of the treatment. The true benefits lie in my comfort and safety. I can't put into words the tremendous impact OIT has had on my quality of life. Nothing short of life changing.

I would like to clarify one more thing. While I may have experienced minor reactions during my treatment, I would like to say emphatically that reactions during treatment are drastically different than accidental exposure. And frankly, a small price to pay for a life of freedom.

Reactions during OIT are controlled and anticipated. Patients are trained and prepared for a reaction. In a life of avoidance, many are unprepared
and there's no telling whether or not your next bite
could kill you. There are some incredibly smart people
in this room who have extensively tested the safety of
OIT.

Now that you've heard my story, and if you
haven't been listening, now's the time. Please
acknowledge the incredible value that these treatments
can deliver. Saving my life, giving me a new life,
every child deserves this. Therapy that provides
freedom, safety and the ability to live without the
fear of food is a choice that should be available and
accessible for every single family. Thank you.

DR. PAUL GREENBERGER: Thank you.

CAPT. SERINA HUNTER-THOMAS: Erin Malawer.

MS. ERIN MALAWER: Hello. I have no conflicts
of interest. My name is Erin Malawer, I'm the
Executive Director of AllergyStrong, an education
advocacy organization. And I'm a food allergy parent.
Food allergies are a challenge that affect
both the physical safety as well as mental health of
patients and caregivers. Bringing AR101 to market as a
A treatment option has the potential to greatly improve the quality of lives for these families.

What is the experience of having food allergies for patients? In the words of my 14-year-old son, it's a second full-time job, and it starts the moment patients wake up. From the toothpaste they use, to the sunscreen they wear, to the laundry detergent we clean our clothes with, to the lip balm I'm wearing when I kiss my son goodnight, everything is a risk.

And then there's the food. Meals, snacks at school, the baseball stadium, the movie theater. Patients must be knowledgeable about ingredients, how and where food is prepared and processed, how to communicate and educate others about their condition. The burden falls on families and caregivers to prepare safe food for holidays, school celebrations, birthday parties, field trips and travel. The thought and preparation is endless. Food allergies are always on our minds. Anything misread, any small misstep could potentially endanger a patient's life.
The solution we've been given to keep him safe is simple, but daunting, avoid. In order to do that effectively, each patient and their caregivers must understand the seriousness of food allergies and the risks of cross contamination. But we also need to be intimately familiar with labeling laws and loopholes, as well as manufacturing practices. That keeps my child relatively safe at home. But what about when he millions of other allergic children step outside and navigate in the real world?

Avoidance is challenging. It relies on the understanding of others, who are less experienced, for our safety and health. Avoidance is cumbersome. Labeling laws are incomplete, manufacturers aren't always forthcoming, and decision making, even at its best, is difficult. Avoidance accepts food allergies and all the associated worry, guilt and burden as a life sentence. And because we all make mistakes, it accepts reactions as inevitable.

From an early age, my son understood these risks. He has lived under the stress and reality that
the next meal could cost him his life. At age eight, my son educated his own grandparents on what it's like to live with food allergies. Grandpa he said, “I can't be careful 75 percent of the time. I need to be perfect 100 percent of the time.”

AR101 has the potential to change that. If only he could have undergone treatment to lessen that incredible emotional burden. AR101 has the potential to make childhood easier for food allergy families.

Food-allergic children and caregivers often struggle with anxiety, depression, and social isolation. Many children experience bullying at the hands of peers as well as adults. In desperation, families are sometimes driven to turn to unregulated alternative treatments that leave them vulnerable and at risk.

Allowing for well-studied, standardized accessible food allergy treatment outlines and established course of action for those looking for help. AR101 would be life changing for patients, offering much needed hope, relieving mental stress,
allowing room for inevitable error and damping accidental exposure and threat of severe reactions. It could specifically be transformative for patients in underserved communities where food allergy resources are often lacking. Where emergency room visits are more common, and where reliance on those outside the food allergy community is necessary.

I'd like to end by saying at the present time my own child is ineligible for this treatment. No matter what the outcome is today, he will continue to live under the specter of food allergies. But professionally, I must advocate for patients whose lives can be improved by AR101 and the possibility of leading a more normal life. With this treatment, it may be possible for food allergy families to thrive and not merely survive. Thank you.

DR. PAUL GREENBERGER: Thank you.

CAPT. SERINA HUNTER-THOMAS: Nina Nichols.

MS. NINA NICHOLS: Good afternoon. My name is Nina Nichols, I'm 17 years old and a senior in high school. Before I get into my story, I want to take the
time to thank, from the bottom of my heart, all of the
doctors who have worked tirelessly for decades to get
us to this point where this clinical trial is possible.

I'm here because I'm anaphylactic to peanuts.
I had my first anaphylactic reaction at the age of two.
I had to be rushed to the hospital, and it took two
epinephrine shots to control my reaction. Fifteen
years later, I'm currently enrolled in a clinical trial
at the National Children's Medical Center in Washington
DC for AR101.

The first day of the clinical trial, I had to
be treated with epinephrine after having an
anaphylactic reaction to one 100th of a peanut. Today,
two years later, I have a daily dose of 300 milligrams
of peanut powder every night. As you know, 300
milligrams is equivalent to one peanut. That may not
sound like a lot to a lot of you, but it has changed my
life.

I can now eat foods that have, “may contain
peanut” warning labels. I also know that I have more
protection from accidental ingestions. I of course
still carry my two epinephrine auto injectors everywhere I go. I still read all the ingredient labels and inquire about food at restaurants. I'm still very vigilant about what I eat. But I have so much more peace of mind.

Though the clinical trial has been difficult at times, I am so grateful for my desensitization to peanuts. Not only has AR101 allowed me to ingest peanut protein for the first time in my life, I've also gained so much knowledge of my own reactions, including that I can easily and confidently give myself epinephrine. This is so important to me now as I prepare to go off to college next year.

In closing, I feel very strongly that I, and all the kids just like me with life threatening allergies, deserve access to this treatment so we can live safer lives. Thank you so much for this opportunity.

DR. PAUL GREENBERGER: Thank you.

CAPT. SERINA HUNTER-THOMAS: Linda Herbert.
DR. LINDA HERBERT: Hi. Thank you so much for giving me the opportunity to speak with you all today. My name is Linda Herbert and I do not have any financial interests to disclose. I am a licensed psychologist and an assistant professor at Children's National in Washington DC; where six years ago I started a clinical program to help children and their parents who have food allergy. Specifically, because they were telling us that the emotional impact of food allergy was that great. I also am a researcher and have been doing grant-funded research on the impact of food allergy now for over a decade.

What I can tell you is that the research that I have done, and that my colleagues have done, indicates that the stress and anxiety as a result of food allergy is comparable to that of other chronic illnesses. And I've illustrated for you all some of the primary factors that factor into this.

We know that there's a mental load due to the time burden of allergen avoidance. And that every single day, families need to be prepared for
emergencies. Not only by carrying epinephrine auto
injectors, but also by knowing how and when to use
them.

The anxiety piece comes in with these other
things at the bottom. This unpredictability of
allergen exposure and the need to trust others every
day to keep your child safe. It is this
unpredictability and the need to trust others that can
sometimes result in increased anxiety and a general
feeling of helplessness, and a lack of control over
your own life.

As a result, many families do seek out mental
health assistance. And to give you both a local and a
national snapshot, I provided this data for you here.
At Children's National we see about 1500 food allergy
patients a year. Last year alone, the psychology team
embedded within our allergy division saw over 50
outpatients for therapy specifically because of anxiety
due to food allergy. The primary driver of this was
that unpredictability of daily allergen exposure.
If we look at this more nationally, I can tell you that I received dozens of phone calls a year from allergists asking me how they can help their patients and who they can send them to. They want to know if I can do telehealth with them. But I'm unable to because of license restrictions. We have such a great need in this area.

I've also conducted some research with FARE, looking at their patient registry. We have over 600 patients and caregivers who thus far have told us whether or not they've sought out mental health due to food allergy. What we find is that about one in five of them have told us, yes, at some point we have sought mental health services, specifically to deal with food allergy concerns.

So in therapy, we are ultimately trying to help families reach what we call balance integration. Vigilance is adaptive, of course, and you have to be prepared for allergic reactions. But at the same time we want families to engage in developmentally appropriate activities and be able to manage their
anxiety. However, right now, families don't really have a choice, they have to avoid. And as a result, they have this feeling of lack of control.

What I'm asking is that we are able to provide additional options for our families, so that we can empower them to make choices. To not feel so out of control when they go about their day to day lives. Ultimately, I want every family to be able to make a decision that is best for them on how they can achieve this balance of vigilance, and participation in all the fun things that life has to offer. Thank you.

DR. PAUL GREENBERGER: Thank you.

CAPT. SERINA HUNTER-THOMAS: Kenneth Mendez.

MR. KENNETH MENDEZ: Thank you. My name is Kenny Mendez. I'm the President/CEO of the Asthma and Allergy Foundation of America. We receive corporate support from Aimmune, but I'm here on my own. I'm also the father of two kids who have severe food allergies.

What I'd like to do with you is kind of show you the research that we've done out of our Kids with Food Allergies Division, that quantifies a lot of the
individual stories that you've seen here. We did a study this summer and we had 853 people in our children and families with food allergies, about what it's like to live with food allergies. And then about 674 respondents to a study that looked at willingness to treat.

So, the psychosocial impact you've heard about here today, but just think about the numbers behind it from our survey. Clearly the mental, social, emotional impact themes that you're hearing, and really the loss of normalcy, that really drives kind of day to day decision making and how you live. So here's some color behind that in terms of the specific questions we asked.

Here 56 percent skipped out of an important school function, 51 percent avoided airline travel, 94 percent avoid certain restaurants, 21 percent changed schools, and 84 percent changed family traditions. And you've heard that from many of the individuals around here as well.
Financial impact and financial burden is another issue for the community. Making sure that you go out and buy the appropriate foods if you need to; and those are usually more expensive. Having to make career decisions. Some parents have decided that they need to stay home in order to manage the child's food allergies. And then the time burden in terms of making sure your child is safe, by volunteering in school and hosting events where you know you can provide them a safe environment.

Here's a quick picture on financial impact. Here, 41 percent basically said they've made a career choice in terms of their child with food allergies. And then, of that 41 percent, 81 percent have basically said it has had a negative impact on their household.

In terms of the implications of this, you've heard it already today, but I just emphasize this. That FDA-approved immunotherapy offers a much-needed option and it's the only option out there other than an avoidance. So it really fulfills an unmet need. And
it will also address some of the psychosocial elements that we talked about earlier.

The therapies that are available now are off-label. They're not FDA approved, and you pay for them out of pocket. So really only those families with money, and who are willing to pay for it, can really access those. So an FDA-approved treatment will provide greater access.

In terms of willingness to treat. The 674 people that we surveyed said 72 percent were willing to treat, or very willing to treat their food allergies with some sort of solution. So again, it's very much top of mind for our community.

There's an appendix in here with other data. I won't run through that. But I would say from the safety side of things, clearly our community, that's one of the questions you need to answer today. In our community, as you can see, it’s very equipped for safety. We're carrying epinephrine, we recommend that, and it's very much part of our day to day lives in the community. Thank you.
DR. PAUL GREENBERGER: Thank you.

