

1 The study itself went fine. He would put the
2 powder in the pudding, and he would eat the pudding
3 nightly. The smell was weird, the taste was too, but
4 he pushed on. We figured out if he ate something with
5 a strong taste after, the weird taste went away. There
6 were a few upset stomachs and a few itchy throats, but
7 nothing like anaphylaxis.

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

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

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

1 **DR. PAUL GREENBERGER:** You can go on.

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

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

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

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

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

1 **MR. CHARLIE PORTER:** I am Charlie Porter and I
2 was brought here by Aimmune.

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

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

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

1 sitting with my friends and eating cake, it was
2 crushing.

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

11 But then I found out about this trial from my
12 parents one night. We discussed all the factors,
13 including the one thing my 14-year-old mind was focused
14 on, money. I accepted and went through with the trial,
15 knowing that I would have to go into anaphylactic
16 shock. But I was prepared. The main thing that made
17 me want to do the study wasn't actually the money, but
18 it was the end result. The chance of not having an
19 allergy anymore, that was something that I had longed
20 for, for 14 years.

1 Before this trial, I was just the kid who had
2 to not eat with friends, not eat certain foods, sit out
3 of class parties and everything else like that. But
4 after the success of the trial, it turned me into a kid
5 who could just hang out with my friends without having
6 to worry about what I ate. Of course, I'm still a
7 picky eater after. This curse have in a way been
8 lifted.

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

19 In the end, this is the best thing that has
20 happened in my life so far. And I really want everyone

1 to be able to experience what I call a scientific
2 miracle. Thank you.

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

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

14 Okay. So this concludes the open session of
15 our meeting. We have a few minutes so I think we will
16 just move forward. We'll take a 15-minute break until
17 2:40.

18 [BREAK]

19

20 **FDA PRESENTATION**

21

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

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

6
7 **DR. KATHLEEN HISE:** Good afternoon. My name
8 is Kathleen Hise. I'm an allergist and medical officer
9 at the FDA in the Division of Vaccines and Related
10 Product Applications. I'll present a summary of the
11 efficacy and safety data submitted to the Palforzia
12 BLA. I will go over the product background, overview
13 of select clinical studies submitted to the BLA,
14 efficacy with a focus on pediatric subjects 4 through
15 17 years of age, safety with a focus on pediatric
16 subjects 4 through 17 years of age, and also focus on
17 systemic allergic reactions, epinephrine use and
18 eosinophilic esophagitis. I'll briefly go over adult
19 data and give a summary.

20 In this section, I will briefly summarize the
21 product background. Palforzia is sourced as dry peanut

1 allergen powder. It's provided in HPMC capsules at 5
2 doses strengths (0.5, 1, 10, 20 and 100mg). It's also
3 provided in a sachet at 1 dosage strength at 300
4 milligrams.

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

17 This schedule continued as tolerated until
18 subjects reached a maintenance dose of 300 milligrams
19 taken daily for 24 weeks. Again, every new dose level
20 was administered under observation. The first dose of
21 the maintenance phase, 300 milligrams, was administered

1 under observation. And if tolerated, subjects would
2 take the daily dose at home.

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

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

17 ARC003 was a Phase 3, randomized, double-
18 blind, placebo-controlled study of efficacy and safety
19 in subjects 4 through 55 years of age. The primary
20 efficacy endpoint was restricted to evaluation in
21 subjects 4 through 17 years of age.

1 ARC007 is a short study focused on safety in
2 the up-dosing period. Data from ARC007 will be
3 summarized in the safety section of this presentation.
4 Note that ARC007 did not include an entry oral food
5 challenge to reflect the clinical population, as it is
6 unlikely clinicians will perform oral food challenges
7 to confirm peanut allergies in subjects electing to
8 undergo oral immunotherapy. These are the
9 uncontrolled, open label follow on studies for ARC003
10 and ARC007.

11 In this section, I will discuss efficacy with
12 a focus on pediatric subjects 4 through 17 years of
13 age. Again, ARC003 was a Phase 3, randomized, double-
14 blind, placebo-controlled study with 555 subjects 4 to
15 55 years of age. The population evaluated to support
16 the primary indication was 4 to 17 years of age, and
17 this included 499 subjects.

18 A screening double-blind placebo-controlled
19 oral food challenge, with up to 100 milligrams of
20 peanut protein to confirm true peanut allergy, was done
21 for entry criteria. Subjects were excluded who had a

1 history of severe uncontrolled asthma, a history of
2 eosinophilic esophagitis, severe or life-threatening
3 anaphylaxis 60 days prior to screening. Safety was
4 monitored through electronic diary cards, clinic visits
5 and telephone follow ups.

6 In study ARC003, subjects began with screening
7 tests including serum IgE to peanuts, skin prick
8 testing to peanut and a baseline oral food challenge to
9 determine eligibility. As reviewed at the beginning of
10 this talk, subjects underwent an initial dose
11 escalation up to 6 milligrams in clinic, then returned
12 the next day for a dose of 3 milligrams under
13 observation. If tolerated, subjects took that dose at
14 home for the next two weeks, and then returned to
15 clinic every two weeks for the next dose in the
16 schedule, under observation, up to 300 milligrams. The
17 maintenance dose of 300 milligrams daily was taken as
18 tolerated for 24 weeks. At the end of this period, a
19 double-blind, placebo-controlled oral food challenge
20 was performed to determine efficacy.

1 I'd like to briefly go over the main points
2 discussed at the APAC in 2016, and the decision to use
3 an oral food challenge as an efficacy endpoint in
4 ARC003. During the APAC, the committee discussed
5 clinical endpoints for food allergies studies. These
6 are the main takeaways from that discussion.

7 A field study evaluating reduction of the rate
8 and/or severity of reactions to accidental food
9 exposure would require large cohorts at long study
10 durations to detect statistically significant
11 differences. There's no substitute for an oral food
12 challenge to determine treatment effectiveness.
13 Meaningful goals for the treatment of peanut allergy
14 include diminishing the risk of life-threatening
15 allergy with accidental exposure and increasing the
16 dose of food ingested without a serious allergic
17 reaction. This is why an oral food challenge was
18 chosen as an efficacy endpoint in study ARC003.

19 The food challenges done in ARC003 were double
20 blind and placebo controlled. This means the person
21 receiving the challenge food, nor the staff judging

1 reactions to the challenge, were aware whether or not
2 the product was peanut protein or placebo. Each
3 challenge took place over one day, peanut protein one
4 day and placebo the next day.

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

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

1 percent confidence interval, was greater than 15
2 percent.

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

20 ARC003 subject demographics. Most subjects in
21 ARC003 were male, white, not Hispanic or Latino, 4

1 through 11 years of age and resided in the United
2 States. These demographics were balanced across
3 treatment groups.

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

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

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

19 Key secondary endpoint number 1 was met. And
20 76 percent of Palforzia recipients ingested 300

1 milligrams of Palforzia with no more than mild symptoms
2 as compared to 8 percent of the placebo group.

3 Key secondary endpoint number 2 was met. And
4 50 percent of Palforzia recipients ingested 1000
5 milligrams of Palforzia with no more than mild
6 symptoms, compared to 2 percent of the placebo group.

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

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

16 Next I will discuss pediatric safety. Most of
17 the data I present will be from the controlled safety
18 population. The BLA included data from uncontrolled
19 studies in an integrated safety population. This data
20 can be found in the briefing document in Section 5.

1 A controlled safety population included
2 subjects 4 through 17 years of age who received
3 Palforzia or placebo in the controlled studies ARC003
4 and ARC007. The integrated safety population consisted
5 of any subject who received one dose of Palforzia. It
6 included studies ARC003 and ARC007, as well as open-
7 label extension studies ARC004 and ARC011.
8 Demographics and safety trends were similar in these
9 extension studies.

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

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

20 This slide summarizes the up-dosing period.
21 Most reactions were mild to moderate. More Palforzia

1 recipients discontinued due to adverse events. A few
2 SAEs occurred with more reports of SAEs in Palforzia
3 recipients. Palforzia recipients reported more
4 systemic allergic reactions and allergic reactions, as
5 AEs, compared to placebo recipients. Palforzia
6 recipients reported fewer episodes of adverse events
7 related to accidental food exposure compared to
8 placebo.

