Application Type	Original Application
STN	125696/0
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Division / Office	DVRPA /OVRR
Committee Chair	Taruna Khurana
Clinical Reviewer(s)	Kathleen Hise
Project Manager	Diana Oram
Priority Review	No
Reviewer Name(s)	Lei Huang
Review Completion Date / Stamped Date	
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Applicant	Aimmune Therapeutics, Inc.
Established Name	Peanut (Arachis hypogaea) Allergen Powder
(Proposed) Trade Name	PALFORZIA
Pharmacologic Class	Allergenic
Formulation(s), including Adjuvants, etc	Peanut protein in capsules of 0.5, 1, 10, 20, and 100 mg dosage strengths, and in a sachet of 300 mg dosage strength.
Dosage Form(s) and Route(s) of Administration	Oral powder to be mixed with age-appropriate food prior to administration
Dosing Regimen	Administered in 3 sequential phases: Initial Dose Escalation, Up-Dosing, and Maintenance.
Indication(s) and Intended Population(s)	An oral immunotherapy indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. Initiation of PALFORZIA is approved in patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy. PALFORZIA may be continued in patients 18 years of age and older.

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GLOSSARY

Abbreviation/Term	Definition
AE	Adverse event
AESI	Adverse event of special interest
Aimmune	Aimmune Therapeutics, Inc.
BIMO	Clinical and bioresearch and monitoring
BLA	Biologics License Application
CI	Confidence Interval
CMC	Chemistry, manufacturing, and controls
CODIT	Characterized oral desensitization immunotherapy
CRO	Contract Research Organization
CSR	Clinical Study Report
DBPCFC	Double-blind, placebo-controlled food challenge
EoE	Eosinophilic Esophagitis
IDE	Initial Dose Escalation
IDMC	Independent data monitoring committee
ISS	Integrated summary of safety
ITT	Intent-To-Treat
MedDRA	Medical dictionary for regulatory activities
NaCl	Sodium chloride
NIDPOE	Notice of Initiation of Disqualification Proceedings and Opportunity to Explain
OIT	oral immunotherapy
PT	Preferred term
RR	Relative risk
SAE	Serious adverse event
SCS	Summary of Clinical Safety
SOC	System organ class

1. EXECUTIVE SUMMARY

Aimmune Therapeutics, Inc. (Aimmune) submitted the original Biologics License Application (BLA 125696) for AR101 (PALFORZIA), a characterized peanut allergen that is used in a regimented oral immunotherapy (OIT) protocol. AR101 is an oral immunotherapy indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. Initiation of AR101 is approved in patients aged 4 through 17 years with a confirmed diagnosis of peanut allergy. AR101 may be continued in patients 18 years of age and older. AR101 is not intended for the immediate relief of peanut allergy symptoms and should be used in conjunction with a peanut-avoidant diet.

The main clinical study supporting clinical efficacy was the Phase 3, international, randomized, double-blind, placebo-controlled pivotal study ARC003. An additional Phase 3, randomized, double-blind, placebo-controlled study, ARC007, evaluated safety during the up-dosing period.

Efficacy

In Study ARC003, treatment with AR101 resulted in a statistically significant treatment effect in the proportion of subjects aged 4 to 17 years who tolerated a single highest dose of at least 600 mg peanut protein with no more than mild symptoms at the exit double-blind, placebo-controlled food challenge (DBPCFC). Of the 372 subjects in the ITT population who received AR101, the desensitization response rate for the primary efficacy endpoint was 67.2% (95% CI: 62.3, 71.8), compared with 4.0% (95% CI: 1.7, 9.1) for 124 subjects who received placebo. The treatment difference (AR101-placebo) was 63.2% (95% CI: 53.0, 73.3; $p < 0.0001$), with the lower bound of the 95% CI exceeding the prespecified margin of 15%. The primary efficacy objective was met. Favorable treatment effects of AR101 compared with placebo were also observed for the key secondary endpoints in the age group of 4-17 years. The key secondary endpoint of tolerating 600 mg peanut protein in the adult group (18-55 years of age) was not met, likely due to small sample size and high discontinuation rate.

Safety

The safety profile of AR101 was based on 4 clinical studies involving 812 subjects aged 4 to 17 years who received at least 1 dose of AR101. These studies included the 2 completed, randomized, double-blind, placebo-controlled, phase 3 studies, ARC003 and ARC007, and their respective ongoing, uncontrolled, follow-on studies, ARC004 and ARC011.

Among subjects 4 to 17 years of age in Study ARC003, 328 (88.2%) AR101-treated subjects and 71 (57.3%) placebo-treated subjects had one or more treatment-related adverse events and symptoms; 43 (11.6%) AR101-treated subjects and 2 (1.6%) placebo-treated subjects discontinued study treatment due to an adverse event and allergy symptoms; 53 (14.2%) AR101-treated subjects and 4 (3.2%) placebo-treated subjects had 1 or more adverse events of systemic allergic reaction by any trigger (study product, food allergen, other allergen); 325 (87.4%) AR101-treated subjects and 86 (69.4%) placebo-

treated subjects had adverse events and symptoms of allergic reaction (hypersensitivity). A total of 8 (2.2%) AR101-treated subjects and 1 (0.8%) placebo-treated subject had 1 or more SAEs. One subject treated with AR101 had a severe, treatment-related adverse event of anaphylaxis during maintenance that was considered serious, required medical intervention, and resulted in study discontinuation. Fifty-two (14.0%) subjects in the AR101 group and 8 (6.5%) subjects in the placebo group had at least 1 episode of epinephrine use.

For subjects 18 to 55 years of age in Study ARC003, the overall pattern of adverse events and symptoms was similar. SAEs were reported during maintenance in 2 AR101-treated subjects (8.0%) and 1 placebo-treated subject (7.1%). No adult subject had an event of anaphylaxis to AR101. A total of 7 (17.1%) subjects in the AR101 group and 1 (7.1%) subjects in the placebo group had at least 1 episode of epinephrine use.

In Study ARC007, 304 (90.2%) AR101-treated subjects and 98 (58.3%) placebo-treated subjects had one or more treatment-related AEs; 41 (12.2%) AR101-treated subjects and 5 (3.0%) placebo-treated subjects discontinued study treatment due to an adverse event and allergy symptoms; 36 (10.7%) AR101-treated subjects and 9 (5.4%) placebo-treated subjects had 1 or more adverse events of systemic allergic reaction by any trigger (study product, food allergen, other allergen); 309 (91.7%) AR101-treated subjects and 126 (75.0%) placebo-treated subjects had adverse events and symptoms of allergic reaction (hypersensitivity). A total of 2 (0.6%) AR101-treated subjects and 2 (1.2%) placebo-treated subject had 1 or more SAEs. Four subjects treated with AR101 had a severe, treatment-related adverse event of anaphylaxis during the up-dosing period. Nonserious Eosinophilic Esophagitis (EoE) was reported in 2 AR101-treated subjects (0.6%). Thirty-seven (11.0%) subjects in the AR101 group and 9 (5.4%) subjects in the placebo group had at least 1 episode of epinephrine use. There was 1 unrelated death in study ARC007 (subject (b) (6), placebo), a craniocerebral injury sustained in a road traffic accident.

An integrated analysis of safety (ISS) was performed using safety data collected in four clinical studies, ARC003, ARC007, ARC004 and ARC011. In the controlled population, 626 (88.3%) AR101-treated subjects and 165 (56.5%) placebo-treated subjects had one or more treatment-related AEs during the initial dose escalation (IDE) and up-dosing combined period, and 159 (51.3%) AR101-treated subjects and 26 (22.0%) placebo-treated subjects had one or more treatment-related AEs during 300 mg/day maintenance dosing. Seventy-four subjects (10.4%) in the AR101 group and 14 subjects (4.8%) in the placebo group had at least 1 episode of epinephrine use during initial dose escalation and up-dosing combined. During 300 mg/day dosing in ARC003, 24 subjects (7.7%) in the AR101 group and 4 subjects (3.4%) in the placebo group had at least 1 episode of epinephrine use.

The overall summary of adverse events for the integrated safety population is consistent with the results for the controlled population. A total of 373 (45.9%), 678 (85.4%), and 352 (53.3%) AR101-treated subjects had one or more treatment-related AEs during IDE, up-dosing, and 300 mg/day maintenance dosing, respectively. Anaphylaxis (severe) was reported in 10 subjects (1.2% overall), including no subjects during initial dose

escalation, 5 subjects (0.6%) during up-dosing, and 5 subjects (0.8%) during all 300 mg/day dosing. The incidence of at least 1 episode of epinephrine use was lowest during initial dose escalation (2.0%) and highest during up-dosing (9.9%); the incidence was 8.2% during all 300 mg/day dosing.

Conclusion and Recommendations

The primary efficacy endpoint for study ARC003 met its pre-specified success criterion. Favorable treatment effects of AR101 compared to placebo were also observed for the key secondary endpoints in the age group of 4-17 years. On the other hand, a higher risk of allergic reaction was observed in AR101-treated subjects, and more subjects required the use of epinephrine to treat allergic reaction across all studies as compared to placebo-treated subjects. I defer to the clinical reviewer regarding the overall benefit-risk assessment of AR101.