CAPT. SERINA HUNTER-THOMAS: Next is Sally and Charlie Porter. Four minutes each. Thanks.

MS. SALLY PORTER: Thank you for having us here today. I'm Sally Porter and we were brought here by the Aimmune study as part of the participants.

Our schools have emergency drills, earthquake, fire, shooter, tornado. We train and prepare for those disasters. Those words, train and prepare are so important for those drill, and for those of us with children with life threatening food allergies.

Our son, Charlie, was one when he had his first bite. It took less than a minute for his face, eyes and throat to swell. It felt like a lot longer for the ambulance to arrive. What we saw that day was terrifying. I'm so sorry. Wow. I practiced even.

A small bite of something that kids eat every day, that his brother eats all the time, that we eat. How could it be? How could something as stupid as a peanut butter and jelly put my baby's life in danger?

That day over 15 years ago was, and still is, seared in
our minds. We had trained ourselves; we had prepared
ourselves for the worst. We trained him and his
brother what to do when the inevitable happened. We
prepared ourselves, our families, our community.

When he was younger, it was easy to control
when and where he would go and who he was with, and
most importantly what he ate. Charlie has entered
middle school. We realized that the control that we
know -- and in high school it would be even less. He
would be making new friends and eat new foods.

Would he have his epinephrine? He knew he was
supposed to carry it all the time. But did he? Would
his friends think he was being dramatic if he needed
help? What if there was cross contamination? We
couldn't train and prepare when we couldn't control.

Teenage boys have the highest death rate
because they’re risk takers; it's what they do.
Whether it's riding a bike too fast or waterskiing at
night or doing flips into a pool. Those are teenage
risks. Eating a cookie or trying a new food should not
be a life-threatening risk.
When Aimmune Therapeutics peanut allergy study came out, we went with Charlie to learn more, and he was ready. We had spent so many years telling him that any peanut exposure would kill him, that he was scared to try it earlier. It was important that he knew he was now ready.

He had to prove he had an allergy. Do I push this? Here we go. He had to prove he had an allergy through skin blood and oral challenges. The first two were relatively easy. But the third one, eating it, was a little bit harder to train for. When you haven't eaten peanuts, the smell and the taste can be odd and hard to ignore.

We talked about what would happen, what we could do and what we would do when it did happen. Yes, he went into anaphylaxis. But this time, once again, it was something we couldn't really control or prepare. This time he had a delayed reaction by a few hours. It was hard for us to believe that once again, even though we had trained and prepared, we were hit out of left field by the unpredictable nature of food allergies.
The study itself went fine. He would put the powder in the pudding, and he would eat the pudding nightly. The smell was weird, the taste was too, but he pushed on. We figured out if he ate something with a strong taste after, the weird taste went away. There were a few upset stomachs and a few itchy throats, but nothing like anaphylaxis.

When he tested out, he ate the equivalent of 8 to 10 peanuts. It was amazing. I think he said that he had a scratchy throat, but that went away fast.

Since he has finished, our life has become less about the food allergy. We don't have to train everyone. We don't have to prepare for the worst. He's able to eat things that say, “may contain” or “made in the same facility,” which is huge.

Candy and foods he had never tried before we're suddenly there. He likes Chinese food. He likes M&Ms. He eats three honey-roasted peanuts a day to keep the levels in his body. That means he can have about on bite of a food with peanut in it, a cookie, a sandwich. Can I go on? Just a little bit more.
DR. PAUL GREENBERGER: You can go on.

MS. SALLY PORTER: Thank you. He knows what it tastes like and he doesn't like to eat it, so he doesn't continue. But that's all that happens.

We don't have to call 911 for this. Nothing happens to him, and he doesn't have to call 911. As his parents to know that if you make some mistake -- because he will, he's a teenage boy. But now the consequences of eating a food won't include death.

When he goes out with friends, he doesn't have to ask what's in the cake, where it's made, if the knife is clean before you use it, what kind of ice cream is it? Is there a warning label? All the prep questions that need to go into a party with non-allergic friends.

He's still carries epinephrine. I think it's because I'm a nag and it makes me feel better. I'm happy he can join in and seems to be able to be a teenager now, first and foremost, and not a food-allergic teenager. Thank you for your time.

DR. PAUL GREENBERGER: Thank you.
MR. CHARLIE PORTER: I am Charlie Porter and I was brought here by Aimmune.

I'm here to talk today about a clinical trial that I underwent. And to me this topic is so important that even as a junior in high school, the most intense year in almost any teenager's life, I am missing two full days of school. This may not sound like a lot, but it is. I'm also missing a robotics competition, that I could be helping my team at, to speak here.

I've grown up in a very generous life, loving parents, a good house, a good bed, good schooling, food on the table and everything else. Yet that food on the table wasn't just any food, it had to have no peanuts. Because at a young age I was diagnosed with severe allergy to peanuts.

This allergy has always felt more like a curse than anything. Because it’s impeded my life in a bunch of ways. Most of which when I was at parties. Most of the times I would have to bring myself some sort of treat, like Twinkies and stuff like that. Because most kids wouldn't think a big deal of this, but to me not
sitting with my friends and eating cake, it was crushing.

As a family, we were very cautious about the entire thing. Even if it just said, “may contain” or “made in the same facility,” we still just wouldn't eat it. Probably the most crushing of times was Halloween where most kids would have massive bags full of candy, and I would have to give up almost 50 percent of mine just because I couldn't eat it. The years were just painful.

But then I found out about this trial from my parents one night. We discussed all the factors, including the one thing my 14-year-old mind was focused on, money. I accepted and went through with the trial, knowing that I would have to go into anaphylactic shock. But I was prepared. The main thing that made me want to do the study wasn't actually the money, but it was the end result. The chance of not having an allergy anymore, that was something that I had longed for, for 14 years.
Before this trial, I was just the kid who had
to not eat with friends, not eat certain foods, sit out
of class parties and everything else like that. But
after the success of the trial, it turned me into a kid
who could just hang out with my friends without having
to worry about what I ate. Of course, I'm still a
picky eater after. This curse have in a way been
lifted.

One question that a lot of people ask is, is
the risk worth it? What's the risk of the trial
anyway? My answer to people thinking about this trial,
is just to look at the best and worst possible
scenarios of the outcome. And look at the chances of
every sort of outcome that could happen. And in the
end, if you're like me and definitely can't make
decisions easily, I just remember my friend telling me
to go and never stop, whenever I’m not able to make a
decision.

In the end, this is the best thing that has
happened in my life so far. And I really want everyone
to be able to experience what I call a scientific miracle. Thank you.

DR. PAUL GREENBERGER: Thank you. That concludes the presentations by those who have registered. And I do thank everyone for their important words and personal stories and viewpoints. That's all part of the deliberations and part of the meeting today.

We actually have a few minutes if there is a potential other speaker, from those of you interested, for about two minutes. You'd have to identify yourself and if you have any conflicts, but we do have time for anyone else.

Okay. So this concludes the open session of our meeting. We have a few minutes so I think we will just move forward. We'll take a 15-minute break until 2:40.

[BREAK]

FDA PRESENTATION
DR. PAUL GREENBERGER: It's time to move on, so I'll ask everybody to take a seat please.

The next presenter is Dr. Kathleen Hise from FDA. After that, we will have a discussion and a round table, and then voting.

DR. KATHLEEN HISE: Good afternoon. My name is Kathleen Hise. I'm an allergist and medical officer at the FDA in the Division of Vaccines and Related Product Applications. I'll present a summary of the efficacy and safety data submitted to the Palforzia BLA. I will go over the product background, overview of select clinical studies submitted to the BLA, efficacy with a focus on pediatric subjects 4 through 17 years of age, safety with a focus on pediatric subjects 4 through 17 years of age, and also focus on systemic allergic reactions, epinephrine use and eosinophilic esophagitis. I'll briefly go over adult data and give a summary.

In this section, I will briefly summarize the product background. Palforzia is sourced as dry peanut
allergen powder. It’s provided in HPMC capsules at 5
doses strengths (0.5, 1, 10, 20 and 100mg). It's also
provided in a sachet at 1 dosage strength at 300
milligrams.

The slide is a representation of how the
initial dose escalation, or IDE, and up-dosing
schedules were administered. During the IDE, subjects
were observed in clinic the entire day for the initial
dose escalation of five steps from 0.5 milligrams to 6
milligrams. If this dose was tolerated with no more
than mild symptoms, subjects returned the next day for
a single 3 milligram dose done under observation. If 3
milligrams was tolerated on the second day, subjects
would stay on this dose for two weeks and returned to
the clinic to be administered the next dose in the
schedule under observation.

This schedule continued as tolerated until
subjects reached a maintenance dose of 300 milligrams
taken daily for 24 weeks. Again, every new dose level
was administered under observation. The first dose of
the maintenance phase, 300 milligrams, was administered
under observation. And if tolerated, subjects would
take the daily dose at home.

The proposed indication. Palforzia is
indicated as a treatment to reduce the incidence and
severity of allergic reactions, including anaphylaxis
after accidental exposure to peanut in patients 4
through 17 years of age with the confirmed diagnosis of
peanut allergy. Palforzia is not intended for the
immediate relief of allergic symptoms. It is to be
used in conjunction with a peanut-avoidant diet.

In this section I will summarize the main
studies submitted to the BLA. Aimmune has already
presented the main studies. This slide and the
following slide just briefly summarizes these studies.
In this presentation I'm going to focus on ARC003 for
evaluation of efficacy.

ARC003 was a Phase 3, randomized, double-
blind, placebo-controlled study of efficacy and safety
in subjects 4 through 55 years of age. The primary
efficacy endpoint was restricted to evaluation in
subjects 4 through 17 years of age.
ARC007 is a short study focused on safety in the up-dosing period. Data from ARC007 will be summarized in the safety section of this presentation. Note that ARC007 did not include an entry oral food challenge to reflect the clinical population, as it is unlikely clinicians will perform oral food challenges to confirm peanut allergies in subjects electing to undergo oral immunotherapy. These are the uncontrolled, open label follow on studies for ARC003 and ARC007.

In this section, I will discuss efficacy with a focus on pediatric subjects 4 through 17 years of age. Again, ARC003 was a Phase 3, randomized, double-blind, placebo-controlled study with 555 subjects 4 to 55 years of age. The population evaluated to support the primary indication was 4 to 17 years of age, and this included 499 subjects.

A screening double-blind placebo-controlled oral food challenge, with up to 100 milligrams of peanut protein to confirm true peanut allergy, was done for entry criteria. Subjects were excluded who had a
a history of severe uncontrolled asthma, a history of eosinophilic esophagitis, severe or life-threatening anaphylaxis 60 days prior to screening. Safety was monitored through electronic diary cards, clinic visits and telephone follow ups.

In study ARC003, subjects began with screening tests including serum IgE to peanuts, skin prick testing to peanut and a baseline oral food challenge to determine eligibility. As reviewed at the beginning of this talk, subjects underwent an initial dose escalation up to 6 milligrams in clinic, then returned the next day for a dose of 3 milligrams under observation. If tolerated, subjects took that dose at home for the next two weeks, and then returned to clinic every two weeks for the next dose in the schedule, under observation, up to 300 milligrams. The maintenance dose of 300 milligrams daily was taken as tolerated for 24 weeks. At the end of this period, a double-blind, placebo-controlled oral food challenge was performed to determine efficacy.
I'd like to briefly go over the main points discussed at the APAC in 2016, and the decision to use an oral food challenge as an efficacy endpoint in ARC003. During the APAC, the committee discussed clinical endpoints for food allergies studies. These are the main takeaways from that discussion.