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

19 The most common adverse events leading to
20 discontinuation were GI disorders, including abdominal
21 pain, vomiting, and nausea. These adverse events

1 occurred more frequently in Palforzia recipients
2 compared to placebo. Fewer subjects discontinued
3 during the maintenance phase, though more Palforzia
4 recipients discontinued compared to placebo. Most of
5 the GI tolerability issues had resolved during
6 maintenance.

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

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

16 This slide summarizes systemic allergic
17 reactions during the initial dose escalation. All
18 participants who reported a systemic reaction reported
19 one systemic reaction each. All episodes were mild,
20 there were no SAEs. Three subjects had systemic

1 reactions at the study site during initial dose
2 escalation.

3 During up-dosing, most participants who
4 reported systemic reactions reported having only one
5 systemic reaction. Most of these episodes were mild to
6 moderate. There were two SAEs. Most reactions were
7 triggered by the study product. While most systemic
8 reactions occurred at home, reactions also occurred
9 under observation at the study site.

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

17 This slide includes data from open label
18 follow on studies. The slide shows reports of systemic
19 allergic reactions over time. As you can see after up-
20 dosing, reports of systemic allergic reactions decrease
21 over time in Palforzia recipients.

1 This slide displays epinephrine used as a
2 rescue medication during the initial dose escalation.
3 Please note that subjects could use epinephrine to
4 treat any symptoms of an allergic reaction, not just
5 systemic reactions. Because the purpose of epinephrine
6 is to prevent an allergic reaction from progressing to
7 a systemic reaction. All participants who reported use
8 of epinephrine used one dose per episode in IDE. Most
9 episodes were mild to moderate. All uses occurred at
10 the study site.

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

17 During maintenance, most participants who
18 reported epinephrine use used one dose of epinephrine
19 per episode. Most episodes are mild to moderate. Most
20 epinephrine used occurred at home during the
21 maintenance phase.

1 In terms of biopsy-confirmed eosinophilic
2 esophagitis, 3 Palforzia recipients in the controlled
3 safety population reported EoE. Of that, 2 improved, 1
4 the outcome is unknown. In the integrated safety
5 population, 5 Palforzia recipients reported EoE. Of
6 that, 1 resolved, 2 improve and 2 the outcome is
7 unknown. Overall, in the entire clinical development
8 program, 12 Palforzia recipients reported EoE. Of
9 that, 6 cases resolved, 2 improved and 4 the outcome is
10 unknown.

11 This slide briefly summarizes the adult safety
12 data. And 55 adults participated in the study ARC003.
13 About 52 percent of Palforzia recipients, versus 7
14 percent of placebo recipients, discontinued study
15 ARC003. And more adult discontinued study ARC003
16 compared to pediatric subjects, 52 percent versus 21
17 percent. Adults reported similar rates and types of
18 adverse reactions and systemic allergic reactions
19 compared to the pediatric population. One adult
20 developed EoE in study ARC004 during maintenance

1 dosing. This age group is not part of the requested
2 indication.

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

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

17 In terms of safety, Palforzia recipients
18 compared to placebo, reported increased systemic
19 allergic reactions, epinephrine use as a rescue
20 medication, increased discontinuation due to adverse
21 events and withdrawal of consent and increased reports

1 of eosinophilic esophagitis. The frequency of adverse
2 events, discontinuations, systemic reactions in
3 epinephrine use decreased during maintenance.

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

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

17 I'd like to thank you all for your attention.
18 This is the end of my presentation.

19 **DR. PAUL GREENBERGER:** Thank you. I would
20 like to ask you if you could comment on the "not more
21 than mild" reaction, what that means.

1 **DR. KATHLEEN HISE:** In terms of the efficacy
2 endpoint?

3 **DR. PAUL GREENBERGER:** Yes.

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

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

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

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

21 **DR. KATHLEEN HISE:** Um hmm.

1 **DR. PAUL GREENBERGER:** Okay. Thank you. This
2 is a time for questions for Dr. Hise. If people want
3 to identify themselves? Dr. Brittain?

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

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

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

17 **DR. PAUL GREENBERGER:** Please identify
18 yourself.

19 **MR. ALEX SMITH:** Alex Smith, Aimmune
20 Biostatistics. Yes. For this particular endpoint, we
21 applied a last observation carried forward in the form

1 of the maximum severity at the screening food
2 challenge; which would be the surrogate if they had
3 missed the exit food challenge.

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

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

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

18 **DR. KATHLEEN HISE:** The sponsor can correct
19 me. I believe what they showed was food exposures
20 related to peanuts specifically. So the numbers are
21 going to look a little different.

1 **DR. ERICA BRITTAIN:** Oh, is that the
2 difference?

3 **DR. KATHLEEN HISE:** Um hmm.

4 **DR. ERICA BRITTAIN:** Okay, thank you.

5 **DR. PAUL GREENBERGER:** Dr. Hawkins.

6 **DR. RANDY HAWKINS:** On the eosinophilic
7 esophagitis, why don't we notice status of all those
8 individuals?

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

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

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

20 **DR. GAILEN MARSHALL:** Gailen Marshall,
21 University of Mississippi. Again, Dr. Hise, I

1 apologize for you talking to my back here. I'm hoping
2 that you can give me a little bit of a vocabulary
3 lesson on these data that you present, from slide 32,
4 particularly, as it moves down to slide 33.

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

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

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

15 **DR. KATHLEEN HISE:** That's my understanding.

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

19 **DR. KATHLEEN HISE:** So it can include systemic
20 allergic reactions.

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

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

18 And it has to do with the issue of safety, and
19 it has to do with the labeling indications as to what
20 you're going to say and not going to say later on. And
21 I'm concerned that we're parsing it out, adverse events

1 as being minor if there is more than one. Just helped
2 me with that.

3 **DR. SOFIA CHAUDHRY:** Sofia Chaudhry, FDA.
4 Perhaps I was not as clear as I intended to be in the
5 morning. We acknowledge that there's differences in
6 the way that anaphylaxis is defined. However, when we
7 are viewing the safety data, from the agency's
8 perspective, we are looking at the systemic allergic
9 reactions. So patients who have more than one system
10 involvement, so the data you're seeing here, we would
11 label it accordingly. Although we are still working
12 through the final labeling language if this gets
13 approved.

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

19 **DR. SOFIA CHAUDHRY:** You're talking about the
20 mild, moderate for the total 8 adverse events?

1 **DR. GAILEN MARSHALL:** It says severe -- in the
2 second line -- subject with one or more AEs. All the
3 math doesn't add up is what I'm trying to say. And I'm
4 trying to understand if that's because you have parsed
5 out the systemic allergic reactions separate from
6 single system symptoms. Say that fast three times.

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

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

19 **DR. SOFIA CHAUDHRY:** Correct.

20 **DR. GAILEN MARSHALL:** Okay.

21 **DR. SOFIA CHAUDHRY:** Correct.

1 **DR. PAUL GREENBERGER:** Dr. Dykewicz.

2 **DR. MARK DYKEWICZ:** I may have missed this.

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

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

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

16 **DR. STEPHEN DILLY:** So we didn't directly
17 measure that in those patients. But what we can look
18 at is the behavior of patients after accidental
19 exposures, and actually the one -- or even intentional
20 exposures. And we did look at sensitivity at baseline

1 at either side of the food challenge. The way we do
2 that is we look at the initial dose escalation day.

3 So remember, we've taken a group of patients
4 and we've exposed them to peanut protein until they've
5 reacted in the baseline challenge. And then we look at
6 how they do a few weeks later in the initial dose
7 escalation. And actually, there is no evidence of a
8 sensitizing effect there. And so, we don't have any a
9 priori reason to do it. But what we do look at is
10 patients who've had a severe reaction, like an
11 anaphylactic shock, we just for safety didn't put into
12 the study for 60 days. But there's no a priori reason
13 to believe that we would sensitize patients.

14 **DR. MARK DYKEWICZ:** I mean, I understand that
15 argument. But I guess the question does remain, in my
16 own mind; since we know that for instance serum IgE
17 levels come up initially with peanut, that you may be
18 looking at a different population of patients in terms
19 of the responsiveness to a desensitization effort. And
20 they may be at increased risk for having more problems

1 with peanut inadvertent exposure going forward. That's
2 my concern.

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

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

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

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

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

16 **DR. KATHLEEN HISE:** Well I didn't have parsed
17 out the allergic reactions as mild, moderate and severe
18 here. But if you're looking at where it says severity
19 of AEs, it would be under one of those.