2. CLINICAL AND REGULATORY BACKGROUND

The AR101 dosing regimen is administered in 3 sequential periods, or phases, i.e. initial dose escalation, up-dosing, and maintenance as follows:

- Initial dose escalation consists of 5 single doses of 0.5, 1, 1.5, 3, and 6 mg given at 20- to 30-minute intervals as tolerated during a single day.
- Dose escalation occurs approximately every 2 weeks with once daily doses of 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, and 300 mg/day.
- Maintenance dosing involves once daily dose of 300 mg.

The AR101 clinical development program in peanut-allergic children, adolescents, and adults includes two phase 2 studies (ARC001, ARC002) and six phase 3 studies (ARC003, ARC004, ARC007, ARC008, ARC010, ARC011). An additional phase 3 study is in start-up (ARC005). The two phase 2 studies (ARC001, ARC002) and two pivotal phase 3 studies (ARC003, ARC007) intended to support the licensure have been completed. The phase 3 follow-on studies (ARC004, ARC008, ARC011) support ongoing treatment. ARC010 supports European clinical development activities, and ARC005 supports the pediatric study plan (PSP)/pediatric investigational plan (PIP). The Food and Drug Administration (FDA) granted fast track designation for AR101 on 05 Sep 2014 for peanut-sensitive adults and children, and breakthrough therapy designation on 15 Jun 2015 for peanut-sensitive children and adolescents aged 4 to 17 years.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

Please refer to the medical and bioresearch monitoring (BIMO) reviews.

3.1 Submission Quality and Completeness

Submission quality is acceptable. The applicant responded to all information requests sent by the agency.

3.2 Compliance With Good Clinical Practices And Data Integrity

Please refer to the BIMO reviews.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

Please refer to the reviews of the corresponding discipline reviewers.

4.1 Chemistry, Manufacturing, and Controls

Please refer to the CMC review.

4.2 Assay Validation

Please refer to the CMC/bioassay reviews.

4.3 Nonclinical Pharmacology/Toxicology

Not applicable.

4.4 Clinical Pharmacology

Not applicable.

4.5 Clinical

Please refer to the medical officer's review.

4.6 Pharmacovigilance

Please refer to the pharmacovigilance review.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The main clinical study supporting clinical efficacy was Study ARC003, and no integrated analysis of efficacy was performed. Therefore, efficacy review focuses on the efficacy data in Study ARC003.

Safety reviews for individual studies ARC003 and ARC007 are performed for all subjects in the safety analysis set in Section 6. ISS is presented in Section 8.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

This review is based on the applicant's original BLA submission (STN125696/0) dated December 21, 2018 and subsequent amendments (Amendments #7, #25, #28, #32, and #35) to the original submission, primarily Modules 2 and 5 in the Electronic document Room (EDR).

5.3 Table of Studies/Clinical Trials

Table 1 provides a summary of clinical studies in the AR101 program in peanut-allergic subjects.

Table 1. Summary of Clinical Studies in the AR101 Program in Peanut-Allergic Subjects

Study [1]	Status, Location	Study design	Ages	Primary outcome measure
ARC001 NCT01987817	Completed US	Phase 2, randomized, double-blind, placebo-controlled	4-26 years	Efficacy: Proportion of subjects who achieve desensitization (tolerate at least 300 mg [443 mg cumulative] of peanut protein with no more than mild symptoms at the exit DBPCFC)
ARC002 NCT02198664	Completed US	Phase 2 open-label follow-on for ARC001	Per prior study	Safety: Incidence of treatment-related adverse events and dosing symptoms occurring with peanut OIT over a treatment period of at least 18 months
ARC003 NCT02635776 2015-004257-41	Completed CA, EU, US	Phase 3, randomized, double-blind, placebo-controlled	4-55 years	Efficacy: Proportion of subjects aged 4-17 years who achieve desensitization (tolerate peanut protein [North America: single highest dose of at least 600 mg, 1043 mg cumulative; Europe: single highest dose of at least 1000 mg, 2043 mg cumulative] with no more than mild symptoms at the exit DBPCFC)
ARC004 NCT02993107 2016-004941-94	Ongoing CA, EU, US	Phase 3 open-label follow-on for ARC003	Per prior study	Safety: Frequency of treatment-related adverse events and serious adverse events during the overall study period
ARC005 NCT03736447 2018-001749-15	Start-up EU, CA, US	Phase 3, randomized, double-blind, placebo-controlled	1 to < 4 years	tolerated dose of at least 600 mg peanut protein with no more than mild symptoms in an exit DBPCFC
ARC007 NCT03126227	Completed CA, US	Phase 3, randomized, double-blind, placebo-controlled	4-17 years	Safety: Frequency of treatment-emergent adverse events including serious adverse events during the overall study period
ARC008 NCT03292484 2017-001334-26	Ongoing CA, EU, US	Open-label follow-on for designated current (ARC002, ARC004, ARC007, ARC010, and ARC011) and future AR101 studies	Per prior study	treatment-emergent adverse events during the overall study period
ARC010 NCT03201003 2016-005004-26	Ongoing EU	Phase 3, randomized, double-blind, placebo-controlled	4-17 years	Efficacy: Proportion of subjects who achieve desensitization (tolerate a single dose of at least 1000 mg [2043 mg cumulative] of peanut protein with no more than mild symptoms at the exit DBPCFC)
ARC011 NCT03337542	Ongoing CA, US	Phase 3 open-label maintenance for ARC007 (AR101-treated)	Per prior study	Safety: Frequency of treatment-emergent adverse events including serious adverse events during the overall study period

- Completed indicates a CSR is available.
[1] Protocol number, ClinicalTrials.gov, EudraCT (as applicable).

CA, Canada; CSR, clinical study report; DBPCFC, double-blind placebo-controlled food challenge; EU, European Union; OIT, oral immunotherapy; US, United States.
Source: Table 1 in Module 2.5 Clinical Overview.

5.4 Consultations

5.4.1 Advisory Committee Meeting

On September 13, 2019, an Allergenic Products Advisory Committee meeting was held to discuss and make recommendations on the safety and efficacy of AR101. The following two questions were presented to the committee:

Question 1: Are the available efficacy data adequate to support the use of PALFORZIA as a treatment to reduce the incidence and severity of allergic reactions, including anaphylaxis, after accidental exposure to peanut in patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy?

Question 2: Are the available safety data, in conjunction with additional safeguards, adequate to support the use of PALFORZIA in patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy?

Seven and two committee members voted Yes and No, respectively, for Question 1, and eight and one committee members voted Yes and No, respectively, for Question 2.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

Studies ARC003 and ARC007 are discussed in the following subsections.

6.1 Trial #1: ARC003

This protocol was entitled “Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE).”

6.1.1 Objectives

Primary Objective
The primary objective is to demonstrate the efficacy of AR101, a pharmaceutical-grade peanut allergen formulation, through reduction in clinical reactivity to limited amounts of peanut allergen in peanut-allergic children (ages 4-17 years, inclusive).

Secondary Objectives

- To demonstrate the safety of AR101 as measured by the incidence of adverse events, including serious adverse events in children (ages 4-17 years, inclusive).
- To evaluate the immunological effects of peanut OIT therapy in children (ages 4-17 years, inclusive).

6.1.2 Design Overview

ARC003 was a phase 3, international, randomized, double-blind, placebo-controlled study consisting of screening and double-blind treatment periods that included initial

dose escalation (2 days), up-dosing (20-40 weeks), and maintenance (approximately 24-28 weeks). Subjects aged 4 to 55 years who had dose-limiting symptoms after consuming ≤ 100 mg peanut protein (144 mg cumulative) of food challenge material in a DBPCFC at screening were randomly assigned (3:1) to AR101 or placebo. Randomization was stratified by broad geographic region (to include North America and Europe) and age (children aged 4-17 years, inclusive, and adults aged 18-55 years, inclusive). At least 80% of subjects were children aged 4 to 17 years.

During initial dose escalation on day 1 at each study site, subjects received escalating doses of AR101 (0.5-6 mg) or placebo at 20- to 30-minute intervals and were monitored for at least 90 minutes after completion of dose escalation. On day 2, tolerability of 3 mg AR101 or placebo was confirmed. During up-dosing, subjects received escalating doses from 3 to 300 mg/day AR101 or placebo at 2-week intervals as tolerated. Study product doses could be reduced, held, or withheld due to adverse events or allergy symptoms at each investigator's discretion. Subjects who tolerated 300 mg/day AR101 or placebo continued receiving that dose for maintenance treatment.

Efficacy was evaluated in an exit DBPCFC for subjects who tolerated 300 mg/day for 24 weeks (end of maintenance). Single doses of 3, 10, 30, 100, 300, 600, and 1000 mg peanut protein (2043 mg cumulative) were evaluated in the DBPCFC. Treatment assignment was unblinded after the DBPCFC; placebo-treated subjects and those receiving AR101 who tolerated at least 300 mg in the DBPCFC could receive AR101 in the follow-on study, ARC004. Maintenance visits were to continue every 30 days until study completion and enrollment in ARC004. Safety assessments included adverse events and allergy symptoms, anaphylaxis, accidental exposures to food allergens, epinephrine use, lung function evaluations, physical examinations, vital signs, concomitant medications, and laboratory analyses as appropriate.