A field study evaluating reduction of the rate and/or severity of reactions to accidental food exposure would require large cohorts at long study durations to detect statistically significant differences. There's no substitute for an oral food challenge to determine treatment effectiveness.

Meaningful goals for the treatment of peanut allergy include diminishing the risk of life-threatening allergy with accidental exposure and increasing the dose of food ingested without a serious allergic reaction. This is why an oral food challenge was chosen as an efficacy endpoint in study ARC003.

The food challenges done in ARC003 were double blind and placebo controlled. This means the person receiving the challenge food, nor the staff judging
reactions to the challenge, were aware whether or not
the product was peanut protein or placebo. Each
challenge took place over one day, peanut protein one
day and placebo the next day.

Screening oral food challenge required that
subjects react to 100 milligrams or less of peanut
protein to be included in this study. The exit oral
food challenge began at 3 milligrams for most subjects,
except for those who reacted at 1 milligram to the
entry food challenge. Then those subjects began at 1
milligram. For the primary efficacy endpoint, subjects
had to tolerate a single dose of 600 milligrams of
peanut protein with no more than mild symptoms.

The primary efficacy endpoint for study ARC003
was the proportion of subjects 4 to 17 years of age who
tolerate at least 600 milligrams of peanut protein,
with no more than mild symptoms at the exit oral food
challenge. This is calculated as the treatment
difference in the response rate relative to placebo.
The pre-specified success criterion for efficacy was
demonstrated at the lower bound of the corresponding 95
percent confidence interval, was greater than 15 percent.

ARC003 had four key secondary endpoints. This includes 1) a proportion of subjects 4 to 17 years of age who tolerated a single highest dose of at least 300 milligrams of peanut protein with no more than mild symptoms at the exit oral food challenge. 2) the proportion of subjects 4 to 17 who tolerated a single highest dose of at least 1000 milligrams of peanut protein with no more than mild symptoms at the exit food challenge. 3) comparing the maximum severity of symptoms in subjects 4 to 17 years of age occurring at any challenge dose during the exit oral food challenge. And 4) the proportion of subjects 18 to 55 years of age who tolerated a single highest dose of at least 600 milligrams of peanut protein with no more than mild symptoms at the exit oral food challenge. These secondary endpoints were sequentially tested in order if the primary endpoint met its success criterion.

ARC003 subject demographics. Most subjects in ARC003 were male, white, not Hispanic or Latino, 4
through 11 years of age and resided in the United States. These demographics were balanced across treatment groups.

The majority of participants reported other atopic conditions such as food allergy other than peanut, allergic rhinitis, asthma and atopic dermatitis. These conditions were balanced across treatment groups.

This slide summarizes the discontinuation data from study ARC003. More subjects who received Palforzia discontinue the study compared to placebo. Most subjects cited adverse events or withdraw of consent as reasons for discontinuation.

Study ARC003 met the primary efficacy endpoint. As you can see, 67 percent of Palforzia-treated subjects ingested 600 milligrams of peanut protein with no more than mild symptoms, compared to 4 percent of placebo subjects.

Key secondary endpoint number 1 was met. And 76 percent of Palforzia recipients ingested 300
milligrams of Palforzija with no more than mild symptoms as compared to 8 percent of the placebo group.

Key secondary endpoint number 2 was met. And 50 percent of Palforzija recipients ingested 1000 milligrams of Palforzija with no more than mild symptoms, compared to 2 percent of the placebo group.

Key secondary endpoint number 3 was met. Overall, compared to placebo, recipients of Palforzija reported symptoms of less maximum severity during the exit oral food challenge. Of note, no fatalities occurred during any food challenge in the study.

Key secondary endpoint number 4 was not met. And 41 percent of adult Palforzija recipients ingested 600 milligrams of Palforzija with no more than mild symptoms, compared to 14 percent of the placebo group.

Next I will discuss pediatric safety. Most of the data I present will be from the controlled safety population. The BLA included data from uncontrolled studies in an integrated safety population. This data can be found in the briefing document in Section 5.
A controlled safety population included subjects 4 through 17 years of age who received Palforzia or placebo in the controlled studies ARC003 and ARC007. The integrated safety population consisted of any subject who received one dose of Palforzia. It included studies ARC003 and ARC007, as well as open-label extension studies ARC004 and ARC011.

Demographics and safety trends were similar in these extension studies.

In the safety summary I will discuss adverse events by dosing period, adverse events leading to discontinuation, serious adverse events, systemic allergic reactions, epinephrine use as a rescue medication and eosinophilic esophagitis.

This slide summarizes the short initial dose escalation periods done over two days. Most reactions were mild to moderate during the IDE. No SAEs were reported. More systemic allergic reactions occurred in Palforzia-treated subjects.

This slide summarizes the up-dosing period. Most reactions were mild to moderate. More Palforzia
recipients discontinued due to adverse events. A few SAEs occurred with more reports of SAEs in Palforzia recipients. Palforzia recipients reported more systemic allergic reactions and allergic reactions, as AEIs, compared to placebo recipients. Palforzia recipients reported fewer episodes of adverse events related to accidental food exposure compared to placebo.

This slide summarizes the maintenance period. Most reactions were mild to moderate. Fewer Palforzia recipients discontinued in the maintenance phase compared to up-dosing. No more discontinued, compared to placebo, due to adverse events. A few SAEs were reported. More Palforzia recipients had systemic allergic reactions compared to placebo. Palforzia recipients reported fewer episodes of adverse events related to accidental food exposure compared to placebo recipients.

The most common adverse events leading to discontinuation were GI disorders, including abdominal pain, vomiting, and nausea. These adverse events
occurred more frequently in Palforzia recipients compared to placebo. Fewer subjects discontinued during the maintenance phase, though more Palforzia recipients discontinued compared to placebo. Most of the GI tolerability issues had resolved during maintenance.

One death occurred in study ARC007. This occurred in the placebo group. It was a fatal craniocerebral injury related to a motor vehicle accident. This was unrelated to the study product.

Overall, serious adverse events were similar in proportion when comparing Palforzia recipients to placebo, 1.4 percent versus 1 percent. However, more Palforzia recipients reported SAEs related to the product compared to placebo.

This slide summarizes systemic allergic reactions during the initial dose escalation. All participants who reported a systemic reaction reported one systemic reaction each. All episodes were mild, there were no SAEs. Three subjects had systemic
During up-dosing, most participants who reported systemic reactions reported having only one systemic reaction. Most of these episodes were mild to moderate. There were two SAEs. Most reactions were triggered by the study product. While most systemic reactions occurred at home, reactions also occurred under observation at the study site.

During maintenance, most participants who reported having systemic allergic reactions reported only one systemic allergic reaction. Most episodes were mild to moderate. There was one SAE reported. Most reactions were due to the study product. Most reactions during maintenance occurred at home or a place other than the study site.

This slide includes data from open label follow on studies. The slide shows reports of systemic allergic reactions over time. As you can see after up-dosing, reports of systemic allergic reactions decrease over time in Palforzia recipients.
This slide displays epinephrine used as a rescue medication during the initial dose escalation. Please note that subjects could use epinephrine to treat any symptoms of an allergic reaction, not just systemic reactions. Because the purpose of epinephrine is to prevent an allergic reaction from progressing to a systemic reaction. All participants who reported use of epinephrine used one dose per episode in IDE. Most episodes were mild to moderate. All uses occurred at the study site.

During up-dosing, most participants who reported epinephrine use used one dose of epinephrine per episode. Most episodes were mild to moderate. Most doses were given at home or a location other than the study site; but about one third were given at the site, under observation, for up-dosing.

During maintenance, most participants who reported epinephrine use used one dose of epinephrine per episode. Most episodes are mild to moderate. Most epinephrine used occurred at home during the maintenance phase.
In terms of biopsy-confirmed eosinophilic esophagitis, 3 Palforzia recipients in the controlled safety population reported EoE. Of that, 2 improved, 1 the outcome is unknown. In the integrated safety population, 5 Palforzia recipients reported EoE. Of that, 1 resolved, 2 improve and 2 the outcome is unknown. Overall, in the entire clinical development program, 12 Palforzia recipients reported EoE. Of that, 6 cases resolved, 2 improved and 4 the outcome is unknown.

This slide briefly summarizes the adult safety data. And 55 adults participated in the study ARC003. About 52 percent of Palforzia recipients, versus 7 percent of placebo recipients, discontinued study ARC003. And more adult discontinued study ARC003 compared to pediatric subjects, 52 percent versus 21 percent. Adults reported similar rates and types of adverse reactions and systemic allergic reactions compared to the pediatric population. One adult developed EoE in study ARC004 during maintenance
dosing. This age group is not part of the requested indication.

In summary, study ARC003 met the prespecified efficacy success criterion for subjects 4 through 17 years of age. This was the proportion of subjects who tolerate at least 600 milligrams of peanut protein with no more than mild symptoms at the exit oral food challenge.

The prespecified success criterion was demonstrated at the lower bound of the corresponding 95 percent confidence interval, was greater than 15, which you can see it is. Study ARC003 also met its first three key secondary endpoints in hierarchical order for subjects 4 through 17 years of age. The fourth key secondary endpoint was not met for adults 18 through 55 years of age.

In terms of safety, Palforzia recipients compared to placebo, reported increased systemic allergic reactions, epinephrine use as a rescue medication, increased discontinuation due to adverse events and withdrawal of consent and increased reports
of eosinophilic esophagitis. The frequency of adverse events, discontinuations, systemic reactions in epinephrine use decreased during maintenance.

Due to these safety issues, the Agency has informed the sponsor that additional risk mitigation strategies are required for approval of this product.

To mitigate the risk of systemic allergic reactions, including anaphylaxis due to Palforzia, the Agency is requiring the following: Documentation that any patient prescribed Palforzia has a valid prescription for injectable epinephrine. Caregivers and patients must attest to carrying injectable epinephrine while on Palforzia. And the initial dose escalation and first dose of each up-dose level must be administered in a certified facility capable of treating systemic allergic reactions.

I'd like to thank you all for your attention.

This is the end of my presentation.

DR. PAUL GREENBERGER: Thank you. I would like to ask you if you could comment on the “not more than mild” reaction, what that means.
DR. KATHLEEN HISE: In terms of the efficacy endpoint?

DR. PAUL GREENBERGER: Yes.

DR. KATHLEEN HISE: So it's graded on no more than mild symptoms, which were graded using the CoFAR scale, grading for allergic reaction. So that would include transient or mild discomfort, no more than minimal medical intervention or therapy required.

DR. PAUL GREENBERGER: Have you seen data on how many patients on the exit challenge were asymptomatic?

DR. KATHLEEN HISE: Yes, I believe we -- let's see if I can go back. Here as part of key secondary endpoint number 3; these are symptoms at any challenge dose, but this is during the exit oral food challenge. When you look at the Column None, you can see 37 percent of Palforzia recipients reported no symptoms compared to about 2 percent of placebo.

DR. PAUL GREENBERGER: So about 2 out of 3 will have something manifested, and 1 of 3 will not.