1 **DR. PAUL GREENBERGER:** Okay. And then if it
2 was acute urticaria plus abdominal pain, no treatments
3 given, no epinephrine given, where does it go?

4 **DR. KATHLEEN HISE:** That would be a systemic
5 reaction.

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

8 **DR. KATHLEEN HISE:** Mm hmm.

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

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

14 **DR. PAUL GREENBERGER:** Okay, thank you. Dr.
15 Kelso.

16 **DR. JOHN KELSO:** It's been mentioned a couple
17 of times, including in the presentation that we just
18 had, that the incidence of need for epinephrine is less
19 in the maintenance phase than in the up-dosing phase.
20 Which is true, but I would point out that that's also
21 true in placebo. So that, for example, in the up-

1 dosing phase there were 10.4 percent of subjects
2 getting the active treatment who had at least one
3 episode of epinephrine use versus 4.8 percent of
4 placebo. And during the maintenance phase, although
5 the numbers are less, 7.7 percent of subjects required
6 epinephrine compared to 3.4 percent of placebo.

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

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

20 **DR. PAUL GREENBERGER:** Dr. Finegold, you with
21 us? You have some questions? Might you join in?

1 **DR. IRA FINEGOLD:** I am, but I don't have a
2 question.

3 **DR. PAUL GREENBERGER:** I'm taking the liberty
4 to call on myself one more time. Sorry.

5 That is on inclusion criteria under asthma. I
6 would like to clarify. I see the word severe asthma
7 and I saw uncontrolled, but this is a patient with
8 severe controlled asthma. Or is this a thinking that
9 they would be excluded from use of this product?

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

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

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

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

19 **DR. KATHLEEN HISE:** Um hmm.

20 **DR. PAUL GREENBERGER:** Okay. Dr. Apter.

1 **DR. ANDREA APTER:** Thank you. Do you have any
2 information -- patients who have a history of severe
3 allergic reactions to peanuts were excluded -- were
4 screened out of the study. Do you have any information
5 on those?

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

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

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

16 **DR. KATHLEEN HISE:** Yes. Thank you.

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

19 **DR. PAUL GREENBERGER:** Does anybody else have
20 information on that?

1 **DR. STEPHEN DILLY:** What we recorded was the
2 incidence of -- the previous one was good, thanks --
3 the history of anaphylaxis, patients reporting it. And
4 what you saw was 70 percent of patients included in the
5 study reported having had a history of anaphylaxis,
6 including some had hospitalizations. But it was really
7 difficult to quantify the exact severity, because some
8 of these were historic several years old.

9 And so all we're saying is we have here that
10 70 percent of the patients in the study reported having
11 had an anaphylactic episode in the past. And we
12 specifically excluded anyone that has had a severe one,
13 including anaphylactic shock or hospitalization in the
14 two months before screening, so we never saw them.

15 **DR. PAUL GREENBERGER:** Okay. Dr. Brittain.

16 **DR. ERICA BRITTAIN:** So maybe you've shown
17 this, and I don't remember. It would be interesting
18 for me to see of the people who were completers on the
19 active arm, during the maintenance phase, what
20 percentage of the doses they had more than mild

1 reactions to. Do you have any data like that? Because
2 I'm just not getting a sense of that.

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

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

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

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

14 **DR. STEPHEN DILLY:** This is all adverse
15 events.

16 **DR. ERICA BRITTAIN:** Right. So, it's not just
17 dose related?

18 **DR. STEPHEN DILLY:** What we do in an abundance
19 of caution is we count everything in this, so it's
20 really hard to parse out in the food-allergic child,
21 with multiple food allergies, what's likely to be

1 related to the dosage and what's not. What we have
2 done is we've looked at the time of dosing and of these
3 adverse events, more than 70 percent are happening
4 within the two hours after the dosing. So it's pretty
5 reasonable to assume the vast majority are -- in fact,
6 here you go.

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

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

18 **DR. STEPHEN DILLY:** That's right. So out
19 there if you look at 11 events per patient per year.
20 And that's not far off what we're seeing in the placebo
21 group during the second half of the ARC003 trial. The

1 challenge we have on those out months and years is we
2 don't have a control group, so we have to compare it to
3 what we saw in the untreated group in the pivotal
4 trial. And it's not very different.

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

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

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

18 So which is it? Is it systemic reaction 70
19 percent have? Or is it the anaphylaxis within that
20 group? And I, of course, by disclosure, think they're

1 all anaphylaxis. But arguing that there may be two
2 different groups.

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

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

15 And beyond that, when people see two remote
16 adverse events, they don't always put two and two
17 together, right. So we went through the entire MedDRA
18 database and we searched for any adverse events that
19 happened at the same time, in two systems, and made
20 sure they were captured as anaphylaxis or systemic
21 allergic reactions, right.

1 So we've got that number you see for our
2 systemic allergic reactions, is the ones that reported
3 as such and the ones we captured by searching for
4 simultaneous adverse events in two systems. So we
5 think we've got the whole iceberg.

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

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

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

21 **DR. PAUL GREENBERGER:** Any other questions?

1 **DR. IRA FINEGOLD:** I have another question.

2 **DR. PAUL GREENBERGER:** Go ahead.

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

8 **DR. PAUL GREENBERGER:** Dr. delay?

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

15 However, if they had a concomitant illness,
16 then they were allowed to take antihistamines for that.
17 But if they were presenting, for instance, an efficacy
18 read out, the food challenge, then the antihistamines
19 were withheld for at least four half-lives before they
20 were exposed.

1 We tried to remove any confounder there. But
2 we did have to allow for the practicalities so that
3 they could manage their other concomitant illnesses.

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

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

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

10 **DR. IRA FINEGOLD:** No.

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

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

19 **DR. PAUL GREENBERGER:** Okay, thank you. Dr.
20 Hawkins.

1 **DR. RANDY HAWKINS:** No, I'm satisfied. Thank
2 you.

3 **DR. PAUL GREENBERGER:** Dr. Maleki?

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

14 I've heard a lot of the consumer advocates
15 today and previously that have spoken out as well. And
16 I just want to say that this product seems to -- it's
17 not perfect and it's not necessarily for everybody.
18 But it's something that -- seeing some of the safety
19 and efficacy data, it's something that I would look
20 into perhaps considering for this.

1 **DR. PAUL GREENBERGER:** Could you inform us
2 whether there's longitudinal data on the character of
3 peanuts and peanut proteins being different over a
4 period of years?

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

8 **DR. PAUL GREENBERGER:** Peanuts themselves as
9 opposed to a product?

10 **DR. SOHEILA MALEKI:** The peanuts themselves --
11 again, and it depends on how you store them. And how
12 they're treated from the time they come out of the
13 ground, to the storage and so forth. So again, they
14 have a pretty long shelf life, as you know, in a lot of
15 products like peanut butter and so forth that are
16 around. So it's actually a good model system for some
17 of these studies because of the stability of allergen.

18 **DR. PAUL GREENBERGER:** I think I didn't quite
19 make it clear enough. That if I were to study peanuts
20 from 10 years ago, and compare them to peanuts now, are

1 there major differences that you're aware of? Because
2 I think you have expertise in that.

3 **DR. SOHEILA MALEKI:** Yeah, actually, I would
4 say no. Because there's been years and years of
5 peanuts collected from all over the world. And there
6 are some differences. But mostly the cultivated
7 peanuts in what are eaten today is probably the same
8 proteins, the same products -- the same peanuts that
9 were available maybe years ago.

10 And the cultivated peanut has different
11 parental types. And without going into the genetics of
12 it, the ones that are cultivated and edible and
13 consumed by consumers all over the world are pretty
14 much the same and have not really changed.

15 **DR. PAUL GREENBERGER:** Okay, thank you. Dr.
16 Marshall.

17 **DR. GAILEN MARSHALL:** I would just like to
18 support the idea for the FDA as you move forward with
19 this and your decision, two particular things. Number
20 one is be very thoughtful about how you define this
21 certified facility.

1 The problem with that comment for me, is that
2 it sounds like a commercial comment. Because the
3 people that are most well trained for this are
4 allergist immunologists who've dealt with this for two
5 years at least, and then their career afterwards. Or
6 emergency medicine physicians who see people come in,
7 in an acute need. I don't think anyone in this room is
8 naive to suggest those are the only people that are
9 going to be engaged in this. But by providing clear
10 guidance, I think that can help a lot in terms of the
11 safety and the use of this.