6.1.3 Population

Subjects aged 4 to 55 years who are allergic to peanut.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The active study product, AR101, is characterized peanut allergen in the form of peanut flour, formulated with a (b) (4) in pre-measured graduated doses, comprising capsules containing 0.5, 1, 10, 20, and 100 mg each of peanut protein. Placebos, containing only excipients that are color-matched to the peanut flour, are provided as matching capsules, identical to the active capsules. For maintenance dosing, 300 mg of peanut protein are provided in sealed, foil-laminate sachets requiring one sachet/day. Matching placebo containing sachets are also provided.

6.1.6 Sites and Centers

The study was conducted in 66 study sites in 10 countries in North America and Europe.

6.1.7 Surveillance/Monitoring

Please refer to the medical officer's review.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint
The primary endpoint is the proportion of subjects aged 4 to 17 years who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC.

AR101 is considered to have met the success criterion for the primary efficacy endpoint if the lower bound of the 95% confidence interval of the difference in response rates (AR101 minus placebo) is greater than the pre-specified margin of 0.15.

Secondary Endpoints
Efficacy (Key secondary endpoints)

- The proportions of subjects aged 4 to 17 years who tolerate a single highest dose of at least 300 mg and 1000 mg (443 mg and 2043 mg cumulative, respectively) of peanut protein with no more than mild symptoms at the Exit DBPCFC
- The maximum severity of symptoms in subjects aged 4 to 17 years occurring at any challenge dose of peanut protein during the Exit DBPCFC
- The proportion of subjects aged 18 to 55 years who tolerate a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC

Safety

- The safety of peanut OIT based on adverse events (AEs) including serious adverse events (SAEs), use of epinephrine as a rescue medication during OIT (Initial Escalation, Up-dosing, and Maintenance Periods), Frequency of anaphylaxis during OIT, in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive
- The frequencies of allergic reaction (hypersensitivity), accidental ingestions of peanut and other allergenic foods, premature discontinuation of dosing due to AEs, and premature discontinuation due to chronic/recurrent gastrointestinal (GI) AEs, in the following 5 age groups: 4 to 17 years, 4 to 11 years, 12 to 17 years, 18 to 55 years, and 4 to 55 years, inclusive

6.1.9 Statistical Considerations & Statistical Analysis Plan

The primary efficacy analysis tested for a treatment difference in the response rate in the ITT population, which included all subjects randomly assigned to treatment who received at least 1 dose of study product. All individuals failing to achieve the success definition were considered treatment failures, as were subjects who failed to achieve and maintain a 300 mg daily dose of study product (escalation failure nonresponders). All individuals who dropped out of the study or discontinued OIT prior to undergoing the Exit DBPCFC were considered treatment failures (i.e. Missing = Failure). The Farrington-Manning test was used to test the null hypothesis that the difference in response rates is equal to 0.15 at the 0.05 significance level.

The statistical analyses for key secondary efficacy endpoints in terms of proportions were similar to that used in the primary efficacy endpoint. The Cochran-Mantel-Haenszel

(CMH) statistic was used to test for treatment difference, stratified by region, for maximum severity of symptoms at the Exit DBPCFC. The key secondary efficacy endpoints were tested hierarchically at the 0.05 level in the order specified in Section 6.1.8. The closed testing procedure maintains the overall type I error rate at 0.05.

The safety population was used for all safety analyses. Safety analyses were summarized by treatment received. Treatment exposure was summarized by age group (4-17 years and 18-55 years), treatment (AR101 and placebo), and study period (initial dose escalation, up-dosing, maintenance, and overall). Adverse events were classified by system organ class and preferred term using the MedDRA version 18.1. Treatment-emergent adverse events were defined as adverse events with onset after the first dose of study product.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 750 subjects aged 4 to 17 years were screened and 499 were randomly assigned to study treatment (374 to AR101 and 125 to placebo). Of the 374 subjects randomly assigned to AR101, 2 did not receive treatment (1 withdrew consent and 1 due to randomization error). Of the 125 subjects randomly assigned to placebo, 1 withdrew consent before receiving treatment.

A total of 92 subjects aged 18 to 55 years were screened and 56 were randomly assigned to study treatment (42 to AR101 and 14 to placebo). Of the 42 subjects randomly assigned to AR101, 1 no longer met eligibility criteria. All 14 subjects randomly assigned to placebo received treatment.

6.1.10.1.1 Demographics

<u>4 to 17 Years</u>

The median age was 9 years and was the same for both treatment groups. Most subjects were male (55.9% AR101, 61.3% placebo) and white (78.5%, 78.2%). The proportion of Asian subjects was higher in the AR101 group (11.0%) compared with the placebo group (6.5%). Black subjects made up less than 2% of the total pediatric population (1.6% AR101, 2.4% placebo). Most subjects were enrolled in North America (81.0%) compared with Europe (19.0%); the proportion of geographic region was similar between treatment groups.

The baseline median total IgE in pediatric subjects was numerically higher in the placebo group (469.0 IU/mL) compared with the AR101 group (416.0 IU/mL). The median mean wheal diameter in the screening skin prick test to peanut was 11.0 mm (range: 0-37 mm) for the AR101 group and 12.0 mm (range: 2-40 mm) for the placebo group. More than half of the subjects in each treatment group had a history of asthma (53.2% AR101 and 52.4% placebo).

<u>18 to 55 Years</u>

The median age of subjects was 24.0 years for the AR101 group and 22.0 years for the placebo group. Sixty-one percent of the subjects in the AR101 group and 42.9% in the

placebo group were male. For the AR101 group, 58.5% were enrolled in North America and 41.5% in Europe. For the placebo group, 64.3% were enrolled in North America and 35.7% in Europe. The baseline median total IgE in adult subjects was numerically higher in the placebo group (281.0 IU/mL) compared with the AR101 group (201.0 IU/mL). The median mean wheal diameter in the screening skin prick test to peanut was 12.5 mm (range: 6-20 mm) for the AR101 group and 12.0 mm (range: 5-29 mm) for the placebo group. More than half of the subjects in both treatment groups had a history of asthma (58.5% AR101 and 85.7% placebo).

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Please refer to the medical officer's review.

6.1.10.1.3 Subject Disposition
4 to 17 Years
A total of 294 of 374 (78.6%) subjects in the AR101 group and 115 of 125 (92.0%) subjects in the placebo group completed the study. The most common reason for discontinuation of study treatment was subject withdrew consent (31 [8.3%] AR101 and 6 [4.8%] placebo), followed by adverse event (34 [9.1%] AR101 and 2 [1.6%] placebo). Other reasons for study treatment discontinuation were reported for 5 (1.0%) or fewer subjects in either treatment group.

18 to 55 Years
A total of 20 of 42 (47.6%) subjects in the AR101 group and 13 of 14 (92.9%) subjects in the placebo group completed the study. The most common reason for discontinuation of study treatment was subject withdrew consent (10 [23.8%] AR101 and 1 [7.1%] placebo), followed by adverse event (6 [14.3%] AR101) and up-dosing failure (2 [4.8%] AR101). Other reasons for study treatment discontinuation were reported in 4 (9.5%) subjects in the AR101 group.

6.1.11 Efficacy Analyses

The ITT population for subjects aged 4 to 17 years (372 AR101-treated subjects, 99.5% and 124 placebo-treated subjects, 99.2%) was used as the primary analysis population for all primary and secondary efficacy endpoints.

6.1.11.1 Analyses of Primary Endpoint(s)

The success criterion for the primary efficacy endpoint was met. As shown in Table 2, treatment with AR101 resulted in a statistically significant treatment effect, consistent with meaningful clinical benefit over placebo, in the proportion of subjects aged 4 to 17 years who tolerated a single highest dose of at least 600 mg peanut protein with no more than mild symptoms at the exit DBPCFC. Of 372 subjects in the ITT population who received AR101, the desensitization response rate for the primary efficacy endpoint was 67.2% (95% CI: 62.3, 71.8) compared with 4.0% (95% CI: 1.7, 9.1) for 124 subjects who received placebo. The treatment difference (AR101-placebo) was 63.2% (95% CI: 53.0, 73.3); $p < 0.0001$, with the lower bound of the 95% CI exceeding the prespecified margin of 0.15 (Table 2).

Table 2. Summary of Primary Efficacy Endpoint (ITT Population)

Primary Endpoint	**AR101 N=372**	**Placebo N=124**
Response rate: proportion of subjects who tolerated 600 mg peanut protein (95% CI), 4-17 y [1]	67.2% (62.3, 71.8)	4.0% (1.7, 9.1)
Treatment difference (compared to placebo) [95% CI] [2]	63.2% (53.0, 73.3)	-
P-value [2]	< 0.0001	-

Subjects without an exit DBPCFC were counted as nonresponders.
[1] Based on Wilson (score) confidence limits.
[2] Based on the Farrington-Manning confidence limits.
Source: adapted from Table 23 of the ARC003 CSR.