DR. KATHLEEN HISE: Um hmm.
DR. PAUL GREENBERGER: Okay. Thank you. This is a time for questions for Dr. Hise. If people want to identify themselves? Dr. Brittain?

DR. ERICA BRITTAIN: Yeah, I have a follow up on this one and maybe you’ve said it. For the people who didn't have the exit food challenge, how are they being evaluated? It looks like the end is the full. Are they in there, or?

DR. KATHLEEN HISE: Off the top of my head I don't know exactly. We might direct that question towards the sponsor to see if they can give a statistical answer for that.

DR. STEPHEN DILLY: We can give a statistical answer. And I'd actually like to ask my statistician to do that, because it's a last observation carried forwards. Sorry.

DR. PAUL GREENBERGER: Please identify yourself.

MR. ALEX SMITH: Alex Smith, Aimmune Biostatistics. Yes. For this particular endpoint, we applied a last observation carried forward in the form...
of the maximum severity at the screening food
challenge; which would be the surrogate if they had
missed the exit food challenge.

DR. ERICA BRITTAIN: And just another
question. On slide 31 and 32 -- maybe we could look at
32. Yes. Maybe 32. This is 31. Yeah. Okay. So
we're seeing it looks like the last row with this
accidental food exposure.

DR. KATHLEEN HISE: Adverse events related to
accidental food exposure.

DR. ERICA BRITTAIN: Yeah. Am I wrong or are
these rates higher than what we saw in this sponsor’s
presentation? I guess the reason I'm asking about it
is this looks like a pretty good size number; that had
you been able to do an intent to treat analysis, you
probably could have gotten a pretty good sense of
perhaps the direct impact on allergen exposure.

DR. KATHLEEN HISE: The sponsor can correct
me. I believe what they showed was food exposures
related to peanuts specifically. So the numbers are
going to look a little different.
DR. ERICA BRITTAIN: Oh, is that the difference?

DR. KATHLEEN HISE: Um hmm.

DR. ERICA BRITTAIN: Okay, thank you.

DR. PAUL GREENBERGER: Dr. Hawkins.

DR. RANDY HAWKINS: On the eosinophilic esophagitis, why don’t we notice status of all those individuals?

DR. KATHLEEN HISE: My understanding is that the time of the safety data submission, there simply wasn’t a -- for instance, like a second EGD done. We just didn’t have the data submitted yet.

DR. STEPHEN DILLY: And the difference to what you saw in the sponsor presentation was we now have additional follow up; which was why we said now we have symptomatic resolution in all 12 and the follow up biopsies. So it was a matter of the time that Dr. Hise’s data was cut versus the one that we showed you.

DR. PAUL GREENBERGER: Dr. Marshall.

DR. GAILEN MARSHALL: Gailen Marshall, University of Mississippi. Again, Dr. Hise, I
apologize for you talking to my back here. I'm hoping
that you can give me a little bit of a vocabulary
lesson on these data that you present, from slide 32,
particularly, as it moves down to slide 33.

And these adverse events, are these single
symptoms or multiple symptoms, or both? What I mean by
that is that would an adverse event of a nasal
congestion, and an adverse event of an itchy skin, be
listed as two adverse events or one, if it was in the
same patient at the same time?

DR. KATHLEEN HISE: What you're saying is if
that would be separate events.

DR. GAILEN MARSHALL: So they would be listed
as separate events?

DR. KATHLEEN HISE: That's my understanding.

DR. GAILEN MARSHALL: So then these adverse
events are distinctly different then the systemic
allergic reaction that's listed further down the table?

DR. KATHLEEN HISE: So it can include systemic
allergic reactions.
DR. GAILEN MARSHALL: All right. So, whatever
that summary number is up there, minus the 27
anaphylactic systemic allergic reactions, the
implication is that those are single symptoms? Single
adverse events of a single system? I can't say that
right. Again, I'm raising the question, and it goes
back -- I keep pounding on this and I'm not going to
stop, until you stop me and then I will. I do not want
to go to jail.

Going back to the idea that, yes, nasal
congestion can be minor, itching could be minor. But
if they itch systemically and had nasal congestion at
the same time, at the minimum, you would agree that
it's a systemic allergic reaction. We can then parse
the argument, many of us in the room would say that's
an anaphylaxis and therefore it's a potentially life-
threatening reaction.

And it has to do with the issue of safety, and
it has to do with the labeling indications as to what
you're going to say and not going to say later on. And
I'm concerned that we're parsing it out, adverse events
as being minor if there is more than one. Just helped me with that.

DR. SOFIA CHAUDHRY: Sofia Chaudhry, FDA.

Perhaps I was not as clear as I intended to be in the morning. We acknowledge that there's differences in the way that anaphylaxis is defined. However, when we are viewing the safety data, from the agency's perspective, we are looking at the systemic allergic reactions. So patients who have more than one system involvement, so the data you're seeing here, we would label it accordingly. Although we are still working through the final labeling language if this gets approved.

DR. GAILEN MARSHALL: So the severity of these AEs in this table, for example, mild, moderate and severe, those are including the anaphylactic systemic allergic reaction, that 27 at the bottom is folded into those numbers somewhere?

DR. SOFIA CHAUDHRY: You’re talking about the mild, moderate for the total 8 adverse events?
DR. GAILEN MARSHALL: It says severe -- in the second line -- subject with one or more AEs. All the math doesn't add up is what I'm trying to say. And I'm trying to understand if that's because you have parsed out the systemic allergic reactions separate from single system symptoms. Say that fast three times.

DR. SOFIA CHAUDHRY: Yes. Yes. That is correct. My understanding of what you're saying, yes, that is correct. Yes.

DR. GAILEN MARSHALL: Okay. So then the idea -- again, the level of concern as a provider who's going to put a patient on this, is a whole lot different if what I'm commonly going to see in the up-dosing is somebody nose gets stopped up, or they're going to itch a little bit, or even they might feel a little bit of a difficulty in breathing -- single system -- as opposed to going to have all three of those all at once.

DR. SOFIA CHAUDHRY: Correct.

DR. GAILEN MARSHALL: Okay.

DR. SOFIA CHAUDHRY: Correct.
DR. PAUL GREENBERGER: Dr. Dykewicz.

DR. MARK DYKEWICZ: I may have missed this.

But my concern is, what do we have in terms of any longitudinal data about the patients who failed to be able to progress through the trial? That is, they had reactions along the way.

And you might say at first, Oh well, the party's over, they're out of this study, that's the end of it. But is it possible, for instance, that they have been increasingly sensitized and maybe at increased risk for future peanut exposure? Do we have any data about that?

DR. KATHLEEN HISE: I'm not aware that we have any data supporting that. And if the sponsor would like to answer, I don't have any data.

DR. STEPHEN DILLY: So we didn't directly measure that in those patients. But what we can look at is the behavior of patients after accidental exposures, and actually the one -- or even intentional exposures. And we did look at sensitivity at baseline
at either side of the food challenge. The way we do that is we look at the initial dose escalation day. So remember, we've taken a group of patients and we've exposed them to peanut protein until they've reacted in the baseline challenge. And then we look at how they do a few weeks later in the initial dose escalation. And actually, there is no evidence of a sensitizing effect there. And so, we don't have any a priori reason to do it. But what we do look at is patients who've had a severe reaction, like an anaphylactic shock, we just for safety didn't put into the study for 60 days. But there's no a priori reason to believe that we would sensitize patients.

DR. MARK DYKEWICZ: I mean, I understand that argument. But I guess the question does remain, in my own mind; since we know that for instance serum IgE levels come up initially with peanut, that you may be looking at a different population of patients in terms of the responsiveness to a desensitization effort. And they may be at increased risk for having more problems
with peanut inadvertent exposure going forward. That's my concern.

**DR. PAUL GREENBERGER:** I'm going to follow up on Dr. Marshall’s question. Just to clarify on slide 32. I have two scenarios. The first is that the subject got acute urticaria and it went away, and no treatment was given. Would that information appear on this slide?

**DR. KATHLEEN HISE:** Yes, as an adverse event, just simple acute urticaria.

**DR. PAUL GREENBERGER:** And would it appear under allergic reaction at the bottom?

**DR. KATHLEEN HISE:** Allergic reaction, yes.

**DR. PAUL GREENBERGER:** So it counts -- and then it would be what severity, mild?

**DR. KATHLEEN HISE:** Well I didn't have parsed out the allergic reactions as mild, moderate and severe here. But if you're looking at where it says severity of AEs, it would be under one of those.
DR. PAUL GREENBERGER: Okay. And then if it was acute urticaria plus abdominal pain, no treatments given, no epinephrine given, where does it go?

DR. KATHLEEN HISE: That would be a systemic reaction.

DR. PAUL GREENBERGER: So that would be one of the 27?

DR. KATHLEEN HISE: Mm hmm.

DR. PAUL GREENBERGER: And then it would appear somewhere under severity?

DR. KATHLEEN HISE: Not on this slide, but on a separate slide we have for systemic allergic reactions.

DR. PAUL GREENBERGER: Okay, thank you. Dr. Kelso.

DR. JOHN KELSO: It's been mentioned a couple of times, including in the presentation that we just had, that the incidence of need for epinephrine is less in the maintenance phase than in the up-dosing phase. Which is true, but I would point out that that's also true in placebo. So that, for example, in the up-
dosing phase there were 10.4 percent of subjects getting the active treatment who had at least one episode of epinephrine use versus 4.8 percent of placebo. And during the maintenance phase, although the numbers are less, 7.7 percent of subjects required epinephrine compared to 3.4 percent of placebo.

So it's less in the maintenance than it is in the up-dosing but you're still twice as likely to require epinephrine if you're getting the treatment. And then somewhere along the line we saw a slide that sort of extended that out even further into the future with smaller numbers. But we really don't have any data about that. I think the dataset that we have in front of us suggests that you're less likely to require epinephrine during maintenance than up-dosing, but still twice as likely to require it on treatment than on placebo.

**DR. KATHLEEN HISE:** Yes, I agree. That's an accurate summary.

**DR. PAUL GREENBERGER:** Dr. Finegold, you with us? You have some questions? Might you join in?
DR. IRA FINEGOLD: I am, but I don’t have a question.

DR. PAUL GREENBERGER: I'm taking the liberty to call on myself one more time. Sorry. That is on inclusion criteria under asthma. I would like to clarify. I see the word severe asthma and I saw uncontrolled, but this is a patient with severe controlled asthma. Or is this a thinking that they would be excluded from use of this product?

DR. KATHLEEN HISE: Yes, severe and/or uncontrolled.

DR. PAUL GREENBERGER: But what about severe and controlled?

DR. KATHLEEN HISE: Yes, they'll be excluded.

DR. PAUL GREENBERGER: Because I understand this could be a step for asthmatic, who might well have qualified otherwise, would be excluded if I understand what you're saying.

DR. KATHLEEN HISE: Um hmm.

DR. PAUL GREENBERGER: Okay. Dr. Apter.
DR. ANDREA APTER: Thank you. Do you have any information -- patients who have a history of severe allergic reactions to peanuts were excluded -- were screened out of the study. Do you have any information on those?

DR. KATHLEEN HISE: Only if they had a reaction within 60 days. So, there could be subjects who had a history of a very severe reaction. But as long as it wasn't within the 60 days of study screening or entering the study.