12 We've heard enough desperation in the voices
13 of some of the commenters today, that if they found in
14 a community there was someone who might not be
15 particularly well trained, but made it available,
16 versus somebody else who was better trained and chose
17 not to make it available, they'd go for the first
18 option. And I think that we need to take leadership in
19 providing the help and support that's necessary.

20 And the second is that we would come to a
21 better understanding -- I'm sorry, a better agreement

1 about the verbiage of anaphylaxis versus systemic
2 allergic reaction. The sponsor clearly has stated,
3 repeatedly, that they're fine with that being a
4 synonym. And I think the burden should fall upon those
5 of you making these decisions to decide why you would
6 want to parse it and not leave it as a synonym. That
7 is clearly a conservative approach. There's no
8 argument about that.

9 But it's pretty hard to go down to ask
10 somebody to treat their runny nose or their stopped-up
11 nose with epinephrine. One of the things that hasn't
12 been mentioned much around here is that as they up-dose
13 and they have to use epinephrine repeatedly, they have
14 to go back to the pharmacy and fill those things. And
15 those are expensive. And that's an added expense to
16 this. And in order to do that, you want them to
17 believe that they have a good reason to do so.

18 And I think few people would think of
19 anaphylaxis as a benign condition. I'm less certain
20 about the term systemic allergic reaction.

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

1 **DR. JOHN KELSO:** I have two comments. The
2 first is that I also want to thank the members,
3 patients and patient advocates who spoke. And to
4 acknowledge that the problem is real and the need for a
5 solution is real. But I don't believe that this is the
6 solution. A good portion of what we heard from
7 patients, I think, could be addressed with education
8 rather than oral immunotherapy.

9 For example, the overwhelming majority of
10 products that contain provisional allergy labeling do
11 not contain allergen. And those that do, do not
12 contain enough allergen to cause a reaction. And we
13 have umpteen studies to demonstrate that.

14 Anaphylaxis requires ingestion. So, for the
15 overwhelming majority of patients with peanut allergy,
16 sitting next to another child eating a peanut butter
17 and jelly sandwich or getting some on the skin will not
18 cause a serious reaction. And for the overwhelming
19 majority of patients, I think that a key part of our
20 job, as allergist, is to educate patients on being
21 appropriately concerned about their condition; but not

1 to have a misunderstanding of the risks of those other
2 exposures such as contaminated products and physical
3 contact. Which we can do with education, which we can
4 back up with data.

5 If necessary, we can open a jar of peanut
6 butter in front of the patient. If necessary, we can
7 put some peanut butter on their arm. But a lot of the
8 benefit that was described as being received from this
9 therapy, I think can be achieved with education.

10 My second comment -- and I want to preface
11 this with I'm a pediatrician, I'm an allergist. I have
12 been practicing full time allergy for almost 30 years.
13 I also want what's best for my patients.

14 But I think that -- as you've heard me say now
15 a couple of times, I don't think this is the answer.
16 And just to reiterate that I am not alone in that
17 conclusion. From one of the papers that was cited
18 earlier, I think this is accurately summarized by
19 saying that current peanut oral immunotherapy regimens
20 can achieve the immunologic goal of desensitization.
21 But that this outcome does not translate into achieving

1 the clinical and patient-desired aim of less allergic
2 reactions and anaphylaxis. Instead the opposite
3 outcome occurs with more allergic and adverse reactions
4 with oral immunotherapy, compared with avoidance.

5 I am sympathetic to the concern and the
6 problem. I also want my patients to have a lower risk
7 of having reactions. But I think from the data that we
8 have had presented to us, that neither the safety nor
9 the efficacy have been demonstrated.

10 **DR. PAUL GREENBERGER:** Thank you. I thank
11 everyone for their involvement, especially on the
12 committee and the sponsor and the agency and all the
13 public. And I have no further comments.

14 **DR. SOHEILA MALEKI:** You're going to do that
15 other side of the table, Paul?

16 **DR. PAUL GREENBERGER:** I'm going around the
17 room. I personally have asked -- for now I have no
18 further comments. Dr. Apter's going next. And then
19 after Dr. Dykewicz, Dr. Gruber's going to address us.

20 **DR. ANDREA APTER:** Yes, I have a number of
21 concerns that I share with the previous speakers. I do

1 share the concern of the definitions of systemic
2 reaction and how they can be very confusing and make
3 the analysis difficult.

4 I share Dr. Kelso's concerned, too, that what
5 we're seeing in these trials are increased allergic
6 reactions to be given increased peanut. And we don't
7 necessarily know -- we wish, but we don't know that
8 this translates further into less allergic reactions
9 down the road.

10 I'm also concerned that we need to know more
11 about -- if we were to persist in this, we need to know
12 more about diverse populations as Dr. Hawkins noted.
13 There were very few African Americans, for example,
14 that were studied. And there may not be a difference,
15 but there may be, and that should be done. There may
16 be other characteristics of populations that aren't
17 studied in these events. We also need to know more
18 about how adverse events that occur are influenced by
19 age as the patients get older.

20 And I'm also concerned -- I agree with the
21 safety elements that you put in. But I also know that

1 my patients don't necessarily carry epinephrine with
2 them, even though we mandate it. And that may be a
3 problem, too, in a potentially dangerous intervention.

4 **DR. ERICA BRITTAIN:** I have a question. Are
5 these our ultimate comments? Or are we going to also
6 comment at the time of voting? I'm just used to the
7 other way.

8 **DR. PAUL GREENBERGER:** Captain Hunter-Thomas
9 can address this.

10 **DR. SOHEILA MALEKI:** Yeah. Are we in a
11 discussion phase or are we in an ultimate --

12 **CAPT. SERINA HUNTER-THOMAS:** We're currently
13 in the committee deliberation phase. And then if
14 there's additional comments that anyone needs to make,
15 please make it. Now is the time to do so. Is that
16 right --

17 **DR. ERICA BRITTAIN:** I guess I'm asking -- I'm
18 used to the advisory committees where whenever we vote
19 we give our comments. It's not like that?

20 **CAPT. SERINA HUNTER-THOMAS:** Dr. Gruber?

1 **DR. MARION GRUBER:** Dr. Greenberg, I think we
2 can invite some additional discussions when people
3 have. And usually, you know, what we do is when people
4 vote on the questions -- when the committee votes on
5 the question -- then usually we ask for comment and
6 perspective on why they voted the way they have voted.

7 But I think we probably have some more time
8 this afternoon. So, I think if there are other
9 perspectives here that the committee would like to
10 express your opinions, then I think we should really
11 take advantage of that because this is a very
12 complicated complex discussion.

13 **DR. PAUL GREENBERGER:** Can I asked. How do we
14 vote? The votes will be shown. And we go around the
15 table and explain the vote, justify the vote?

16 **DR. MARION GRUBER:** Yeah, I think that's what
17 we usually do. Serina, is that okay?

18 **CAPT. SERINA HUNTER-THOMAS:** That's fine.

19 **DR. ERICA BRITTAIN:** Okay. So knowing that I
20 will ultimately have more to say. I mean, this is just
21 sort of a side issue, but I just had a comment for the

1 FDA. And I guess you probably have heard me say it.
2 But it would have been nice if -- at least maybe for
3 future studies -- that patients who are discontinued
4 are followed for everything. I know, you can't do the
5 oral food challenge for them at the end, but normally
6 we want to follow everybody as much as we can.

7 And for example, I think it's disappointing
8 that we don't have the accidental exposure data on
9 those patients. Then we could have had an intent to
10 treat. Perhaps the event rates are way too low to be
11 informative, but I think I think it would have been
12 helpful. And I suggest that you consider doing that in
13 future studies.

14 I think, you know, obviously, the treatment
15 effective for the primary endpoint was a fantastic
16 result. The scary part here is that the indication
17 isn't exactly matching what the primary endpoint is.
18 So you know, that's, again, why I'm interested in the
19 accidental exposure data. Because that really does
20 match it to the extent that it does exist.

1 I guess the other thing I am wondering about
2 is this is a lifetime treatment. And we don't have a
3 lot of long-term data. And I guess that's a little bit
4 troubling that we don't know long term. There's a
5 number of leaps of faith that we're making here.

6 **DR. PAUL GREENBERGER:** You don't have long
7 term follow up of treated patients. Is that what
8 you're saying?