Reviewer Comments

1. *The applicant performed a series of sensitivity analyses for the primary efficacy endpoint, including worst-case imputation (placebo-treated subjects with missing exit DBPCFC data were considered as responders, while AR101-treated subjects with missing exit DBPCFC data were considered nonresponders), tipping point analysis, exclusion of subjects with indeterminate exit DBPCFC, and stratification by geographic region and/or age group. The results were consistent with the primary ITT analysis with statistical significance at the 0.05 level in all sensitivity analyses, except for the subgroup for the European region aged 12-17 years where treatment difference (95% CI) was estimated as 25.9% (-33.2%, 85.0%). However, the lack of statistical significance is likely due to limited sample size in this stratum (N=27 and N=3 for AR101 and placebo groups, respectively). Overall, I consider the efficacy analysis results robust.*

2. *A total of 24 subjects (all 4-17 years of age, 16 in AR101 group and 8 in placebo group) had a more than mild allergic reaction towards the placebo challenge at the exit DBPCFC. The applicant performed sensitivity analysis with the 24 subjects who did not pass 1000 mg placebo challenge excluded, and results did not change the overall efficacy conclusion. An additional 2 subjects (both 4-17 years of age and in the AR101 group) did not participate in DBPCFC with placebo challenge. I consider it more appropriate to exclude these 2 subjects in the sensitivity analysis as well. Nevertheless, both subjects failed to tolerate 600 mg peanut protein. Hence, the impact of these two subjects on the sensitivity analysis results is considered minimal.*

3. *A total of 36 subjects either did not have planned exit DBPCFC sequence or did not follow the planned exit DBPCFC sequence, 29 of which were aged 4-17 years and 7 of which were aged 18-55 years. In the July 30, 2019 IR response, the applicant clarified that the study sites used the incorrect (screening) module in the interactive response system for 14 subjects, and it was unclear why a sequence was not obtained for the other 22 subjects. The applicant concluded that the difference in randomization sequence did not create any concern about*

subject safety or serious breach of good clinical practice. I performed additional analysis excluding these subjects, and the results did not change the conclusion.

6.1.11.2 Analyses of Secondary Endpoints

The success criteria for the key secondary endpoints of the proportions of subjects who tolerated a single highest dose of at least 300 mg and 1000 mg peanut protein, respectively, with no more than mild symptoms at the exit DBPCFC were met. Of 372 subjects aged 4 to 17 years in the ITT population who received AR101, the desensitization response rate was 76.6% (95% CI: 72.1, 80.6) compared with 8.1% (95% CI: 4.4, 14.2) for 124 subjects who received placebo, and 50.3% (95% CI: 45.2, 55.3) compared with 2.4% (95% CI: 0.8, 6.9) for 124 subjects who received placebo, at 300 mg and 1000mg, respectively. The treatment difference (AR101-placebo) was 68.5% (95% CI: 58.6, 78.5) and 47.8% (95% CI: 38.0, 57.7) at 300 mg and 1000 mg, respectively. The p-values were < 0.0001 for both challenge doses.

The success criterion for the key secondary endpoint of the maximum severity of symptoms at any challenge dose at the exit DBPCFC for subjects aged 4 to 17 years was met. At any dose of peanut protein tested, AR101-treated subjects had less chance of developing more severe levels of symptoms compared with placebo-treated subjects. The maximum severity of symptoms was none for 37.6% of subjects in the AR101 group and 2.4% of subjects in the placebo group. The maximum severities of symptoms were mild for 32.0% and 28.2% of subjects (AR101 and placebo), moderate for 25.3% and 58.9%, and severe for 5.1% and 10.5%. The p-value was < 0.0001 for the treatment difference in maximum severity of symptoms at any challenge dose.

The key secondary efficacy endpoint of the proportion of subjects aged 18 to 55 years in the ITT population who tolerated a single highest dose of at least 600 mg peanut protein with no more than mild symptoms at the exit DBPCFC was 41.5% (95 CI: 27.8, 56.6) for the AR101 group and 14.3% (95% CI: 4.0, 39.9) for the placebo group. The success criterion for this endpoint was not met. The treatment difference (AR101-placebo) was 27.2% (95% CI: -1.7, 56.0) and was not statistically significantly different than a treatment difference of 0% (p = 0.0648) or 15% (p = 0.3672).

The efficacy results for key secondary endpoints are summarized in Table 3.

Table 3. Summary of Key Secondary Efficacy Endpoints (ITT Population)

Key Secondary Endpoints	**AR101**	**Placebo**
Subjects Aged 4-17 y, n	N=372	N=124
Response rate: proportion of subjects who tolerated 300 mg peanut protein (95% CI), 4-17 y [1]	76.6% (72.1, 80.6)	8.1% (4.4, 14.2)
Treatment difference (compared to placebo) [95% CI] [2]	68.5% (58.6, 78.5)	-
P-value [2]	< 0.0001	-
Response rate: proportion of subjects who tolerated 1000 mg peanut protein (95% CI), 4-17 y [1]	50.3% (45.2, 55.3)	2.4% (0.8, 6.9)
Treatment difference (compared to placebo) [95% CI] [2]	47.8% (38.0, 57.7)	-
P-value [2]	< 0.0001	-
Max severity of symptoms at any challenge dose, 4-17 y [3]		
None	140 (37.6%)	3 (2.4%)
Mild	119 (32.0%)	35 (28.2%)
Moderate	94 (25.3%)	73 (58.9%)
Severe or higher (life-threatening or fatal) [4]	19 (5.1%)	13 (10.5%)
P-value [5]	< 0.0001	-
Subjects Aged 18-55 y, n	N = 41	N = 14
Response rate: proportion of subjects who tolerated 600 mg peanut protein (95% CI), 18-55 y [1]	41.5% (27.8, 56.6)	14.3% (4.0, 39.9)
Treatment difference (compared to placebo) [95% CI] [2]	27.2% (-1.7, 56.0)	-
P-value [2]	0.0648	-

Subjects without an exit DBPCFC were counted as nonresponders.
[1] Based on Wilson (score) confidence limits.
[2] Based on the Farrington-Manning confidence limits.
[3] Subjects without an exit DBPCFC were assigned the maximum severity of symptoms during the screening DBPCFC (no change from screening).
[4] No subjects had symptoms considered life-threatening or fatal.
[5] Treatment difference was tested using the Cochran-Mantel-Haenszel statistic (with equally spaced scores) stratified by geographic region (North America, Europe).
Source: Adapted from Table 29 in the ARC003 CSR.

Reviewer Comments

1. *Regarding the third key secondary endpoint (maximum severity of symptoms at any challenge dose at the exit DBPCFC for subjects aged 4 to 17 years), I have the following comments:*
    a. *The applicant included "tables regionn*aval*trtn / cmh2" in the submitted SAS analysis programs. Since the Cochran-Mantel-Haenszel test in SAS compares mean row scores, the applicant's program compared the mean treatment scores (with AR101 being 1 and placebo being 2) across each severity level stratified by region instead of the mean severity scores across each treatment arm. The correct specification should be* (b) (4) *. Nevertheless, the p-value was <0.0001 in either analysis, and hence the conclusion stays the same.*
    b. *The applicant used the CMH statistic to summarize the maximum severity of symptoms. This is essentially equivalent to a stratified ANOVA test for the mean score across two treatment groups. It should be noted that the maximum severity of none, mild, moderate, and severe or higher were assigned scores of 0, 1, 2, and 3, respectively. The interpretability of the mean score may be challenging from a clinical perspective, i.e. two groups with comparable mean scores may not be clinically comparable. For example, in Group 1 with 2 subjects, one subject has mild symptoms (score=1) and one subject has moderate symptoms (score=2); in Group 2 with 2 subjects, one subject has no symptoms (score=0) and one subject has severe symptoms (score=3). The mean scores for both groups are equivalent (mean score=1.5), while the clinical interpretation of safety for the two groups may be different.*
    c. *I fitted a cumulative logit model with proportional odds and continuation-ratio logits model including treatment and region as covariates as sensitivity analyses. Some violation of the assumption of proportional odds was observed. I also tried combining severity categories in various ways (None v.s. Mild+Moderate+Severe or higher, None+Mild v.s. Moderate+Severe or higher, and None+Mild+Moderate v.s. Severe or higher) to collapse the table into a two-by-two table with a variety of statistical methods applied. In any case, the treatment difference is statistically significant at 0.05 level indicating a higher odds ratio towards lower severity for the AR101 group. Collectively, I consider the conclusion regarding this endpoint to be robust.*
2. *In the Response to FDA Information Request #11 (Email Correspondence dated 05 July 2019) submitted to STN 125696/0.25, the applicant provided additional analyses of the primary endpoint by eliciting dose of peanut protein in the entry DBPCFC (1 mg, 3 mg, 10 mg, 30 mg, and 100 mg), stratified by age group. The point estimates of treatment effect ranged from 47.0% to 67.9% for subjects 4-17 years of age, and from 14.3% to 27.9% for subjects 18- 55 years of age. No discernible trend of efficacy versus eliciting dose at entry DBPCFC was observed.*

6.1.11.3 Subpopulation Analyses

Subgroup analyses of the primary efficacy endpoint were performed by sex, race and ethnicity, and results were all consistent with statistical significance at the 0.05 level, except for the black and African American subgroup, where treatment difference was estimated as 66.7% (-2.2%, 100.0%). The lower bound of the CI did not exceed 15% likely because of the small sample size in this subgroup (6 in the AR101 group and 3 in the placebo group).

6.1.12 Safety Analyses

The median overall exposure to the study treatments was 330.5 days for the AR101 group and 328.0 days for the placebo group in subjects 4 to 17 years old; the median overall exposure was 315.0 days for the AR101 group and 327.0 days for the placebo group in subjects 18 to 55 years old.