DR. ANDREA APTER: Can you describe some of those patients that were excluded?

DR. KATHLEEN HISE: I'm sorry, just to clarify. Would you like me to describe what kind of reactions they had?

DR. KATHLEEN HISE: Yes. Thank you.

DR. KATHLEEN HISE: Oh, I'm sorry. I don't know that off the top of my head.

DR. PAUL GREENBERGER: Does anybody else have information on that?
DR. STEPHEN DILLY: What we recorded was the incidence of -- the previous one was good, thanks -- the history of anaphylaxis, patients reporting it. And what you saw was 70 percent of patients included in the study reported having had a history of anaphylaxis, including some had hospitalizations. But it was really difficult to quantify the exact severity, because some of these were historic several years old.

And so all we’re saying is we have here that 70 percent of the patients in the study reported having had an anaphylactic episode in the past. And we specifically excluded anyone that has had a severe one, including anaphylactic shock or hospitalization in the two months before screening, so we never saw them.

DR. PAUL GREENBERGER: Okay. Dr. Brittain.

DR. ERICA BRITTAIN: So maybe you've shown this, and I don't remember. It would be interesting for me to see of the people who were completers on the active arm, during the maintenance phase, what percentage of the doses they had more than mild
reactions to. Do you have any data like that? Because I’m just not getting a sense of that.

DR. STEPHEN DILLY: The only way we can do that was you saw our exposure-adjusted rates of adverse events going down over time. You saw in the original core presentation, the common adverse events. The problem with a lot of these is it's sporadic.

DR. ERICA BRITTAIN: I mean, you did have the LT-16 that we looked at earlier.

DR. STEPHEN DILLY: I'm actually looking at that on my screen right now.

DR. ERICA BRITTAIN: This is not just dose related, right?

DR. STEPHEN DILLY: This is all adverse events.

DR. ERICA BRITTAIN: Right. So, it’s not just dose related?

DR. STEPHEN DILLY: What we do in an abundance of caution is we count everything in this, so it’s really hard to parse out in the food-allergic child, with multiple food allergies, what's likely to be
related to the dosage and what's not. What we have done is we've looked at the time of dosing and of these adverse events, more than 70 percent are happening within the two hours after the dosing. So it's pretty reasonable to assume the vast majority are -- in fact, here you go.

What we have here is peanut -- given a peanut preparation with generally recognized as safe ingredients, given to a peanut-allergic population. So almost by definition, it's going to be allergic reactions that are going to be driving this. And they're going to occur close to the time of dosing.

**DR. ERICA BRITTAIN:** I mean, just to answer my question, I think, we would go back to the LT-16. Just to get a sense of it. So again, during maintenance -- and these are the computers -- they're having like maybe a little bit more than one event per month.

**DR. STEPHEN DILLY:** That's right. So out there if you look at 11 events per patient per year. And that's not far off what we're seeing in the placebo group during the second half of the ARC003 trial. The
challenge we have on those out months and years is we
don't have a control group, so we have to compare it to
what we saw in the untreated group in the pivotal
trial. And it's not very different.

DR. PAUL GREENBERGER: Dr. Marshall.

DR. GAILEN MARSHALL: Dr. Dilly, if you would
indulge me for a moment. And thank you very much for
your -- all those exercises you do with your knees
help. You can get up and down out of that chair
easily.

You said 70 percent of the study population
had a history of anaphylaxis. Are you using the
definition from your study document that Aimmune and
the FDA came in agreement to? That would include
systemic reactions within the context of anaphylaxis,
because you parsed that out very carefully in that
definition.

So which is it? Is it systemic reaction 70
percent have? Or is it the anaphylaxis within that
group? And I, of course, by disclosure, think they're
all anaphylaxis. But arguing that there may be two
different groups.

DR. STEPHEN DILLY: I think we're actually in
violent agreement here. So we have to use the verbatim
term that the patient understands and can report. The
question was, have you had an anaphylactic reaction to
peanut? And the answer to that, in 72 percent of the
time, was Yes. Okay?

Then, here's the definition that we use, and
we're trying to serve two masters here. One of them is
we're trying to capture every single event that could
possibly be counted as an anaphylactic reaction. And
to do that, it's anything of any severity that happens
in two systems, exactly as you're saying.

And beyond that, when people see two remote
adverse events, they don't always put two and two
together, right. So we went through the entire MedDRA
database and we searched for any adverse events that
happened at the same time, in two systems, and made
sure they were captured as anaphylaxis or systemic
allergic reactions, right.
So we've got that number you see for our systemic allergic reactions, is the ones that reported as such and the ones we captured by searching for simultaneous adverse events in two systems. So we think we've got the whole iceberg.

**DR. GAILEN MARSHALL:** And I'm very comfortable with your presentation and those here about what you consider to be anaphylaxis and systemic allergic reaction as being synonyms. I'm a little bit less comfortable simply because in the document, that you provided for us -- the briefing document -- it parses the two terms out. And the concern is that -- and I'm reassured with what you've said. It is that the concern practically speaking for providers giving advice to patients, is that we're talking about the same thing, whether we call it a systemic allergic reaction or whether we call it anaphylaxis.

**DR. STEPHEN DILLY:** And the most important thing of all is that they are trained to intervene.

**DR. GAILEN MARSHALL:** Precisely. Thank you.

**DR. PAUL GREENBERGER:** Any other questions?
DR. IRA FINEGOLD: I have another question.

DR. PAUL GREENBERGER: Go ahead.

DR. IRA FINEGOLD: The question is, is it correct to assume that during the up-dosing, patients weren't taking antihistamines. But during the maintenance phase, were they allowed to take usual medicines?

DR. PAUL GREENBERGER: Dr. delay?

DR. STEPHEN DILLY: Yes. So the answer is they were not allowed to take prophylactic antihistamines before any of the doses at any stage in the trial. We just specifically emphasized that it happened during the initial dose escalation and during the up-dosing visits.

However, if they had a concomitant illness, then they were allowed to take antihistamines for that. But if they were presenting, for instance, an efficacy read out, the food challenge, then the antihistamines were withheld for at least four half-lives before they were exposed.
We tried to remove any confounder there. But we did have to allow for the practicalities so that they could manage their other concomitant illnesses.

**DR. IRA FINEGOLD:** Under the same idea, where any of them on SCIT or SLIT throughout?

**DR. STEPHEN DILLY:** No. They were not allowed to be undergoing two sets of desensitization at the same time.

**DR. PAUL GREENBERGER:** Dr. Finegold, anymore?

**DR. IRA FINEGOLD:** No.

**DR. PAUL GREENBERGER:** Okay. Thank you. What I would like to do is go around the table for people to make comments, sort of final comments, individually, regarding information they might request or like additional information from the company or the agency. And I'd like to start with Dr. Nolte.

**DR. HENDRIK NOLTE:** I don't have any questions, or comments.

**DR. PAUL GREENBERGER:** Okay, thank you. Dr. Hawkins.
DR. RANDY HAWKINS:  No, I'm satisfied. Thank you.

DR. PAUL GREENBERGER:  Dr. Maleki?

DR. SOHEILA MALEKI:  Yes. Soheila Maleki with USDA? I just have a comment, really, which is, I think, the reason I'm probably here. I've been in this field of allergy in a unique position to interact with the allergy community all the way -- as I was mentioning, from the peanut farmers to the Grocery Manufacturers, to the food industry, to the clinicians and pharmaceutical industry. This has been something that's been a long time in the works. And has either support of developing something for the food allergy.

I've heard a lot of the consumer advocates today and previously that have spoken out as well. And I just want to say that this product seems to -- it's not perfect and it's not necessarily for everybody. But it's something that -- seeing some of the safety and efficacy data, it's something that I would look into perhaps considering for this.
DR. PAUL GREENBERGER: Could you inform us whether there's longitudinal data on the character of peanuts and peanut proteins being different over a period of years?

DR. SOHEILA MALEKI: Over years, perhaps, they're very stable for a very long time, the product itself.

DR. PAUL GREENBERGER: Peanuts themselves as opposed to a product?

DR. SOHEILA MALEKI: The peanuts themselves -- again, and it depends on how you store them. And how they're treated from the time they come out of the ground, to the storage and so forth. So again, they have a pretty long shelf life, as you know, in a lot of products like peanut butter and so forth that are around. So it's actually a good model system for some of these studies because of the stability of allergen.

DR. PAUL GREENBERGER: I think I didn't quite make it clear enough. That if I were to study peanuts from 10 years ago, and compare them to peanuts now, are
there major differences that you're aware of? Because I think you have expertise in that.

DR. SOHEILA MALEKI: Yeah, actually, I would say no. Because there's been years and years of peanuts collected from all over the world. And there are some differences. But mostly the cultivated peanuts in what are eaten today is probably the same proteins, the same products -- the same peanuts that were available maybe years ago.

And the cultivated peanut has different parental types. And without going into the genetics of it, the ones that are cultivated and edible and consumed by consumers all over the world are pretty much the same and have not really changed.

DR. PAUL GREENBERGER: Okay, thank you. Dr. Marshall.

DR. GAILEN MARSHALL: I would just like to support the idea for the FDA as you move forward with this and your decision, two particular things. Number one is be very thoughtful about how you define this certified facility.
The problem with that comment for me, is that it sounds like a commercial comment. Because the people that are most well trained for this are allergist immunologists who've dealt with this for two years at least, and then their career afterwards. Or emergency medicine physicians who see people come in, in an acute need. I don't think anyone in this room is naive to suggest those are the only people that are going to be engaged in this. But by providing clear guidance, I think that can help a lot in terms of the safety and the use of this.

We've heard enough desperation in the voices of some of the commenters today, that if they found in a community there was someone who might not be particularly well trained, but made it available, versus somebody else who was better trained and chose not to make it available, they'd go for the first option. And I think that we need to take leadership in providing the help and support that's necessary.

And the second is that we would come to a better understanding -- I'm sorry, a better agreement
about the verbiage of anaphylaxis versus systemic allergic reaction. The sponsor clearly has stated, repeatedly, that they're fine with that being a synonym. And I think the burden should fall upon those of you making these decisions to decide why you would want to parse it and not leave it as a synonym. That is clearly a conservative approach. There's no argument about that.

But it's pretty hard to go down to ask somebody to treat their runny nose or their stopped-up nose with epinephrine. One of the things that hasn't been mentioned much around here is that as they up-dose and they have to use epinephrine repeatedly, they have to go back to the pharmacy and fill those things. And those are expensive. And that's an added expense to this. And in order to do that, you want them to believe that they have a good reason to do so.

And I think few people would think of anaphylaxis as a benign condition. I'm less certain about the term systemic allergic reaction.

**DR. PAUL GREENBERGER:** Dr. Kelso?
DR. JOHN KELSO: I have two comments. The first is that I also want to thank the members, patients and patient advocates who spoke. And to acknowledge that the problem is real and the need for a solution is real. But I don't believe that this is the solution. A good portion of what we heard from patients, I think, could be addressed with education rather than oral immunotherapy.

For example, the overwhelming majority of products that contain provisional allergy labeling do not contain allergen. And those that do, do not contain enough allergen to cause a reaction. And we have umpteen studies to demonstrate that.