9 **DR. ERICA BRITTAIN:** Yeah. You know, I mean,
10 there's some. There's some data past that first year.
11 But, you know, we're talking about potentially a
12 lifetime treatment. I mean, I'm not that concerned. I
13 mean, I'm basically feeling pretty good about things.
14 But that is one issue that does give me pause.

15 **DR. PAUL GREENBERGER:** But there are
16 continuing studies. I don't think the data is locked
17 on your studies yet. But you showed us that the
18 studies are ongoing. Dr. Maleki?

19 **DR. SOHEILA MALEKI:** Just one comment. For
20 what you were saying that it is probably a lifetime
21 treatment. Again, there's no long-term studies to look

1 at that. For me, hearing the patients say, and also
2 knowing from experience of being in the field, that
3 they don't have to necessarily take the actual product
4 or the drug. They can go to an actual food. So they
5 eat peanut butter, or they eat peanut M&Ms, or
6 something they like better. So it becomes part of
7 their diet is one way to think about that, too.

8 **DR. PAUL GREENBERGER:** Does anyone from the
9 company want to comment on that? Were the subjects
10 introducing peanut butter back into their diet, so to
11 speak?

12 **DR. STEPHEN DILLY:** What we know is at the
13 moment with oral immunotherapy, continued exposure to
14 the allergen is necessary to maintain desensitization.
15 During the early phase, while patients are still having
16 adverse events associated with dosing, it's really
17 important to be accurate with dosing.

18 Now, over a period of years, many patients
19 achieve a level of desensitization whereby that
20 accuracy may be less important. And what we are
21 actively studying right now is in the out years,

1 whether you can actually reduce the dose frequency.
2 Whether you can go to every other day or whatever. But
3 those data are preliminary, and those studies are not
4 complete.

5 What we have done, and we've already
6 published, is we've looked out beyond the 12-month
7 period to show that desensitization is maintained to 18
8 months and beyond. We continue to follow our sentinel
9 cohort. And we are very serious about managing that
10 long-term observational studies and looking for what
11 happens when this is introduced, in terms of signal
12 acquisition.

13 And there are two things we're worried about.
14 The systemic allergic reactions however you define
15 them. We need to know that we're not increasing those.
16 And we also need to look out for eosinophilic
17 esophagitis. And the beautiful thing about that is,
18 those are low frequencies signals that to really
19 characterize you need lots and lots of patients.

20 And so this is all about pharmacovigilance in
21 the context of a robust, implemented risk management

1 plan. And that's what we're here to do. Because oral
2 immunotherapy is already a reality. And what we're
3 trying to do, is we're trying to bring it under
4 control, under regulation, so we actually get those
5 data. Because if we don't, then it will continue to be
6 small studies, randomly conducted with cohorts of
7 patients that are too small to tell anything. So,
8 that's what we're trying to achieve.

9 **DR. PAUL GREENBERGER:** Dr. Brittain and Dr.
10 Dykewicz.

11 **DR. ERICA BRITTAIN:** So just a little follow
12 up on that. It sounds like, potentially, you have the
13 opportunity to do some randomize studies within your --
14 like, you know, of the people who get to two years out,
15 you could potentially randomize them to get -- you
16 know, every other day versus one day. Is that a
17 possibility?

18 **DR. STEPHEN DILLY:** If you would indulge me.
19 Could I show the schematic for study 004 please? So
20 we're going to have to switch slides.

1 This is a study that is already ongoing. And
2 in fact, many of the cohorts are nearing completion.
3 The reason we did this study was actually to answer the
4 question, what happens in the out months if people
5 start missing doses? It was called a Dose-forgiveness
6 Study. Whereby we could look at if they weren't quite
7 as diligent and they missed doses.

8 And this is on the paradigm that once you've
9 achieved the sensitization, the time course of it
10 fading is actually relatively slow. And it's about
11 regular exposure to the allergen. And so we have
12 cohorts in here, including with complementary food
13 challenges. And the preliminary read on it is that
14 every other day seems to be reasonably well tolerated.
15 Early evidence is that desensitization is maintained.
16 But only in patients that have already been through 18
17 months of daily therapy before they did that.

18 Now, these are open-label data. They're small
19 numbers, they're preliminary. What they're telling us
20 is that it's an experiment certainly worth doing down
21 the line. Because we have this great question. Which

1 is, so you've got these people on immunotherapy,
2 they've been through that work to get to
3 desensitization, now what?

4 And we do have the tools to follow them. We
5 can look at their peanut specific IgE. We show it goes
6 up and comes down to baseline. As you follow it
7 further, it continues to go down. The same thing.
8 Their IgG4 goes up and stays up. Their TH2 cells
9 change over time. We have their skin prick test. We
10 can look for quiescence. So, in some cases, long
11 enough, it may well be appropriate to back off dosing
12 in patients. But that's really the field for future
13 study.

14 **DR. ERICA BRITTAIN:** Are those groups
15 randomized, or how do people get in those cohorts?

16 **DR. STEPHEN DILLY:** So the first cohort was
17 sequential because we wanted to acquire at least 100
18 patients that kept going on their daily dosing to see
19 what happened with them. And then the Cohort 3 is
20 randomized. Okay? So Cohort 2 was programmatic. That
21 was a safety test to say no signals came out of that,

1 and then Cohort 3 was randomized. So we're acquiring
2 those data.

3 **DR. MARK DYKEWICZ:** I wanted to review the
4 data that was presented about, shall we say, cofactors
5 that were associated with increased risk for systemic
6 reactions when patients were, for instance, already on
7 their maintenance dose. I believe it might have been
8 Slide AN-20 by the sponsor. And it was looking at
9 things -- for instance, if there was increased asthma,
10 fever, illness.

11 **DR. STEPHEN DILLY:** Hold on.

12 **DR. MARK DYKEWICZ:** Yes. That's the one. And
13 what I'm thinking ahead. Is should the product be
14 approved in some way communicating to the patients,
15 perhaps with some card that would be co-dispensed with
16 either the up-dosing photo card or the daily
17 maintenance sachets. That it would almost be a little
18 checklist that the patient should go through and say,
19 you know, not only don't exercise within two hours but,
20 you know, if you're having an intercurrent illness -- I
21 don't know how we define that, fever or whatever. We

1 put down some of the ones that are evidence based here
2 that are associated with an increased risk for systemic
3 reactions. And in an effort to try to more safely
4 administer the product, give that type of guidance to
5 the patient.

6 It also dovetails with some of the comments
7 that I heard during the public comments session, which
8 I think was very helpful and informative. But what
9 struck me with some of the comments was the idea that
10 people didn't have to worry anymore about accidental
11 ingestion. And I think it has to be absolutely
12 emphasized that avoidance really must be advised along
13 with the use of the immunotherapy.

14 And because of these sorts of scenarios, where
15 you could have somebody who's doing fine for the most
16 part, and maybe they do have an illness and then they
17 get zapped with either, if you will, natural ingestion
18 or the sachet dispensing. People have to be aware that
19 there still is the potential for a reaction down the
20 road.

1 **DR. STEPHEN DILLY:** We are completely in
2 agreement with you. And again, that's the reason why
3 the product should only be presented to the patient
4 coupled with a label, with training, with patient
5 information. And that's got to be consistent.

6 Because at the moment, you know, it's up to
7 the doctor that's doing their own immunotherapy to come
8 up with what they're going to brief on. And here's
9 some of the draft dosing instructions that we've got.
10 But things like avoiding hot showers and baths.

11 Now, there's also art in this in what is
12 exercise. You know, one of the patients that we went
13 into in great detail said, "I didn't exercise before I
14 had a systemic allergic reaction." Well, what she'd
15 been doing was stacking shelves in a hot supermarket.
16 Right? And that's exercise. And so we've got to train
17 people into thinking about stuff like that.

18 Also, you know, the hot shower, all that. And
19 what to do if they have got a scratchy throat or
20 they're coming down with a cold. And so that's part of
21 the patient education that we're going to do, the

1 labeling the training. And this is what it's all
2 about, making sure it's done as safely as we possibly
3 can.

4 **DR. MARK DYKEWICZ:** Thank you.

5 **DR. PAUL GREENBERGER:** Dr. Gruber.

6 **DR. MARION GRUBER:** Again, I would really like
7 to thank the committee for the many comments, questions
8 and opinions and perspectives expressed. But I think
9 at this point if there are no additional comments, I
10 think we should really put up the questions and move to
11 the vote.