6.1.12.1 Adverse Events

4 to 17 Years

Treatment-emergent AEs, excluding those that occurred during the exit DBPCFC, are summarized in Table 4 for the pediatric population. Overall, 98.7% of subjects in the AR101 group and 95.2% of subjects in the placebo group had one or more AEs and allergy symptoms. The overall exposure-adjusted AE rate (the total number of events divided by the total exposure in terms of subject-years) was 53.80 events per subject-year for the AR101 group and 18.33 events per subject-year for the placebo group. Exposure-adjusted adverse event rates declined from up-dosing to maintenance in both groups (76.67 to 27.02 for AR101 and 25.00 to 11.29 for placebo). Most adverse events and symptoms were mild or moderate intensity in severity.

Overall, 328 (88.2%) AR101-treated subjects and 71 (57.3%) placebo-treated subjects had one or more treatment-related adverse events and symptoms; 43 (11.6%) AR101-treated subjects and 2 (1.6%) placebo-treated subjects discontinued study treatment due to an adverse event and allergy symptom; 53 (14.2%) AR101-treated subjects and 4 (3.2%) placebo-treated subjects had 1 or more adverse events of systemic allergic reaction by any trigger (study product, food allergen, other allergen); 325 (87.4%) AR101-treated subjects and 86 (69.4%) placebo-treated subjects had adverse events and symptoms of allergic reaction (hypersensitivity); Accidental food allergen exposures and adverse events associated with accidental food allergen exposures were less common overall in the AR101 group (73 subjects; 19.6%) compared with the placebo group (41 subjects; 33.1%).

The most common treatment-related AEs in the AR101 group are abdominal pain (47.6%), oral pruritus (39.0%), and throat irritation (36.8%), as compared to 19.4%, 12.9%, and 12.9% respectively in the placebo group.

Table 4. Overview of Treatment-Emergent AEs and Symptoms (ARC003 Safety population, 4-17 Year)

	IDE	**IDE**	**Up- Dosing**	**Up-Dosing**	**Maintenance**	**Maintenance**	**Overall**	**Overall**
	AR101 (N=372)	**Placebo (N=124)**	**AR101 (N=366)**	**Placebo (N=123)**	**AR101 (N=310)**	**Placebo (N=118)**	**AR101 (N=372)**	**Placebo (N=124)**
Total exposure (years)	2.02	0.68	155.43	50.56	149.58	57.55	307.03	108.79
Total AEs	561	80	11917	1264	4041	650	16519	1994
Total SAE	0	0	4	0	5	1	9	1
Subjects with at least 1 AE	189 (50.8%)	36 (29.0%)	353 (96.4%)	108 (87.8%)	270 (87.1%)	94 (79.7%)	367 (98.7%)	118 (95.2%)
AE by severity [1]								
Mild	170 (45.7%)	33 (26.6%)	147 (40.2%)	69 (56.1%)	161 (51.9%)	57 (48.3%)	129 (34.7%)	62 (50.0%)
Moderate	19 (5.1%)	3 (2.4%)	197 (53.8%)	38 (30.9%)	101 (32.6%)	37 (31.4%)	222 (59.7%)	55 (44.4%)
Severe	0	0	9 (2.5%)	1 (0.8%)	8 (2.6%)	0	16 (4.3)	1 (0.8%)
Life-threatening or death	0	0	0	0	0	0	0	0
AE by relationship to study product [2]								
Not related	16 (4.3%)	9 (7.3%)	46 (12.6%)	45 (36.6%)	111 (35.8%)	68 (57.6%)	39 (10.5%)	47 (37.9%)
Related	173 (46.5%)	27 (21.8%)	307 (83.9%)	63 (51.2%)	159 (51.3%)	26 (22.0%)	328 (88.2%)	71 (57.3%)
AE leading to study product discontinuation	4 (1.1%)	1 (0.8%)	35 (9.6%)	1 (0.8%)	4 (1.3%)	0	43 (11.6%)	2 (1.6%)
AE of systemic allergic reaction (anaphylactic reaction), including anaphylaxis [3]	1 (0.3%)	0	31 (8.5%)	2 (1.6%)	27 (8.7%)	2 (1.7%)	53 (14.2%)	4 (3.2%)
AE of allergic reaction	174 (46.8%)	28 (22.6%)	293 (80.1%)	68(55.3%)	169 (54.5%)	48 (40.7%)	325 (87.4%)	86 (69.4%)
AE associated with an accidental food allergen exposure	1 (0.3%)	1 (0.8%)	54 (14.8%)	26 (21.1%)	28 (9.0%)	24 (20.3%)	73 (19.6%)	41 (33.1%)
Subjects with at least 1 SAE	0	0	4 (1.1%)	0	4 (1.3%)	1 (0.8%)	8 (2.2%)	1 (0.8%)
SAE by severity [1]								
Mild	0	0	1 (0.3%)	0	0	1 (0.8%)	1 (0.3%)	1 (0.8%)
Moderate	0	0	2 (0.5%)	0	2 (0.6%)	0	4 (1.1%)	0
Severe	0	0	1 (0.3%)	0	2 (0.6%)	0	3 (0.8%)	0
Life-threatening or death	0	0	0	0	0	0	0	0
SAE by relationship to study product [2]								
Not related	0	0	1 (0.3%)	0	3 (1.0%)	1 (0.8%)	4 (1.1%)	1 (0.8%)
Related	0	0	3 (0.8%)	0	1 (0.3%)	0	4 (1.1%)	0

Table 4. Overview of Treatment-Emergent AEs and Symptoms (ARC003 Safety population, 4-17 Year)- cont'd

	IDE	IDE	Up- Dosing	Up-Dosing	Maintenance	Maintenance	Overall	Overall
	AR101 (N=372)	**Placebo (N=124)**	**AR101 (N=366)**	**Placebo (N=123)**	**AR101 (N=310)**	**Placebo (N=118)**	**AR101 (N=372)**	**Placebo (N=124)**
Exposure-adjusted events rate, events (rate) [4]								
AEs	561 (277.65)	80(118.30)	11917 (76.67)	1264 (25.00)	4041 (27.02)	650 (11.29)	16519 (53.80)	1994 (18.33)
AEs related to study product	519 (256.86)	63 (93.16)	9284 (59.73)	469 (9.28)	2686 (17.96)	85 (1.48)	12489 (40.68)	617 (5.67)
AEs with severity of severe or greater	0	0	11 (0.07)	1 (0.02)	16 (0.11)	0	27 (0.09)	1 (0.01)
SAEs	0	0	4 (0.03)	0	5 (0.03)	1 (0.03)	9 (0.03)	1 (0.01)
SAEs related to study product	0	0	3 (0.02)	0	1 (0.01)	0	4 (0.01)	0
SAEs with severity of severe or greater	0	0	1 (0.01)	0	2 (0.01)	0	3 (0.01)	0

Maintenance and overall columns exclude symptoms recorded during the exit double-blind, placebo-controlled food challenge.
[1] Subjects with more than 1 adverse event were counted only once using the highest severity.
[2] Subjects with more than 1 adverse event were counted only once using the closest relationship to study product.
[3] One subject had an event of anaphylaxis.
[4] Exposure-adjusted event rates were defined as the total number of events divided by the total exposure in terms of subject-years during the period.
Source: Table 50 in the ARC003 CSR

18 to 55 Years
The overall pattern of adverse events and symptoms for adult subjects aged 18 to 55 years was similar to that for pediatric subjects. The most common AEs in the AR101 group are abdominal pain (43.9%), nausea (43.9%), and oral pruritus (36.6%), as compared to 35.7%, 7.1%, and 7.1% respectively in the placebo group.

Reviewer Comments
It appears that the total exposure in Table 4 might be underestimated. The applicant appears to have summarized the number of days a subject consumed investigational product, instead of the number of days at risk. Discrepancies occur when there is a gap between two doses. For example, Subject ARC003-(b) (6) *had initial Escalation Day 1 visit on June 2, 2016 and initial Escalation Day 2 visit on June 9, 2016. The number of days at risk for the IDE period should have been 8 in my opinion, while the applicant considers it as 2. The applicant's approach is reasonable if all AEs are expected to occur only on the same day of dosing. The total exposure I calculated for IDE, up-dosing, maintenance and overall periods are 2.67, 155.46, 151.15, and 309.28 years for the AR101 group, and 1.02, 50.56, 58.02, and 109.60 years for the placebo group, respectively. The discrepancies are generally small as compared to the applicant's numbers, except for the IDE period. Nevertheless, there does not appear to be any impact on the safety conclusion.*

6.1.12.3 Deaths

No subject died in this study.

6.1.12.4 Nonfatal Serious Adverse Events

4 to 17 Years
A total of 8 (2.2%) AR101-treated subjects and 1 (0.8%) placebo-treated subject had 1 or more SAEs: 4 (1.1%) AR101-treated subjects and no placebo-treated subjects during up-dosing and 4 (1.3%) AR101-treated subjects and 1 (0.8%) placebo-treated subject during maintenance. SAEs were considered treatment related for 3 (0.8%) AR101-treated subjects during up-dosing and 1 (0.3%) during maintenance.

18 to 55 Years
SAEs were reported during maintenance in 2 AR101-treated subjects (8.0%) and 1 placebo-treated subject (7.1%); 1 subject in the AR101 group had a SAE that was considered treatment related.