Anaphylaxis requires ingestion. So, for the overwhelming majority of patients with peanut allergy, sitting next to another child eating a peanut butter and jelly sandwich or getting some on the skin will not cause a serious reaction. And for the overwhelming majority of patients, I think that a key part of our job, as allergist, is to educate patients on being appropriately concerned about their condition; but not
to have a misunderstanding of the risks of those other exposures such as contaminated products and physical contact. Which we can do with education, which we can back up with data.

If necessary, we can open a jar of peanut butter in front of the patient. If necessary, we can put some peanut butter on their arm. But a lot of the benefit that was described as being received from this therapy, I think can be achieved with education.

My second comment -- and I want to preface this with I'm a pediatrician, I'm an allergist. I have been practicing full time allergy for almost 30 years. I also want what's best for my patients.

But I think that -- as you've heard me say now a couple of times, I don't think this is the answer. And just to reiterate that I am not alone in that conclusion. From one of the papers that was cited earlier, I think this is accurately summarized by saying that current peanut oral immunotherapy regimens can achieve the immunologic goal of desensitization. But that this outcome does not translate into achieving
the clinical and patient-desired aim of less allergic
reactions and anaphylaxis. Instead the opposite
outcome occurs with more allergic and adverse reactions
with oral immunotherapy, compared with avoidance.

I am sympathetic to the concern and the
problem. I also want my patients to have a lower risk
of having reactions. But I think from the data that we
have had presented to us, that neither the safety nor
the efficacy have been demonstrated.

DR. PAUL GREENBERGER: Thank you. I thank
everyone for their involvement, especially on the
committee and the sponsor and the agency and all the
public. And I have no further comments.

DR. SOHEILA MALEKI: You’re going to do that
other side of the table, Paul?

DR. PAUL GREENBERGER: I'm going around the
room. I personally have asked -- for now I have no
further comments. Dr. Apter’s going next. And then
after Dr. Dykewicz, Dr. Gruber’s going to address us.

DR. ANDREA APTER: Yes, I have a number of
concerns that I share with the previous speakers. I do
share the concern of the definitions of systemic
reaction and how they can be very confusing and make
the analysis difficult.

I share Dr. Kelso’s concerned, too, that what
we're seeing in these trials are increased allergic
reactions to be given increased peanut. And we don't
necessarily know -- we wish, but we don't know that
this translates further into less allergic reactions
down the road.

I'm also concerned that we need to know more
about -- if we were to persist in this, we need to know
more about diverse populations as Dr. Hawkins noted.
There were very few African Americans, for example,
that were studied. And there may not be a difference,
but there may be, and that should be done. There may
be other characteristics of populations that aren't
studied in these events. We also need to know more
about how adverse events that occur are influenced by
age as the patients get older.

And I'm also concerned -- I agree with the
safety elements that you put in. But I also know that
my patients don't necessarily carry epinephrine with them, even though we mandate it. And that may be a problem, too, in a potentially dangerous intervention.

DR. ERICA BRITTAIN: I have a question. Are these our ultimate comments? Or are we going to also comment at the time of voting? I'm just used to the other way.

DR. PAUL GREENBERGER: Captain Hunter-Thomas can address this.

DR. SOHEILA MALEKI: Yeah. Are we in a discussion phase or are we in an ultimate --

CAPT. SERINA HUNTER-THOMAS: We're currently in the committee deliberation phase. And then if there's additional comments that anyone needs to make, please make it. Now is the time to do so. Is that right --

DR. ERICA BRITTAIN: I guess I'm asking -- I'm used to the advisory committees where whenever we vote we give our comments. It's not like that?

CAPT. SERINA HUNTER-THOMAS: Dr. Gruber?
DR. MARION GRUBER: Dr. Greenberg, I think we can invite some additional discussions when people have. And usually, you know, what we do is when people vote on the questions -- when the committee votes on the question -- then usually we ask for comment and perspective on why they voted the way they have voted.

But I think we probably have some more time this afternoon. So, I think if there are other perspectives here that the committee would like to express your opinions, then I think we should really take advantage of that because this is a very complicated complex discussion.

DR. PAUL GREENBERGER: Can I asked. How do we vote? The votes will be shown. And we go around the table and explain the vote, justify the vote?

DR. MARION GRUBER: Yeah, I think that's what we usually do. Serina, is that okay?

CAPT. SERINA HUNTER-THOMAS: That's fine.

DR. ERICA BRITTAIN: Okay. So knowing that I will ultimately have more to say. I mean, this is just sort of a side issue, but I just had a comment for the
FDA. And I guess you probably have heard me say it. But it would have been nice if -- at least maybe for future studies -- that patients who are discontinued are followed for everything. I know, you can't do the oral food challenge for them at the end, but normally we want to follow everybody as much as we can.

And for example, I think it's disappointing that we don't have the accidental exposure data on those patients. Then we could have had an intent to treat. Perhaps the event rates are way too low to be informative, but I think I think it would have been helpful. And I suggest that you consider doing that in future studies.

I think, you know, obviously, the treatment effective for the primary endpoint was a fantastic result. The scary part here is that the indication isn't exactly matching what the primary endpoint is. So you know, that's, again, why I'm interested in the accidental exposure data. Because that really does match it to the extent that it does exist.
I guess the other thing I am wondering about is this is a lifetime treatment. And we don’t have a lot of long-term data. And I guess that’s a little bit troubling that we don't know long term. There’s a number of leaps of faith that we're making here.

**DR. PAUL GREENBERGER:** You don't have long term follow up of treated patients. Is that what you're saying?

**DR. ERICA BRITTA:** Yeah. You know, I mean, there's some. There's some data past that first year. But, you know, we're talking about potentially a lifetime treatment. I mean, I'm not that concerned. I mean, I'm basically feeling pretty good about things. But that is one issue that does give me pause.

**DR. PAUL GREENBERGER:** But there are continuing studies. I don't think the data is locked on your studies yet. But you showed us that the studies are ongoing. Dr. Maleki?

**DR. SOHEILA MALEKI:** Just one comment. For what you were saying that it is probably a lifetime treatment. Again, there's no long-term studies to look
at that. For me, hearing the patients say, and also
knowing from experience of being in the field, that
they don't have to necessarily take the actual product
or the drug. They can go to an actual food. So they
eat peanut butter, or they eat peanut M&Ms, or
something they like better. So it becomes part of
their diet is one way to think about that, too.

**DR. PAUL GREENBERGER:** Does anyone from the
company want to comment on that? Were the subjects
introducing peanut butter back into their diet, so to
speak?

**DR. STEPHEN DILLY:** What we know is at the
moment with oral immunotherapy, continued exposure to
the allergen is necessary to maintain desensitization.
During the early phase, while patients are still having
adverse events associated with dosing, it's really
important to be accurate with dosing.

Now, over a period of years, many patients
achieve a level of desensitization whereby that
accuracy may be less important. And what we are
actively studying right now is in the out years,
whether you can actually reduce the dose frequency.

Whether you can go to every other day or whatever. But
those data are preliminary, and those studies are not complete.

What we have done, and we've already published, is we've looked out beyond the 12-month period to show that desensitization is maintained to 18 months and beyond. We continue to follow our sentinel cohort. And we are very serious about managing that long-term observational studies and looking for what happens when this is introduced, in terms of signal acquisition.

And there are two things we're worried about. The systemic allergic reactions however you define them. We need to know that we're not increasing those. And we also need to look out for eosinophilic esophagitis. And the beautiful thing about that is, those are low frequencies signals that to really characterize you need lots and lots of patients.

And so this is all about pharmacovigilance in the context of a robust, implemented risk management
plan. And that's what we're here to do. Because oral immunotherapy is already a reality. And what we're trying to do, is we're trying to bring it under control, under regulation, so we actually get those data. Because if we don't, then it will continue to be small studies, randomly conducted with cohorts of patients that are too small to tell anything. So, that's what we're trying to achieve.

**DR. PAUL GREENBERGER:** Dr. Brittain and Dr. Dykewicz.

**DR. ERICA BRITTAIN:** So just a little follow up on that. It sounds like, potentially, you have the opportunity to do some randomize studies within your -- like, you know, of the people who get to two years out, you could potentially randomize them to get -- you know, every other day versus one day. Is that a possibility?

**DR. STEPHEN DILLY:** If you would indulge me. Could I show the schematic for study 004 please? So we're going to have to switch slides.
This is a study that is already ongoing. And in fact, many of the cohorts are nearing completion. The reason we did this study was actually to answer the question, what happens in the out months if people start missing doses? It was called a Dose-forgiveness Study. Whereby we could look at if they weren't quite as diligent and they missed doses.

And this is on the paradigm that once you've achieved the sensitization, the time course of it fading is actually relatively slow. And it's about regular exposure to the allergen. And so we have cohorts in here, including with complementary food challenges. And the preliminary read on it is that every other day seems to be reasonably well tolerated. Early evidence is that desensitization is maintained. But only in patients that have already been through 18 months of daily therapy before they did that.

Now, these are open-label data. They're small numbers, they're preliminary. What they're telling us is that it's an experiment certainly worth doing down the line. Because we have this great question. Which
is, so you've got these people on immunotherapy, they've been through that work to get to desensitization, now what?

And we do have the tools to follow them. We can look at their peanut specific IgE. We show it goes up and comes down to baseline. As you follow it further, it continues to go down. The same thing. Their IgG4 goes up and stays up. Their TH2 cells change over time. We have their skin prick test. We can look for quiescence. So, in some cases, long enough, it may well be appropriate to back off dosing in patients. But that's really the field for future study.

DR. ERICA BRITTAIEN: Are those groups randomized, or how do people get in those cohorts?

DR. STEPHEN DILLY: So the first cohort was sequential because we wanted to acquire at least 100 patients that kept going on their daily dosing to see what happened with them. And then the Cohort 3 is randomized. Okay? So Cohort 2 was programmatic. That was a safety test to say no signals came out of that,
and then Cohort 3 was randomized. So we're acquiring those data.

**DR. MARK DYKEWICZ**: I wanted to review the data that was presented about, shall we say, cofactors that were associated with increased risk for systemic reactions when patients were, for instance, already on their maintenance dose. I believe it might have been Slide AN-20 by the sponsor. And it was looking at things -- for instance, if there was increased asthma, fever, illness.

**DR. STEPHEN DILLY**: Hold on.

**DR. MARK DYKEWICZ**: Yes. That's the one. And what I'm thinking ahead. Is should the product be approved in some way communicating to the patients, perhaps with some card that would be co-dispensed with either the up-dosing photo card or the daily maintenance sachets. That it would almost be a little checklist that the patient should go through and say, you know, not only don't exercise within two hours but, you know, if you're having an intercurrent illness -- I don't know how we define that, fever or whatever. We
put down some of the ones that are evidence based here that are associated with an increased risk for systemic reactions. And in an effort to try to more safely administer the product, give that type of guidance to the patient.

It also dovetails with some of the comments that I heard during the public comments session, which I think was very helpful and informative. But what struck me with some of the comments was the idea that people didn't have to worry anymore about accidental ingestion. And I think it has to be absolutely emphasized that avoidance really must be advised along with the use of the immunotherapy.