12 **DR. PAUL GREENBERGER:** As I said, after the
13 vote, yes or no, with your device, and then we will go
14 around the table and justify the vote one way or the
15 other. And see if other information is needed that
16 hasn't been expressed so far. And then we'll do the
17 second question. Right. So do you want to read the
18 first?

19 **DR. MARION GRUBER:** The question one. Are the
20 available efficacy data adequate to support the use of
21 Palforzia as a treatment to reduce the incidence and

1 severity of allergic reactions, including anaphylaxis
2 after accidental exposure to peanut in patients aged 4
3 to 17 years with a confirmed diagnosis of peanut
4 allergy? Please vote yes or no.

5 **CAPT. SERINA HUNTER-THOMAS:** And before they
6 vote, yeah. Thanks, Jim. Okay, that fob, you're not
7 going to use the buttons on the mic. You're going to
8 use that. I guess that's clear. Okay. Jim, is it
9 okay for them to press the buttons now? Okay. So go
10 ahead and submit your vote for question one. And I
11 submitted Dr. Finegold's vote.

12 Okay, so I'm just going to read out everyone's
13 response for the record. It was a total of nine
14 eligible to vote. So starting with Dr. Apter, she
15 voted no. Dr. Brittain, yes. Dr. Marshall, yes. Dr.
16 Finegold, yes. Dr. Kelso, no. Dr. Dykewicz, yes. Dr.
17 Greenberger, yes. Dr. Hawkins, yes. And Dr. Maleki,
18 yes. So that's a total of seven yes votes, two no
19 votes and zero abstain for question number one.

20 And I guess we could go around the table for
21 everyone to discuss.

1 **DR. PAUL GREENBERGER:** I think we'll start
2 with Dr. Finegold, please.

3 **DR. IRA FINEGOLD:** Well, I voted yes because I
4 thought the data was quite clear. And I would actually
5 compliment the sponsor on the extent and caliber of the
6 studies. While I have the microphone, I did want to
7 ask about the next question. Before we vote on it,
8 would I have an opportunity to ask them questions?

9 **DR. PAUL GREENBERGER:** You will? Okay, thank
10 you. I'm going to start with Dr. Dykewicz and work
11 around this way, please.

12 **DR. MARK DYKEWICZ:** I do think that -- first
13 off to be cognizant that I and several other members of
14 the panel, in 2016, were on the APAC panel that defined
15 the endpoint as being a successful reduction in
16 reactions with controlled food challenge. And I think
17 that the evidence does demonstrate benefit at that
18 endpoint.

19 As we discussed back in 2016, and have
20 discussed today, this does not directly mean that we
21 have any evidence yet that with accidental exposure to

1 peanut, that it's going to, in a large number of
2 patients, reduce the risk for reactions. We hope so.
3 And that's why the endpoint was chosen that was chosen.
4 But there is still some need, I think, for further
5 follow up longitudinal studies to assess that.

6 **DR. PAUL GREENBERGER:** Okay. Thank you. Dr.
7 Brittain.

8 **DR. ERICA BRITTAIN:** I voted yes. Obviously,
9 the pre-specified endpoint was an extremely strong
10 result. I guess, as we've discussed already, we have
11 to do a leap of faith to believe that then means that
12 the accidental exposure will be lessened. It seems
13 like a pretty reasonable leap of faith, but it is one.

14 To whatever extent they can follow -- the
15 observational data will be helpful in that regard,
16 although it's still not the same as doing the
17 impossible study; which I understand you can't do,
18 really having that accidental exposure be the endpoint.

19 And again I reiterate that in future studies,
20 I think there should be an attempt to get accidental
21 exposure data from everybody randomized.

1 **DR. PAUL GREENBERGER:** Dr. Apter.

2 **DR. ANDREA APTER:** I think this is an
3 important effort and I certainly understand patients
4 fear of accidental ingestion, and of their parents and
5 caregivers likewise having that fear. I think that the
6 way the design of the study makes it -- because the
7 endpoints are ingestion, we don't know enough about
8 whether accidental ingestion will diminish or not.

9 And I do think it will be important to go
10 forward with looking at some of the other details that
11 still need to be ascertained about, age and diversity
12 and other elements as you go forward.

13 **DR. PAUL GREENBERGER:** Thank you. This is
14 Paul Greenberger. I voted yes. And I'm also reading
15 into the question passing double-blind exit challenge
16 and accidental exposure. This is desensitization. But
17 there was over 60 percent of the actively treated
18 participants passed the exit challenge compared to a
19 very, very small number relatively on placebo. So I
20 voted yes.

1 **DR. JOHN KELSO:** John Kelso, I voted no. The
2 question asks about reducing reactions to accidental
3 exposures. And as several others have said, that was
4 not directly assessed and would be very difficult to
5 directly assess.

6 And so, I understand the rationale of
7 substituting the surrogate of passing the food
8 challenge. But I think that because the treatment
9 itself represents a challenge every time a dose is
10 given, and the end result being that patients who are
11 on the treatment are twice as likely to have a reaction
12 requiring epinephrine, that effectiveness of the
13 treatment has, in fact, not been demonstrated.

14 It may be demonstrated on the day that that
15 particular oral food challenges done. But over a
16 longer period of time when the patients are having a
17 challenge every day, in the form of a dose of
18 medication, that actually increases rather than
19 decreases their likelihood of a reaction.

20 **DR. PAUL GREENBERGER:** Thank you. Dr.
21 Marshall.

1 **DR. GAILEN MARSHALL:** Gailen Marshall. I
2 voted yes, actually using the same logic with a
3 different conclusion. And that is that we approve
4 surrogate markers for indications all the time that
5 don't directly affect patient care. But we extrapolate
6 from that to affect the patient care.

7 I like the idea -- I mean, I really appreciate
8 the idea of getting a therapy from a pharmaceutical
9 company as opposed to the grocery store and all the
10 other nice arguments that have been leveled. But in
11 the final analysis, I think, what we've demonstrated
12 with a well-defined in part surrogate marker that was
13 reviewed and agreed upon in previous iterations. This
14 product and the studies that are represented by this
15 product has met that standard and deserves a chance to
16 be seen in the marketplace and see where it floats.

17 I would assume, and that certainly hope, that
18 the FDA won't just stamp this and say fine, very, very
19 good, enjoy yourself and good luck. That it will be
20 monitoring to see if this translates over a period of

1 time. Again, as has been done in the past with many
2 new therapies. That was my rationale.

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

4 **DR. SOHEILA MALEKI:** Again, stating that just
5 being immersed in this field for so long and seeing the
6 beginnings of why this started in the first place. And
7 that was based on small immunotherapy treatments that
8 allowed, I guess, as a gung-ho allergist to go out
9 there and start trying to do oral immunotherapy without
10 any kind of control dosage or measurement.

11 And this whole company, I think, came about
12 because the consumer advocates -- and again, this goes
13 all the way to -- it started with the consumers, but
14 also from my unique experience from the peanut farmers,
15 to the food industry that have to label their food.
16 And the absence of knowing a threshold dose and all
17 those complications, to restaurants, food preparing
18 people and so forth. Food allergy in general affects a
19 much larger population than you would actually have for
20 most other diseases. And so it affects, cross-

1 sectionally, a lot of the population from what you
2 wouldn't think of.

3 So when they started giving these doses
4 without controlled measurements, that's when it would
5 be dangerous. And that's what the community came
6 together and said. We need to have some kind of
7 controlled dosage to not let this get out of control
8 and really cause a danger to the community.

9 If you think of it in the context of that
10 history, of how this came about from the community, all
11 of us all coming together, then it changes the
12 perspective of where we are right now. And that's why
13 I said yes. Also, the efficacy of the data. Again, it
14 was a very impressive results.

15 **DR. PAUL GREENBERGER:** Thank you. Dr.
16 Hawkins.

17 **DR. RANDY HAWKINS:** Thank you. So I think the
18 data supported my answer for yes. I do want more
19 diversity in the studies of this nature. And this one,
20 specifically more Hispanics, particularly in Southern
21 California, African Americans and Asians.

1 I was a little concerned about -- and this was
2 not about all consumers. I hope there will not be
3 cavalier approach to a consumption of peanut products
4 just because something like this is available.

5 I'm pleased that they're going to be looking
6 at the eosinophilic esophagitis in ongoing studies. I
7 think the labeling is going to be really, really
8 important. I think everybody realizes that. And I
9 think it's going to be really, really important to
10 educate the prescribers. And hopefully, early on the
11 prescriber will have an opportunity to give feedback to
12 the FDA so that we can understand better what the
13 limitations of this product should be.