6.1.12.5 Adverse Events of Special Interest (AESI)

Anaphylaxis
The term anaphylaxis is used to distinguish anaphylactic reaction events that were severe. One subject in the pediatric age group treated with AR101 had a severe, treatment-related adverse event of anaphylaxis during maintenance that was considered serious, required medical intervention, and resulted in study discontinuation. The subject (b) (6) received 3 doses of epinephrine and the event was considered resolved about 4 hours after its onset. No adult subject had an event of anaphylaxis to AR101.

GI Events

In the pediatric safety population, GI disorders was the most common system organ class of adverse events and allergy symptoms reported overall with AR101 treatment (85.8% AR101-treated subjects and 69.4% placebo-treated subjects). GI adverse events and symptoms were overwhelmingly mild to moderate in severity (99% in both groups). About half of subjects in both treatment groups overall had mild events; 33.1% of AR101-treated subjects and 17.7% of placebo-treated subjects had moderate events, and 1.1% AR101-treated subjects and 0.8% placebo-treated subjects had severe events. All of the severe events were reported during up-dosing: 4 AR101-treated subjects had 1 or more severe events of abdominal pain, upper abdominal pain, and nausea; and 1 placebo-treated subject had a severe event of constipation. All severe events resolved during the study, and all except 1 AR101-treated subject completed the study. GI disorders led to discontinuation of study product in 21 (5.6%) AR101-treated subjects and none placebo-treated subjects.

Accidental Food Allergen Exposure

Accidental exposures to food allergens were lower for the AR101 group compared with the placebo group. In the pediatric safety population, 77 (20.7%) AR101-treated subjects had a total of 106 accidental food allergen exposures, and 40 (32.3%) placebo-treated subjects had a total of 56 accidental food allergen exposures. The numbers of adult subjects in each group who reported any accidental food allergen exposure during the study was low (9 subjects, 22.0% AR101; 4 subjects, 28.6% placebo), precluding any meaningful conclusions.

Use of Epinephrine as Rescue Medication (Excluding Epinephrine Use during the DBPCFC)

4 to 17 Years

In the pediatric safety population, 52 (14.0%) subjects in the AR101 group and 8 (6.5%) subjects in the placebo group had at least 1 episode of epinephrine use. An episode is defined as the administration of 1 or more epinephrine doses within 2 hours. In the AR101 group, 32 (8.6%) subjects had 1 episode, 16 (4.3%) had 2 episodes, 2 (0.5%) had 3 episodes, and 2 (0.5%) had 6 episodes. In the placebo group, 7 (5.6%) subjects had 1 episode and 1 (0.8%) subject had 2 episodes. Most episodes required 1 dose of epinephrine (92.7% AR101, 100.0% placebo). In the AR101 group, 5 episodes (6.1%) required 2 doses of epinephrine and 1 (3.4%) episode required 3 doses. No episode required 4 or more doses. Most (93.9%) epinephrine use in the AR101 group was for grade 1 or 2 AEs, while all (100%) epinephrine use in the placebo group was for grade 1 or 2 AEs.

18 to 55 Years

A total of 7 (17.1%) subjects in the AR101 group and 1 (7.1%) subject in the placebo group had at least 1 episode of epinephrine use. Most (87.5%) epinephrine use in the AR101 group was for grade 1 or 2 AEs, while all (100%) epinephrine use in the placebo group was for grade 1 or 2 AEs.

6.1.12.6 Clinical Test Results

Please refer to the medical officer's review.

6.1.12.7 Dropouts and/or Discontinuations

4 to 17 Years

In the pediatric safety population, 43 (11.6%) AR101-treated subjects and 2 (1.6%) placebo-treated subjects discontinued study product due to 1 or more adverse events and allergy symptoms. Most subjects discontinued study product during up-dosing (35 [9.6%] AR101 and 1 [0.8%] placebo) compared with initial dose escalation (4 [1.1%] AR101 and 1 [0.8%] placebo) and maintenance (4 [1.3%] AR101 and 0 placebo). Overall, most subjects discontinued study product due to 1 or more events in the GI disorders system organ class (24 [6.5%] AR101 and 1 [0.8%] placebo); followed by respiratory, thoracic, and mediastinal disorders (11 [3.0%] and 2 [1.6%]); immune system disorders (7 [1.9%] and 0%); skin and subcutaneous tissue disorders (5 [1.3%] and 1 [0.8%]); infections and infestations and general disorders and administration site conditions (each 4 [1.1%] and 0%); nervous system disorders (3 [0.8%] and 0%); and eye disorders, psychiatric disorders, and vascular disorders (each 1 [0.3%] and 0%).

18 to 55 Years

In the adult safety population, 7 (17.1%) AR101-treated subjects and no placebo-treated subject discontinued study product due to 1 or more events. Five subjects discontinued due to events during up-dosing and 1 subject each discontinued study product during initial dose escalation and maintenance. Overall, most subjects discontinued study product due to 1 or more events in the GI disorders system organ class (4 subjects); followed by immune system disorders and respiratory, thoracic, and mediastinal disorders (2 subjects each); and general disorders and administration site conditions, infections and infestations, and skin and subcutaneous tissue disorders (1 subject each).

6.2 Trial #2: ARC007

This protocol was entitled "Real-World AR101 Market-Supporting Experience Study in Peanut-Allergic Children Ages 4 to 17 Years (RAMSES)."

6.2.1 Objectives

Primary Objective

The primary objective is to assess the safety and tolerability of AR101 when used in a characterized oral desensitization immunotherapy (CODIT) regimen for approximately 6 months in peanut-allergic children.

Secondary Objectives

The secondary objectives are to characterize the frequency of all treatment-related AEs by study period, especially those of interest, and AR101's effect on asthma control and immune parameters.

6.2.2 Design Overview

ARC007 was a phase 3, multicenter, randomized, double-blind, placebo-controlled study consisting of a screening phase and a double-blind treatment phase that includes an initial 2-day escalation period and an up-dosing period. Up to 500 peanut-allergic children aged 4 to 17 years were randomized in a 2:1 ratio to AR101 or placebo. Randomization was stratified by age group (4 to 11 years and 12 to 17 years).

After completion of the up-dosing period, all study exit procedures, and treatment unblinding, subjects who received AR101 may participate in an open-label maintenance trial, known as Study ARC011; subjects who received placebo will be offered up-dosing and maintenance treatments with AR101 in Study ARC008.

6.2.3 Population

Subjects aged 4 to 17 years who are allergic to peanut.

6.2.4 Study Treatments or Agents Mandated by the Protocol

AR101 and placebo

6.2.6 Sites and Centers

The study was conducted in 64 study sites in North America (59 in US and 5 in Canada).

6.2.7 Surveillance/Monitoring

Please refer to the medical officer's review.

6.2.8 Endpoints and Criteria for Study Success

Primary Endpoint
The primary endpoint is the frequency of Treatment-Emergent AEs (TEAEs), including SAEs, during the overall study period. ARC007 was a safety study, therefore no success criterion was pre-defined.

Secondary Endpoints
Secondary endpoints include frequencies of premature discontinuation of dosing due to AEs, and due to chronic/recurrent GI AEs, proportion of chronic/recurrent GI AEs resolving at 2, 4, and ≥12 weeks following cessation of dosing, frequency of allergic reaction (hypersensitivity) AEs occurring during up-dosing, normalized for duration of treatment, frequency of anaphylaxis, frequency of use of epinephrine as a rescue medication, frequency of accidental ingestion of peanut and other allergenic foods and severity of any resultant reactions, and assessment of asthma control using the ACT questionnaire and frequency of use of asthma rescue medication (short acting beta-agonists) in subjects with asthma.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The safety population was used for all safety analyses. Safety analyses were summarized by treatment received. Adverse events were classified by system organ class and

preferred term using the MedDRA version 19.1. Treatment-emergent adverse events were defined as adverse events with onset after the first dose of study product. Subjects experiencing more than 1 treatment-emergent adverse event were counted only once within each study period.

Since ARC007 was amended to allow subjects to continue to receive 300 mg dose in ARC007 after the expected rollover date while waiting for activation of ARC008 or ARC011, the up-dosing period was split into the following two periods for statistical analyses:

- Up-dosing is defined as the time beginning with the date and time of the first dose of study product at 3 mg at home and ending with the date and time of first dose at 300 mg at the study site.
- 300 mg QD period is defined as the time beginning with the date and time of first dose of study product at 300 mg at home and ending with the date of the last dose of study product.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

A total of 506 subjects aged 4 to 17 years were randomly assigned to study treatment (338 to AR101 and 168 to placebo). Of the 338 subjects randomly assigned to AR101, 1 withdrew consent before receiving treatment. All 168 subjects assigned to placebo received treatment.

6.2.10.1.1 Demographics

The median age of the 505 subjects was 9.0 years. Most subjects in both treatment groups were aged 4 to 11 years (67.1% AR101, 67.9% placebo), and most subjects were male (64.7% AR101, 60.7% placebo) and white (82.2% AR101, 73.2% placebo). The proportion of race was similar in both treatment groups for Asian (18.1% AR101, 19.0% placebo), black (4.5% AR101, 4.2% placebo), Native Hawaiian or other Pacific Islander subjects (1.2% AR101, 0.6% placebo), and American Indian or Alaska Native (0.6% each). A total of 5.5% of the population was of “other” race (3.9% AR101, 8.9% placebo). The proportion of Hispanic or Latino ethnicity was similar between treatment groups (5.6% AR101, 4.8% placebo).