And because of these sorts of scenarios, where you could have somebody who's doing fine for the most part, and maybe they do have an illness and then they get zapped with either, if you will, natural ingestion or the sachet dispensing. People have to be aware that there still is the potential for a reaction down the road.
DR. STEPHEN DILLY: We are completely in agreement with you. And again, that's the reason why the product should only be presented to the patient coupled with a label, with training, with patient information. And that's got to be consistent.

Because at the moment, you know, it's up to the doctor that's doing their own immunotherapy to come up with what they're going to brief on. And here's some of the draft dosing instructions that we've got. But things like avoiding hot showers and baths.

Now, there's also art in this in what is exercise. You know, one of the patients that we went into in great detail said, "I didn't exercise before I had a systemic allergic reaction." Well, what she'd been doing was stacking shelves in a hot supermarket. Right? And that's exercise. And so we've got to train people into thinking about stuff like that.

Also, you know, the hot shower, all that. And what to do if they have got a scratchy throat or they're coming down with a cold. And so that's part of the patient education that we're going to do, the
labeling the training. And this is what it's all about, making sure it's done as safely as we possibly can.

DR. MARK DYKEWICZ: Thank you.

DR. PAUL GREENBERGER: Dr. Gruber.

DR. MARION GRUBER: Again, I would really like to thank the committee for the many comments, questions and opinions and perspectives expressed. But I think at this point if there are no additional comments, I think we should really put up the questions and move to the vote.

DR. PAUL GREENBERGER: As I said, after the vote, yes or no, with your device, and then we will go around the table and justify the vote one way or the other. And see if other information is needed that hasn't been expressed so far. And then we’ll do the second question. Right. So do you want to read the first?

DR. MARION GRUBER: The question one. Are the available efficacy data adequate to support the use of Palforzia as a treatment to reduce the incidence and
severity of allergic reactions, including anaphylaxis after accidental exposure to peanut in patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy? Please vote yes or no.

CAPT. SERINA HUNTER-THOMAS: And before they vote, yeah. Thanks, Jim. Okay, that fob, you're not going to use the buttons on the mic. You're going to use that. I guess that's clear. Okay. Jim, is it okay for them to press the buttons now? Okay. So go ahead and submit your vote for question one. And I submitted Dr. Finegold’s vote.

Okay, so I'm just going to read out everyone's response for the record. It was a total of nine eligible to vote. So starting with Dr. Apter, she voted no. Dr. Brittain, yes. Dr. Marshall, yes. Dr. Finegold, yes. Dr. Kelso, no. Dr. Dykewicz, yes. Dr. Greenberger, yes. Dr. Hawkins, yes. And Dr. Maleki, yes. So that's a total of seven yes votes, two no votes and zero abstain for question number one.

And I guess we could go around the table for everyone to discuss.
DR. PAUL GREENBERGER: I think we’ll start with Dr. Finegold, please.

DR. IRA FINEGOLD: Well, I voted yes because I thought the data was quite clear. And I would actually compliment the sponsor on the extent and caliber of the studies. While I have the microphone, I did want to ask about the next question. Before we vote on it, would I have an opportunity to ask them questions?

DR. PAUL GREENBERGER: You will? Okay, thank you. I’m going to start with Dr. Dykewicz and work around this way, please.

DR. MARK DYKEWICZ: I do think that -- first off to be cognizant that I and several other members of the panel, in 2016, were on the APAC panel that defined the endpoint as being a successful reduction in reactions with controlled food challenge. And I think that the evidence does demonstrate benefit at that endpoint.

As we discussed back in 2016, and have discussed today, this does not directly mean that we have any evidence yet that with accidental exposure to
peanut, that it's going to, in a large number of
patients, reduce the risk for reactions. We hope so.
And that's why the endpoint was chosen that was chosen.
But there is still some need, I think, for further
follow up longitudinal studies to assess that.

**DR. PAUL GREENBERGER:** Okay. Thank you. Dr.
Brittain.

**DR. ERICA BRITTA**

DR. ERICA BRITTA: I voted yes. Obviously,
the pre-specified endpoint was an extremely strong
result. I guess, as we’ve discussed already, we have
to do a leap of faith to believe that then means that
the accidental exposure will be lessened. It seems
like a pretty reasonable leap of faith, but it is one.
To whatever extent they can follow -- the
observational data will be helpful in that regard,
although it's still not the same as doing the
impossible study; which I understand you can't do,
really having that accidental exposure be the endpoint.

And again I reiterate that in future studies,
I think there should be an attempt to get accidental
exposure data from everybody randomized.
DR. PAUL GREENBERGER: Dr. Apter.

DR. ANDREA APTER: I think this is an important effort and I certainly understand patients fear of accidental ingestion, and of their parents and caregivers likewise having that fear. I think that the way the design of the study makes it -- because the endpoints are ingestion, we don't know enough about whether accidental ingestion will diminish or not.

And I do think it will be important to go forward with looking at some of the other details that still need to be ascertained about, age and diversity and other elements as you go forward.

DR. PAUL GREENBERGER: Thank you. This is Paul Greenberger. I voted yes. And I’m also reading into the question passing double-blind exit challenge and accidental exposure. This is desensitization. But there was over 60 percent of the actively treated participants passed the exit challenge compared to a very, very small number relatively on placebo. So I voted yes.
DR. JOHN KELSO: John Kelso, I voted no. The question asks about reducing reactions to accidental exposures. And as several others have said, that was not directly assessed and would be very difficult to directly assess.

And so, I understand the rationale of substituting the surrogate of passing the food challenge. But I think that because the treatment itself represents a challenge every time a dose is given, and the end result being that patients who are on the treatment are twice as likely to have a reaction requiring epinephrine, that effectiveness of the treatment has, in fact, not been demonstrated.

It may be demonstrated on the day that that particular oral food challenges done. But over a longer period of time when the patients are having a challenge every day, in the form of a dose of medication, that actually increases rather than decreases their likelihood of a reaction.

DR. GAILEN MARSHALL: Gailen Marshall. I voted yes, actually using the same logic with a different conclusion. And that is that we approve surrogate markers for indications all the time that don't directly affect patient care. But we extrapolate from that to affect the patient care.

I like the idea -- I mean, I really appreciate the idea of getting a therapy from a pharmaceutical company as opposed to the grocery store and all the other nice arguments that have been leveled. But in the final analysis, I think, what we've demonstrated with a well-defined in part surrogate marker that was reviewed and agreed upon in previous iterations. This product and the studies that are represented by this product has met that standard and deserves a chance to be seen in the marketplace and see where it floats.

I would assume, and that certainly hope, that the FDA won't just stamp this and say fine, very, very good, enjoy yourself and good luck. That it will be monitoring to see if this translates over a period of
time. Again, as has been done in the past with many new therapies. That was my rationale.

DR. PAUL GREENBERGER: Thank you. Dr. Maleki.

DR. SOHEILA MALEKI: Again, stating that just being immersed in this field for so long and seeing the beginnings of why this started in the first place. And that was based on small immunotherapy treatments that allowed, I guess, as a gung-ho allergist to go out there and start trying to do oral immunotherapy without any kind of control dosage or measurement.

And this whole company, I think, came about because the consumer advocates -- and again, this goes all the way to -- it started with the consumers, but also from my unique experience from the peanut farmers, to the food industry that have to label their food. And the absence of knowing a threshold dose and all those complications, to restaurants, food preparing people and so forth. Food allergy in general affects a much larger population then you would actually have for most other diseases. And so it affects, cross-
sectionally, a lot of the population from what you wouldn't think of.

So when they started giving these doses without controlled measurements, that's when it would be dangerous. And that's what the community came together and said. We need to have some kind of controlled dosage to not let this get out of control and really cause a danger to the community.

If you think of it in the context of that history, of how this came about from the community, all of us all coming together, then it changes the perspective of where we are right now. And that's why I said yes. Also, the efficacy of the data. Again, it was a very impressive results.

DR. PAUL GREENBERGER: Thank you. Dr. Hawkins.

DR. RANDY HAWKINS: Thank you. So I think the data supported my answer for yes. I do want more diversity in the studies of this nature. And this one, specifically more Hispanics, particularly in Southern California, African Americans and Asians.
I was a little concerned about -- and this was not about all consumers. I hope there will not be cavalier approach to a consumption of peanut products just because something like this is available.

I'm pleased that they’re going to be looking at the eosinophilic esophagitis in ongoing studies. I think the labeling is going to be really, really important. I think everybody realizes that. And I think it’s going to be really, really important to educate the prescribers. And hopefully, early on the prescriber will have an opportunity to give feedback to the FDA so that we can understand better what the limitations of this product should be.

**DR. PAUL GREENBERGER:** Okay, thank you. And we'll go to Dr. Gruber with question number 2. And then Dr. Feingold, we're going to come to you.

**DR. IRA FINEGOLD:** Okay.

**DR. MARION GRUBER:** Dr. Greenberger, with your permission and in light of the comments and some of the concerns expressed by the committee, and in light of the fact that we frame our question regarding the
safety data on the background that we will require a
Risk Evaluation and Mitigation Strategy, I would want
to take a couple of minutes to really explain what a
REMS, or a Risk Evaluation and Mitigation Strategy is.
And why it's different from a usual pharmacovigilance
or risk management plan. I think that maybe it will
help for the committee to understand why we ask the
safety question in the context thereof. Yeah? Thank
you so much.

As we've discussed this morning, or as was
mentioned, the usual and typical method for
communicating safety information about a drug product,
we use the professional labeling or the prescribing
information. However, if the Agency does not deem that
sufficient to clearly communicate the risks and
benefits of the drug, then we can require a drug
manufacturer to use what we refer to as a Risk
Evaluation and Mitigation Strategy, or REMS. And that
is in addition to, but beyond the professional labeling
to ensure that the benefits of the drug outweigh the
risks. And in this case, of course, we have identified a safety signal.

Now FDA has the authority, then, to impose a REMS program as a condition of approval. That is, if the Agency requires for a REMS to be put in place, then the drug would not be approved, or could not be approved, without such REMS. So in considering whether a REMS is warranted, the Agency considers a couple of factors:

Such as, what is the seriousness of any known or potential adverse event that may be related to the drug? What is the expected benefit of the drug with respect to the disease or condition? And what is the seriousness of the disease or condition that is to be treated with the drug?

And there are a couple of other considerations, but I don't really want to take too much time here.

But then, importantly, so if FDA determines that a REMS program is necessary to mitigate the risks of the use of the drug, the sponsor then must, and is
required to, develop a proposed REMS program. And FDA, then, reviews and approves this REMS program. And this is what we referred to this morning when we said we have initiated discussions; and this is a work in progress.

Each REMS program is very unique because it is intended to address specific safety measures that are tailored to the safety risks that are associated with the drug. And there is a series of specific elements that can be in a REMS program, such as a medication guide or patient package insert, a communication plan and elements to assure safe use.

And the questions to the committee here -- if we want to look at the slide for a minute. We list and we thought that three elements to assure safe use of Palforzia are important. And that is the documentation that any patient prescribed Palforzia has a valid prescription for injectable epinephrine. That caregivers and patients must attest to carrying injectable epinephrine while on Palforzia. And that the initial dose escalation, and the first dose of each
up-dosing level, must be administered in a certified facility capable of treating systemic allergic reactions. Again, we are in the process of discussing this REMS program with the company.