14 **DR. PAUL GREENBERGER:** Okay, thank you. And
15 we'll go to Dr. Gruber with question number 2. And
16 then Dr. Feingold, we're going to come to you.

17 **DR. IRA FINEGOLD:** Okay.

18 **DR. MARION GRUBER:** Dr. Greenberger, with your
19 permission and in light of the comments and some of the
20 concerns expressed by the committee, and in light of
21 the fact that we frame our question regarding the

1 safety data on the background that we will require a
2 Risk Evaluation and Mitigation Strategy, I would want
3 to take a couple of minutes to really explain what a
4 REMS, or a Risk Evaluation and Mitigation Strategy is.
5 And why it's different from a usual pharmacovigilance
6 or risk management plan. I think that maybe it will
7 help for the committee to understand why we ask the
8 safety question in the context thereof. Yeah? Thank
9 you so much.

10 As we've discussed this morning, or as was
11 mentioned, the usual and typical method for
12 communicating safety information about a drug product,
13 we use the professional labeling or the prescribing
14 information. However, if the Agency does not deem that
15 sufficient to clearly communicate the risks and
16 benefits of the drug, then we can require a drug
17 manufacturer to use what we refer to as a Risk
18 Evaluation and Mitigation Strategy, or REMS. And that
19 is in addition to, but beyond the professional labeling
20 to ensure that the benefits of the drug outweigh the

1 risks. And in this case, of course, we have identified
2 a safety signal.

3 Now FDA has the authority, then, to impose a
4 REMS program as a condition of approval. That is, if
5 the Agency requires for a REMS to be put in place, then
6 the drug would not be approved, or could not be
7 approved, without such REMS. So in considering whether
8 a REMS is warranted, the Agency considers a couple of
9 factors:

10 Such as, what is the seriousness of any known
11 or potential adverse event that may be related to the
12 drug? What is the expected benefit of the drug with
13 respect to the disease or condition? And what is the
14 seriousness of the disease or condition that is to be
15 treated with the drug?

16 And there are a couple of other
17 considerations, but I don't really want to take too
18 much time here.

19 But then, importantly, so if FDA determines
20 that a REMS program is necessary to mitigate the risks
21 of the use of the drug, the sponsor then must, and is

1 required to, develop a proposed REMS program. And FDA,
2 then, reviews and approves this REMS program. And this
3 is what we referred to this morning when we said we
4 have initiated discussions; and this is a work in
5 progress.

6 Each REMS program is very unique because it is
7 intended to address specific safety measures that are
8 tailored to the safety risks that are associated with
9 the drug. And there is a series of specific elements
10 that can be in a REMS program, such as a medication
11 guide or patient package insert, a communication plan
12 and elements to assure safe use.

13 And the questions to the committee here -- if
14 we want to look at the slide for a minute. We list and
15 we thought that three elements to assure safe use of
16 Palforzia are important. And that is the documentation
17 that any patient prescribed Palforzia has a valid
18 prescription for injectable epinephrine. That
19 caregivers and patients must attest to carrying
20 injectable epinephrine while on Palforzia. And that
21 the initial dose escalation, and the first dose of each

1 up-dosing level, must be administered in a certified
2 facility capable of treating systemic allergic
3 reactions. Again, we are in the process of discussing
4 this REMS program with the company.

5 What I also wanted to mention -- and perhaps
6 that goes in regard to a comment that was made by Dr.
7 Marshall. There is also an implementation plan. So
8 the company is required to take reasonable steps to
9 monitor and to evaluate the execution of the REMS by
10 health care providers, by pharmacists and others in the
11 health care system who are responsible.

12 And the point is, if there are violations to
13 the REMS, then there would be consequences to the
14 manufacturer. Because the drug could then be deemed
15 misbranded if there would be violations of the REMS.

16 So, I just thought I wanted to explain this to
17 you in order to better understand why we put all this
18 language here on this slide. Are there any questions
19 regarding this REMS before I read the safety question?

20 **DR. IRA FINEGOLD:** Yes.

21 **DR. PAUL GREENBERGER:** Dr. Finegold, go ahead.

1 **DR. IRA FINEGOLD:** Yeah. The question I have,
2 which falls in very nicely with this, is in the
3 question 2, in conjunction with "these." Why say these
4 if it's all in negotiation? Why don't say, "with
5 additional safeguards?"

6 Because I think there are more safeguards than
7 (a), (b) and (c). And interestingly enough, (b)
8 obviates (a) because you can't carry it unless it's
9 been prescribed. So why say both, but that's a little
10 -- anyway.

11 However, I think things like a black box
12 warning. I think like in a dosage-miss schedule, as I
13 asked about before. I think an informed consent.
14 Because it's clear that this therapy can hurt some
15 patients. And it's actually scheduled that patients
16 will have reactions. And somehow this has to be quite
17 clear that when people begin therapy, they know that in
18 advance. And so, I would love to say, yes, knowing
19 that it's going to be more than (a), (b) and (c).

1 **DR. MARION GRUBER:** To clarify, there will be
2 a med guide. There will be a black box warning in the
3 prescribing information.

4 The Agency felt that these three elements that
5 we referred to as "elements to assure safe use" are
6 important in addition to the other safeguards. That
7 being that are already put in place, either medication
8 guide and black box warning.

9 That being said, if the committee feels that
10 there are additional safeguards that should be
11 required, or that should be discussed here, we would be
12 happy to get your comments and suggestions on that.

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

14 **DR. GAILEN MARSHALL:** Dr. Gruber, one of the
15 things that comes up right away, that goes along with
16 this, is the issue of documentation. That it has been
17 discussed or agreed to -- again, pick the right verb --
18 with the patient and the family that this is for
19 prevention of accidental exposure as opposed -- we
20 heard the spectrum that I would have expected in the
21 public comments. And some people describing that now I

1 went through X and I can eat peanut butter and I can do
2 all that. It's very distinct from what the sponsor
3 presented. And it's very distinct from what's on the
4 table today.

5 And I happen to think all three of those, of
6 course, always picks out the right thing, and he's
7 right. Item (b) is redundant to (a) because you can't
8 do (b) until you've done (a). Though, I can argue that
9 there could be a parsing of that.

10 But regardless of that, is the idea of
11 actually also documentation somewhere so that the
12 provider is comfortable, and the caregiver/adolescent
13 patient is comfortable that desensitization is not
14 immune tolerance. The term tolerance gets thrown
15 around here; and I understand that because that's a
16 pharmaceutical term. But it's distinct from an immune
17 term of immune tolerance. And nowhere has the sponsor
18 claimed immune tolerance -- quite the contrary.
19 They've been very careful to parse out the difference
20 between tolerance and desensitization requiring
21 continued administration.

1 So in my mind, some commentary in there, if
2 you're going to do that, in that REMS, which I happen
3 to like -- I had heard about this, but I didn't know
4 the details. I think that it would be very important
5 to add that piece of it to it as well.

6 **DR. SOFIA CHAUDHRY:** Sofia Chaudhry, FDA.
7 Thank you for that feedback. This is very important to
8 us. I think you've probably heard, in multiple
9 committee discussions, often the discussion is more
10 important than the vote. So we appreciate that, and we
11 will take all of this into consideration.

12 I think some of the difficulties with (b)
13 being redundant to (a), we perhaps incorrectly we're
14 trying to boil down what comes across as legal and
15 statutory factors into clinical terminology. And we
16 failed.

17 But we are given certain legal factors that we
18 can pick. And then we work it out with the lawyers,
19 and we will discuss with Aimmune in terms of which
20 satisfies what. But what we want to hear from the
21 committee are what elements from a clinical perspective

1 -- and then we can work that out with them -- you're
2 interested in seeing.

3 **DR. PAUL GREENBERGER:** I would want something
4 that's not too burdensome. But I have two comments.
5 One is to have the Agency and the sponsor work together
6 to I guess give some "how to do it's." Like we have
7 for allergen immunotherapy. If you're a week late, you
8 can still go up on the dose, so to speak. That kind of
9 thing.

10 And perhaps this has to come from professional
11 societies, but I would like to see it from the
12 expertise from this side of the room with the expertise
13 on that side of the room. So if my patient gets hives
14 on the chest, again -- to my same story -- what do I do
15 the next day? And it said individual determinations,
16 but I have a feeling many of you over there know what
17 to do if there are hives on the chest. Or if my
18 stomach hurts a lot, what do I do?