The baseline characteristics of peanut allergy were similar between treatment groups for median total IgE (519.00 IU/mL AR101, 518.00 IU/mL placebo) and peanut-specific IgG4 (0.7 mgA/L in both groups). Baseline peanut-specific IgE was 97.30 kUA/L in the AR101 group and 81.50 kUA/L in the placebo group. The median ratio of peanut-specific IgE to IgG4 was similar in both groups (145.11 AR101, 142.78 placebo). A total of 50.1% of the overall population reported a history of asthma based on the number of subjects who completed the ACT at screening (52.2% AR101, 45.8% placebo).

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Please refer to the medical officer’s review.

6.2.10.1.3 Subject Disposition

A total of 260 of 338 (76.9%) subjects in the AR101 group and 158 of 168 (94.0%) subjects in the placebo group completed the study. The most common reason for study discontinuation in the AR101 group was chronic/recurrent GI adverse events/symptoms (20 subjects, 5.9%), followed by subject withdrew consent (18, 5.3%), allergic adverse event (12, 3.6%), dosing symptom (8, 2.4%), and sponsor decision (8, 2.4%); other reasons for study discontinuation were reported for 7 (2.1%) subjects. The most common reason for study discontinuation in the placebo group was withdrew consent (3 subjects, 1.8%), followed by dosing symptom (2, 1.2%). All other reasons for study discontinuation were reported for 1 subject each (0.6%).

6.2.11 Efficacy Analyses

Not applicable.

6.2.12 Safety Analyses

The median overall exposure was 5.59 months for the AR101 group and 5.56 months for the placebo group.

6.2.12.1 Adverse Events

An overall summary of adverse events by treatment group and study period is provided in Table 5. Overall, 99.1% of subjects in the AR101 group and 94.6% of subjects in the placebo group had one or more AEs. The overall exposure-adjusted AE rate was 72.01 events per subject-year for the AR101 group and 25.57 events per subject-year for the placebo group. Most adverse events and symptoms were mild or moderate in severity (95.5% AR101, 93.4% placebo). Severe events were reported for 3.3% AR101 and 0.6% placebo. One AR101-treated subject (0.3%) had an adverse event that was life-threatening and 1 placebo-treated subject had an adverse event that resulted in death.

Overall, 304 (90.2%) AR101-treated subjects and 98 (58.3%) placebo-treated subjects had one or more treatment-related AEs; 41 (12.2%) AR101-treated subjects and 5 (3.0%) placebo-treated subjects discontinued study treatment due to an adverse event and allergy symptom; 36 (10.7%) AR101-treated subjects and 9 (5.4%) placebo-treated subjects had 1 or more adverse events of systemic allergic reaction by any trigger (study product, food allergen, other allergen); 309 (91.7%) AR101-treated subjects and 126 (75.0%) placebo-treated subjects had adverse events and symptoms of allergic reaction (hypersensitivity); adverse events associated with accidental food allergen exposures were less common overall in the AR101 group (26 subjects; 7.7%) compared with the placebo group (31 subjects; 18.5%).

Table 5. Overview of Treatment-Emergent AEs and Symptoms (ARC 007 Safety population, 4-17 Year)

	IDE	**IDE**	**Up- Dosing**	**Up-Dosing**	**300 mg/day**	**300 mg/day**	**Overall**	**Overall**
	AR101 (N=337)	**Placebo (N=168)**	**AR101 (N=327)**	**Placebo (N=166)**	**AR101 (N=265)**	**Placebo (N=158)**	**AR101 (N=337)**	**Placebo (N=168)**
Total exposure (years)	1.82	0.92	135.04	68.08	13.89	8.50	150.81	77.52
Total AEs	453	104	10003	1760	404	118	10860	1982
Subjects with at least 1 AE	187 (55.5%)	57 (33.9%)	323 (98.8%)	156 (94.0%)	120 (45.3%)	56 (35.4%)	334 (99.1%)	159 (94.6%)
AE by severity [1]								
Mild	170 (50.4%)	54 (32.1%)	172 (52.6%)	111 (66.9%)	107 (40.4%)	49 (31.0%)	171 (50.7%)	110 (65.5%)
Moderate	17 (5.0%)	3 (1.8%)	139 (42.5%)	43 (25.9%)	13 (4.9%)	7 (4.4%)	151 (44.8%)	47 (28.0%)
Severe	0	0	11 (3.4%)	1 (0.6%)	0	0	11 (3.3)	1 (0.6%)
Life-threatening	0	0	1 (0.3%)	0	0	0	1 (0.3%)	0
Death	0	0	0	1 (0.6%)	0	0	0	1 (0.6%)
AE by relationship to study product [2]								
Not related	24 (7.1%)	16 (9.5%)	31 (9.5%)	76 (45.8%)	38 (14.3%)	47 (29.7%)	30 (8.9%)	61 (36.3%)
Related	163 (48.4%)	41 (24.4%)	292 (89.3%)	80 (48.2%)	82 (30.9%)	9 (5.7%)	304 (90.2%)	98 (58.3%)
AE leading to discontinuation of study product	9 (2.7%)	2 (1.2%)	32 (9.8%)	3 (1.8%)	0	0	41 (12.2%)	5 (3.0%)
AE of systemic allergic reaction (anaphylactic reaction), including anaphylaxis	4 (1.2%)	1 (0.6%)	32 (9.8%)	8 (4.8%)	3 (1.1%)	0	36 (10.7%)	9 (5.4%)
AE of allergic reaction	170 (50.4%)	48 (28.6%)	296 (90.5%)	113 (68.1%)	87 (32.8%)	20 (12.7%)	309 (91.7%)	126 (75.0%)
AE associated with an accidental food allergen exposure	0	1 (0.6%)	26 (8.0%)	29 (17.5%)	1 (0.4%)	3 (1.9%)	26 (7.7%)	31 (18.5%)
Subjects with at least 1 SAE	0	0	2 (0.6%)	2 (1.2%)	0	0	2 (0.6%)	2 (1.2%)
SAE by severity [1]								
Mild	0	0	0	0	0	0	0	0
Moderate	0	0	1 (0.3%)	0	0	0	1 (0.3%)	0
Severe	0	0	0	1 (0.6%)	0	0	0	1 (0.6%)
Life-threatening	0	0	1 (0.3%)	0	0	0	1 (0.3%)	0
Death	0	0	0	1 (0.6%)	0	0	0	1 (0.6%)

Table 5. Overview of Treatment-Emergent AEs and Symptoms (ARC 007 Safety population, 4-17 Year)- Cont'd

	IDE	**IDE**	**Up- Dosing**	**Up-Dosing**	**300 mg/day**	**300 mg/day**	**Overall**	**Overall**
	AR101 (N=337)	**Placebo (N=168)**	**AR101 (N=327)**	**Placebo (N=166)**	**AR101 (N=265)**	**Placebo (N=158)**	**AR101 (N=337)**	**Placebo (N=168)**
Total SAEs	0	0	2	2	0	0	2	2
SAE by relationship to study product [2]								
Not related	0	0	2 (0.6%)	2 (1.2%)	0	0	2 (0.6%)	2 (1.2%)
Related	0	0	0	0	0	0	0	0
Exposure-adjusted events rate, events (rate) [3]								
AEs	453 (248.81)	104 (113.39)	10003 (74.07)	1760 (25.85)	404 (29.09)	118 (13.88)	10860 (72.01)	1982 (25.57)
AEs related to study product	401 (220.25)	75 (81.77)	7826 (57.95)	673 (9.89)	286 (20.60)	22 (2.59)	8513 (56.45)	770 (9.93)
AEs with severity of severe or greater	0	0	19 (0.14)	2 (0.03)	0	0	19 (0.14)	2 (0.03)
SAEs	0	0	2 (0.14)	2 (0.03)	0	0	2 (0.14)	2 (0.03)
SAEs related to study product	0	0	0	0	0	0	0	0
SAEs with severity of severe or greater	0	0	1 (0.01)	2 (0.03)	0	0	1 (0.01)	2 (0.03)

[1] Subjects with more than 1 adverse event were counted only once using the highest severity.
[2] Subjects with more than 1 adverse event were counted only once using the closest relationship to study product.
[3] Exposure-adjusted event rates were defined as the total number of events divided by the total exposure in terms of subject-years during the period.
Source: Table 21 in the ARC007 CSR.

The most common treatment-related AEs in the AR101 group are abdominal pain (49.6%), throat irritation (45.1%), and abdominal discomfort (37.7%) as compared to 15.5%, 13.7%, and 11.9% respectively in the placebo group.