What I also wanted to mention -- and perhaps that goes in regard to a comment that was made by Dr. Marshall. There is also an implementation plan. So the company is required to take reasonable steps to monitor and to evaluate the execution of the REMS by health care providers, by pharmacists and others in the health care system who are responsible.

And the point is, if there are violations to the REMS, then there would be consequences to the manufacturer. Because the drug could then be deemed misbranded if there would be violations of the REMS.

So, I just thought I wanted to explain this to you in order to better understand why we put all this language here on this slide. Are there any questions regarding this REMS before I read the safety question?

DR. IRA FINEGOLD: Yes.

DR. PAUL GREENBERGER: Dr. Finegold, go ahead.
DR. IRA FINEGOLD:  Yeah.  The question I have, which falls in very nicely with this, is in the question 2, in conjunction with “these.”  Why say these if it's all in negotiation? Why don't say, “with additional safeguards?”

Because I think there are more safeguards than (a), (b) and (c). And interestingly enough, (b) obviates (a) because you can’t carry it unless it's been prescribed. So why say both, but that's a little -- anyway.

However, I think things like a black box warning. I think like in a dosage-miss schedule, as I asked about before. I think an informed consent. Because it's clear that this therapy can hurt some patients. And it's actually scheduled that patients will have reactions. And somehow this has to be quite clear that when people begin therapy, they know that in advance. And so, I would love to say, yes, knowing that it's going to be more than (a), (b) and (c).
DR. MARION GRUBER: To clarify, there will be a med guide. There will be a black box warning in the prescribing information.

The Agency felt that these three elements that we referred to as “elements to assure safe use” are important in addition to the other safeguards. That being that are already put in place, either medication guide and black box warning.

That being said, if the committee feels that there are additional safeguards that should be required, or that should be discussed here, we would be happy to get your comments and suggestions on that.

DR. PAUL GREENBERGER: Dr. Marshall.

DR. GAILEN MARSHALL: Dr. Gruber, one of the things that comes up right away, that goes along with this, is the issue of documentation. That it has been discussed or agreed to -- again, pick the right verb -- with the patient and the family that this is for prevention of accidental exposure as opposed -- we heard the spectrum that I would have expected in the public comments. And some people describing that now I
went through X and I can eat peanut butter and I can do all that. It's very distinct from what the sponsor presented. And it's very distinct from what's on the table today.

And I happen to think all three of those, of course, always picks out the right thing, and he's right. Item (b) is redundant to (a) because you can't do (b) until you've done (a). Though, I can argue that there could be a parsing of that.

But regardless of that, is the idea of actually also documentation somewhere so that the provider is comfortable, and the caregiver/adolescent patient is comfortable that desensitization is not immune tolerance. The term tolerance gets thrown around here; and I understand that because that's a pharmaceutical term. But it's distinct from an immune term of immune tolerance. And nowhere has the sponsor claimed immune tolerance -- quite the contrary. They've been very careful to parse out the difference between tolerance and desensitization requiring continued administration.
So in my mind, some commentary in there, if you're going to do that, in that REMS, which I happen to like -- I had heard about this, but I didn't know the details. I think that it would be very important to add that piece of it to it as well.

**DR. SOFIA CHAUDHRY:** Sofia Chaudhry, FDA.

Thank you for that feedback. This is very important to us. I think you've probably heard, in multiple committee discussions, often the discussion is more important than the vote. So we appreciate that, and we will take all of this into consideration.

I think some of the difficulties with (b) being redundant to (a), we perhaps incorrectly we're trying to boil down what comes across as legal and statutory factors into clinical terminology. And we failed.

But we are given certain legal factors that we can pick. And then we work it out with the lawyers, and we will discuss with Aimmune in terms of which satisfies what. But what we want to hear from the committee are what elements from a clinical perspective
-- and then we can work that out with them -- you're interested in seeing.

**DR. PAUL GREENBERGER:** I would want something that's not too burdensome. But I have two comments. One is to have the Agency and the sponsor work together to I guess give some “how to do it's.” Like we have for allergen immunotherapy. If you're a week late, you can still go up on the dose, so to speak. That kind of thing.

And perhaps this has to come from professional societies, but I would like to see it from the expertise from this side of the room with the expertise on that side of the room. So if my patient gets hives on the chest, again -- to my same story -- what do I do the next day? And it said individual determinations, but I have a feeling many of you over there know what to do if there are hives on the chest. Or if my stomach hurts a lot, what do I do?

And I don't know what's allowed statutory-wise, but I think it'd be very informative so that
there can be optimal use of this product should it come to be.

And the other one was perhaps considering like a designated person in the office who has responsibility for answering patient questions. Dr. Brittain.

**DR. ERICA BRITTAIN:** I'm a little out of my lane commenting on this, and maybe this isn't a REMS issue at all. But it seems like one of the really important things is that a year down the line, that there's still some communication going on. That yes, you have to continue -- if you're going to keep -- you know, you have to continue with your maintenance or else -- you know, things -- you can't -- especially if people are getting a little more laxed about their eating or their exposure, that they have to continue with their maintenance.

And again, maybe that's not a REMS thing.

**DR. JOHN KELSO:** I think it's hard to argue that this product is safe when it increases the risk of the thing it is designed to prevent. I think another
thing that needs to be factored into that in this risk
management strategy, is the complexity. We've already
said that beyond (a), (b), and (c), there's these
issues that some circumstance has to be created around
the administration of each dose. Where you're not
exercising, you're not taking a hot shower, you're not
too tired, you don't have a cold.

The complexity of that, I think, contributes
to the safety issue because it adds an additional level
of risk. Because as I stated, in my opinion, even when
you're following the plan exactly, or you're in the
protocol, and you're doing all the things you're
supposed to, it still was risky.

But then if you add the additional layer of
complexity that with the administration of each dose,
you have to be in this very special circumstance, and
the issue of missed doses -- which are invariably going
to happen -- and the uncertainty about how many you can
miss before you have to back up and so forth. I just
think that complexity of that adds an additional layer
of risks that needs to be considered.
DR. PAUL GREENBERGER: Dr. Dykewicz.

DR. MARK DYKEWICZ: Just one other perspective on this. What struck me not only with some of the sponsors presentation, but also comments from the public, was the importance of shared decision making for this particular therapy. Shared decision making is always important in medicine. But it's particularly so here because of the complexity of the issue and because of the risks.

I think as part of the REMS approach, we want to make sure that patients and families are being fully informed about the risks involved. That there may be an increased risk for need for epinephrine. But, you know, really try to make sure that there's complete understanding from the patient family perspective as well as the practitioner perspective of risk/benefits.

DR. PAUL GREENBERGER: Okay. Dr. Gruber.

DR. MARION GRUBER: Well, in light of these discussions, I think I would like to propose a slight modification of Q2. I would like to propose to delete
the word “these” in front of additional. And I can
read the question then and it would be as follows:

“The available safety data in conjunction with
additional safeguards, adequate to support the use of
Palforzia in patients age 4 to 17 years with their
confirmed diagnosis of peanut allergy. Please vote yes
or no.”

CAPT. SERINA HUNTER-THOMAS: Okay. So we have
all nine votes in. Total of eight yes votes and one no
vote. And reading individually: Dr. Apter, yes. Dr.
Brittain, yes. Dr. Marshall, yes. Dr. Finegold, yes.
Dr. Kelso, no. Dr. Dykewicz, yes. Dr. Greenberger,
yes. Dr. Hawkins, yes. And Dr. Maleki, yes.

DR. PAUL GREENBERGER: We’ll go around the
room starting over on this side with Dr. Hawkins,
please.

DR. RANDY HAWKINS: Yes. I have nothing else
to add?

DR. PAUL GREENBERGER: Dr. Maleki.

DR. SOHEILA MALEKI: Yeah. I also don't have
much to add except that -- and this might not be quite
to the question. But I feel like the safety of
increasing the dose tolerance, which is probably more
to the last question, it is much safer for the patient
than perhaps maybe the accidental ingestion.

But in this case, I think with the provisions
that are added here -- and it's something that I think
that's already been thought about. And with the
clinician and patient engagement, is something as you
mentioned, the shared communications. And that's why I
said yes, basically.

DR. PAUL GREENBERGER: To interpret, your
voting yes, but it doesn't say like (d), patient shared
values or any of that, but you're voting yes?

DR. SOHEILA MALEKI: Yes.


DR. GAILEN MARSHALL: I voted yes, and
particularly given the Agency’s comments to take out
the word “these” and just simply expanding this,
they're going to think about it and work with the
sponsor. It just increases my comfort level.

DR. PAUL GREENBERGER: Thank you. Dr. Kelso.
DR. JOHN KELSO: And I voted no for reasons previously stated.

DR. PAUL GREENBERGER: Thanks. I voted yes, I think, for reasons what I’ve said. And I think this is a good approach. Dr. Apter.

DR. ANDREA APTER: I voted yes because I think the REMS is very, very important to ensure the safety of this product.

DR. PAUL GREENBERGER: Dr. Brittain.

DR. ERICA BRITTAIN: I voted yes. I did want to make a couple of comments that the safety data were a little hard to interpret because the groups were changing over time. And we were losing a lot of the reactive people in the active arm so that made the safety hard to interpret. And here the safety and efficacy are sort of not really different from each other. They're very intermingled.

Also, just as I mentioned before, I think it's important to think about long-term monitoring of these patients; not just, you know, the period in which
they're doing they're up-dosing and early maintenance, but, you know, year one, year two, year three?

DR. PAUL GREENBERGER: Are the available safety data adequate to support the use of -- and you're voting yes?

DR. ERICA BRITTAINE: I'm voting yes. I mean, I'm just saying that it's not a perfect -- it's not easy to interpret. So you know, it’s just inherently challenging because of the design.

DR. PAUL GREENBERGER: Okay. Thanks. Dr. Dykewicz.

DR. MARK DYKEWICZ: Yes, for reasons previously stated. With the one reminder of a comment I made earlier about there may be a need to look at patients who stop or fail to be able to tolerate the course and what happens to them.

DR. PAUL GREENBERGER: Thank you. Dr. Finegold.

DR. IRA FINEGOLD: I was just thinking. It’s about two months and fifty years since I gave my first allergy shot as a resident or fellow. And we simply
didn't have the kind of data that we've heard today, and the safety information and standardized product. So allergen immunotherapy has come a long way.

And so, I think, even though this isn't perfect, and it's obviously not for everybody, it’ll go a long way in helping patients and their quality of life.

While I have the bully pulpit, so to speak, and the FDA is listening in, my wife wanted me to say something about the vaping epidemic and the need to control that. It's not peanut allergy.

DR. PAUL GREENBERGER: You're an excellent physician and that's an important subject in itself. Thank you. Dr. Gruber, final comments?

DR. MARION GRUBER: We’re sort of the Center for Biologics, so vaping, these type of drugs are really not under our purview. So you would have to go to a different Center. And I'm really relieved, because that’s not our responsibility.

I actually wanted to say that I really very much appreciate this discussion. I appreciate the
comments as much as I appreciate the concerns that were expressed. Because we all will take this in consideration, especially as we work with Aimmune to really work out the details of the REMS program to really ensure that the benefits of this product really outweigh the risks.

I thank the committee very much for a very productive discussion.

**DR. PAUL GREENBERGER:** And I thank everybody here, and in particular the committee. And this meeting is adjourned.

**[MEETING ADJOURNED]**