19 And I don't know what's allowed statutory-
20 wise, but I think it'd be very informative so that

1 there can be optimal use of this product should it come
2 to be.

3 And the other one was perhaps considering like
4 a designated person in the office who has
5 responsibility for answering patient questions. Dr.
6 Brittain.

7 **DR. ERICA BRITTAIN:** I'm a little out of my
8 lane commenting on this, and maybe this isn't a REMS
9 issue at all. But it seems like one of the really
10 important things is that a year down the line, that
11 there's still some communication going on. That yes,
12 you have to continue -- if you're going to keep -- you
13 know, you have to continue with your maintenance or
14 else -- you know, things -- you can't -- especially if
15 people are getting a little more laxed about their
16 eating or their exposure, that they have to continue
17 with their maintenance.

18 And again, maybe that's not a REMS thing.

19 **DR. JOHN KELSO:** I think it's hard to argue
20 that this product is safe when it increases the risk of
21 the thing it is designed to prevent. I think another

1 thing that needs to be factored into that in this risk
2 management strategy, is the complexity. We've already
3 said that beyond (a), (b), and (c), there's these
4 issues that some circumstance has to be created around
5 the administration of each dose. Where you're not
6 exercising, you're not taking a hot shower, you're not
7 too tired, you don't have a cold.

8 The complexity of that, I think, contributes
9 to the safety issue because it adds an additional level
10 of risk. Because as I stated, in my opinion, even when
11 you're following the plan exactly, or you're in the
12 protocol, and you're doing all the things you're
13 supposed to, it still was risky.

14 But then if you add the additional layer of
15 complexity that with the administration of each dose,
16 you have to be in this very special circumstance, and
17 the issue of missed doses -- which are invariably going
18 to happen -- and the uncertainty about how many you can
19 miss before you have to back up and so forth. I just
20 think that complexity of that adds an additional layer
21 of risks that needs to be considered.

1 **DR. PAUL GREENBERGER:** Dr. Dykewicz.

2 **DR. MARK DYKEWICZ:** Just one other perspective
3 on this. What struck me not only with some of the
4 sponsors presentation, but also comments from the
5 public, was the importance of shared decision making
6 for this particular therapy. shared decision making is
7 always important in medicine. But it's particularly so
8 here because of the complexity of the issue and because
9 of the risks.

10 I think as part of the REMS approach, we want
11 to make sure that patients and families are being fully
12 informed about the risks involved. That there may be
13 an increased risk for need for epinephrine. But, you
14 know, really try to make sure that there's complete
15 understanding from the patient family perspective as
16 well as the practitioner perspective of risk/benefits.

17 **DR. PAUL GREENBERGER:** Okay. Dr. Gruber.

18 **DR. MARION GRUBER:** Well, in light of these
19 discussions, I think I would like to propose a slight
20 modification of Q2. I would like to propose to delete

1 the word "these" in front of additional. And I can
2 read the question then and it would be as follows:

3 "The available safety data in conjunction with
4 additional safeguards, adequate to support the use of
5 Palforzia in patients age 4 to 17 years with their
6 confirmed diagnosis of peanut allergy. Please vote yes
7 or no."

8 **CAPT. SERINA HUNTER-THOMAS:** Okay. So we have
9 all nine votes in. Total of eight yes votes and one no
10 vote. And reading individually: Dr. Apter, yes. Dr.
11 Brittain, yes. Dr. Marshall, yes. Dr. Finegold, yes.
12 Dr. Kelso, no. Dr. Dykewicz, yes. Dr. Greenberger,
13 yes. Dr. Hawkins, yes. And Dr. Maleki, yes.

14 **DR. PAUL GREENBERGER:** We'll go around the
15 room starting over on this side with Dr. Hawkins,
16 please.

17 **DR. RANDY HAWKINS:** Yes. I have nothing else
18 to add?

19 **DR. PAUL GREENBERGER:** Dr. Maleki.

20 **DR. SOHEILA MALEKI:** Yeah. I also don't have
21 much to add except that -- and this might not be quite

1 to the question. But I feel like the safety of
2 increasing the dose tolerance, which is probably more
3 to the last question, it is much safer for the patient
4 than perhaps maybe the accidental ingestion.

5 But in this case, I think with the provisions
6 that are added here -- and it's something that I think
7 that's already been thought about. And with the
8 clinician and patient engagement, is something as you
9 mentioned, the shared communications. And that's why I
10 said yes, basically.

11 **DR. PAUL GREENBERGER:** To interpret, your
12 voting yes, but it doesn't say like (d), patient shared
13 values or any of that, but you're voting yes?

14 **DR. SOHEILA MALEKI:** Yes.

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

16 **DR. GAILEN MARSHALL:** I voted yes, and
17 particularly given the Agency's comments to take out
18 the word "these" and just simply expanding this,
19 they're going to think about it and work with the
20 sponsor. It just increases my comfort level.

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

1 **DR. JOHN KELSO:** And I voted no for reasons
2 previously stated.

3 **DR. PAUL GREENBERGER:** Thanks. I voted yes, I
4 think, for reasons what I've said. And I think this is
5 a good approach. Dr. Apter.

6 **DR. ANDREA APTER:** I voted yes because I think
7 the REMS is very, very important to ensure the safety
8 of this product.

9 **DR. PAUL GREENBERGER:** Dr. Brittain.

10 **DR. ERICA BRITTAIN:** I voted yes. I did want
11 to make a couple of comments that the safety data were
12 a little hard to interpret because the groups were
13 changing over time. And we were losing a lot of the
14 reactive people in the active arm so that made the
15 safety hard to interpret. And here the safety and
16 efficacy are sort of not really different from each
17 other. They're very intermingled.

18 Also, just as I mentioned before, I think it's
19 important to think about long-term monitoring of these
20 patients; not just, you know, the period in which

1 they're doing they're up-dosing and early maintenance,
2 but, you know, year one, year two, year three?

3 **DR. PAUL GREENBERGER:** Are the available
4 safety data adequate to support the use of -- and
5 you're voting yes?

6 **DR. ERICA BRITTAIN:** I'm voting yes. I mean,
7 I'm just saying that it's not a perfect -- it's not
8 easy to interpret. So you know, it's just inherently
9 challenging because of the design.

10 **DR. PAUL GREENBERGER:** Okay. Thanks. Dr.
11 Dykewicz.

12 **DR. MARK DYKEWICZ:** Yes, for reasons
13 previously stated. With the one reminder of a comment
14 I made earlier about there may be a need to look at
15 patients who stop or fail to be able to tolerate the
16 course and what happens to them.

17 **DR. PAUL GREENBERGER:** Thank you. Dr.
18 Finegold.

19 **DR. IRA FINEGOLD:** I was just thinking. It's
20 about two months and fifty years since I gave my first
21 allergy shot as a resident or fellow. And we simply

1 didn't have the kind of data that we've heard today,
2 and the safety information and standardized product.
3 So allergen immunotherapy has come a long way.

4 And so, I think, even though this isn't
5 perfect, and it's obviously not for everybody, it'll go
6 a long way in helping patients and their quality of
7 life.

8 While I have the bully pulpit, so to speak,
9 and the FDA is listening in, my wife wanted me to say
10 something about the vaping epidemic and the need to
11 control that. It's not peanut allergy.

12 **DR. PAUL GREENBERGER:** You're an excellent
13 physician and that's an important subject in itself.
14 Thank you. Dr. Gruber, final comments?

15 **DR. MARION GRUBER:** We're sort of the Center
16 for Biologics, so vaping, these type of drugs are
17 really not under our purview. So you would have to go
18 to a different Center. And I'm really relieved,
19 because that's not our responsibility.

20 I actually wanted to say that I really very
21 much appreciate this discussion. I appreciate the

1 comments as much as I appreciate the concerns that were
2 expressed. Because we all will take this in
3 consideration, especially as we work with Aimmune to
4 really work out the details of the REMS program to
5 really ensure that the benefits of this product really
6 outweigh the risks.

7 I thank the committee very much for a very
8 productive discussion.

9 **DR. PAUL GREENBERGER:** And I thank everybody
10 here, and in particular the committee. And this
11 meeting is adjourned.

12 **[MEETING ADJOURNED]**