Reviewer Comments

1. *It appears that the total exposure in Table 5 is slightly underestimated for IDE. Similar to Study ARC003, the applicant appears to have summarized the number of days a subject consumed investigational product, instead of the number of days at risk. Discrepancies occur when there is a gap between two doses. For example, Subject ARC007-*(b) (6) *had initial Escalation Day 1 visit on* (b) (6) *and initial Escalation Day 2 visit on* (b) (6) *. The number of days at risk for the IDE period should have been 9 in my opinion, while the applicant considers it as 2. The applicant's approach is reasonable if all AEs are expected to occur only on the same day of dosing. There were 7 subjects (4 in the AR101 group and 3 in the placebo group) that had similar gaps between the doses in the IDE period. The total exposures I calculated for IDE are 1.88 for the AR101 group and 0.94 for the placebo group. The discrepancies are small and not likely to have any impact on the safety conclusion.*
2. *A total of 9 records of allergic adverse events from 4 subjects in the AE domain had missing start date. The applicant assigned all these events to the up-dosing phase. I checked the last dose date in the SUPPAE domain for these events. One record of Urticaria and one record of allergic rhino-conjunctivitis for Subject ARC007-*(b) (6) *(AR101 group) had the last dose dates as the IDE Day 1. Therefore, it is likely that these two records took place in the IDE period. In addition, two records from two subjects had partial start date. The first record was fatigue (Subject ARC007-*(b) (6)*, placebo). The partial date suggests that this record took place either in the IDE or the up-dosing period. The applicant assigned it as an IDE record. The second record was gastroesophageal reflux disease (Subject ARC007-*(b) (6) *. The partial date suggests that this record took place during the up-dosing period, which matches the applicant's assignment. Overall, the missingness and partial missingness of start date do not appear to impact the safety analyses significantly and are not likely to affect the safety profile.*

6.2.12.3 Deaths

There was 1 death during the study (subject (b) (6), placebo), a craniocerebral injury sustained in a road traffic accident. The investigator considered the relationship between the fatal serious adverse event of craniocerebral injury and study product to be not related.

6.2.12.4 Nonfatal Serious Adverse Events

Four subjects experienced a total of 4 serious adverse events; in the AR101 group 1 subject each had acute lymphocytic leukemia and mycoplasma pneumonia, and in the placebo group 1 subject each had appendicitis and craniocerebral injury. All events

occurred during up-dosing and were considered by investigators to be unrelated to study treatment.

6.2.12.5 Adverse Events of Special Interest (AESI)

Anaphylaxis

A total of 36 (10.7%) AR101-treated subjects and 9 (5.4%) placebo-treated subjects had 1 or more adverse events of systemic allergic reaction (including 4 anaphylaxis) by any trigger (study product, food allergen, other allergen) during 1 or more treatment periods.

GI Events

GI disorders was the most common system organ class of adverse events reported overall in this study (87.8% AR101-treated subjects and 57.1% placebo-treated subjects). Subjects had GI adverse events that were generally mild to moderate in severity (98% AR101, 100% placebo). Six (1.8%) AR101-treated subjects and no placebo-treated subject had 1 or more severe events of abdominal pain, vomiting, and oral pruritus during up-dosing; all events were considered treatment related except vomiting in 1 subject. No subject in either treatment group had a serious adverse event in the GI disorders system organ class.

Nonserious Eosinophilic Esophagitis (EoE) was reported in 2 AR101-treated subjects (0.6%). Twenty AR101-treated subjects (5.9%) and no placebo-treated subject discontinued from the study due to chronic/recurrent GI adverse events.

Accidental Food Allergen Exposure

Accidental exposures to food allergens were lower for the AR101 group compared with the placebo group (7.7% vs 18.5%) and associated epinephrine use was less in the AR101 group compared with the placebo group (1.2% vs 4.2%). Accidental exposure to peanut was also less common in the AR101 group (2.7%) compared with the placebo group (10.7%).

Use of Epinephrine as Rescue Medication (Excluding Epinephrine Use during the DBPCFC)

Overall, 37 (11.0%) subjects in the AR101 group and 9 (5.4%) subjects in the placebo group had at least 1 episode of epinephrine use. In the AR101 group, 30 (8.9%) subjects had 1 episode, 5 (1.5%) had 2 episodes, 1 (0.3%) had 3 episodes, and 1 (0.3%) had > 3 episodes. In the placebo group, 9 (5.4%) subjects had 1 episode. Most episodes required 1 dose of epinephrine (85.1% AR101 and 88.9% placebo). In the AR101 group, 6 episodes (12.8%) required 2 doses of epinephrine and 1 episode (2.1%) required 3 doses. No episode required 4 or more doses. Most epinephrine use was associated with mild and moderate adverse events and symptoms (87.2% AR101 and 100.0% placebo). In the AR101 group, epinephrine was associated with 6 (12.8%) severe adverse events.

6.2.12.6 Clinical Test Results

Please refer to the medical officer's review.

6.2.12.7 Dropouts and/or Discontinuations

A total of 41 subjects (36 AR101, 10.7% and 5 placebo, 3.0%) discontinued from the study due to 1 or more adverse events. Most subjects discontinued due to adverse events during up-dosing (27 subjects, 8.3% AR101 and 3 subjects, 1.8% placebo). No subject discontinued study product due to adverse events while receiving 300 mg/day.

7. INTEGRATED OVERVIEW OF EFFICACY

Not applicable. Efficacy of AR101 was supported by a single pivotal Phase 3 study (ARC003). Supportive efficacy data from a Phase 2 study (ARC001) and its open-label follow-on study (ARC002) were not integrated due to differences in study design and key study endpoints.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Database

The safety profile of AR101 in patients with peanut allergy is derived from 4 clinical studies (two completed, randomized, double-blind, placebo-controlled, Phase 3 studies, ARC003 and ARC007; two ongoing, uncontrolled, follow-on studies, ARC004 and ARC011 with data cutoff date July 15, 2018) involving 812 unique subjects aged 4 to 17 years who received at least 1 dose of AR101 study product. Together these four studies include 709 subjects treated with AR101 and 292 subjects treated with placebo in the combined controlled population (hereafter, controlled population), and 812 subjects treated with AR101 that make up the population of all treated subjects (hereafter, integrated safety population).

Safety data for the controlled population were presented by treatment group for initial dose escalation and up-dosing combined and 300 mg/day maintenance periods. Safety data for the integrated population of all AR101 treated subjects were presented by period (initial dose escalation, up-dosing, 300 mg/day maintenance, and overall).

Demographics

Demographic and baseline characteristics were similar between treatment groups in the controlled population and were similar for the integrated safety population.

Disposition

In the controlled population, 554 of 712 subjects (77.8%) randomly assigned to AR101 and 273 of 293 subjects (93.2%) randomly assigned to placebo completed the originating study (ARC003 or ARC007). A total of 3 subjects (2 in ARC003 and 1 in ARC007) randomized to the AR101 group and 1 subject (in ARC003) randomized to the placebo group did not receive study product.

In the integrated safety population of subjects who received at least 1 dose of AR101, a total of 657 of 812 subjects (80.9%) completed the placebo-controlled studies and 535 of

812 subjects (65.9%) entered a follow-on study (ARC004 or ARC011); 130 subjects (16.0%) completed the follow-on study and 345 (42.5%) are ongoing.

The most common primary reason for study discontinuation from the originating or follow-on study was adverse events (9.6% AR101, 1.4% placebo in the controlled population, 9.2% AR101 once daily in the integrated safety population), followed by withdrawal of consent (6.9%, 3.1%, 9.7%).

8.2 Safety Results

8.2.1 Deaths

There was 1 unrelated death in study in ARC007 (subject (b) (6), placebo), a craniocerebral injury sustained in a road traffic accident.

8.2.2 Overall Summary of Adverse Events

Controlled Population

An overall summary of treatment-emergent adverse events is presented by treatment group for initial dose escalation and up-dosing combined and 300 mg/day dosing in ARC003 for the controlled population in Table 6. The majority of adverse events were mild or moderate in severity. For the AR101 group, a higher proportion of subjects had moderate adverse events during initial dose escalation and up-dosing combined (49.1%) than during 300 mg/day dosing in ARC003 (32.6%). The incidence of moderate adverse events was similar (approximately 30%) in both study periods for the placebo group. The incidence of severe adverse events was low: 2.8% AR101 and 1.4% placebo during initial dose escalation and up-dosing combined, and 2.6% AR101 and 0% placebo during 300 mg/day dosing. The incidence of serious adverse events was low and similar between treatment groups (0.8% AR101 and 0.7% placebo during initial dose escalation and up-dosing combined; 1.3% and 0.8% during 300 mg/day dosing).

Table 6. Overall Summary of Treatment-Emergent AEs (Controlled Population)

Period	**Combined IDE and Up-Dosing**	**Combined IDE and Up-Dosing**	**Study ARC003 300 mg/Day**	**Study ARC003 300 mg/Day**
Group	**AR101 (N = 709)**	**Placebo (N = 292)**	**AR101 (N = 310)**	**Placebo (N = 118)**
Total no. exposure-years	294.35	120.23	149.54	57.55
Total no. adverse events (exposure-adj)	22934 (77.9)	3208 (26.7)	4041 (27.0)	650 (11.3)
No. (%) subjects with at least 1:				
Adverse event	694 (97.9%)	269 (92.1%)	270 (87.1%)	94 (79.7%)
By severity				
Grade 1: Mild	325 (45.8%)	180 (61.6%)	161 (51.9%)	57 (48.3%)
Grade 2: Moderate	348 (49.1%)	84 (28.8%)	101 (32.6%)	37 (31.4%)
Grade 3: Severe	20 (2.8%)	4 (1.4%)	8 (2.6%)	0
Grade 4: Life-threatening	1 (0.1%)	0	0	0
Grade 5: Death	0	1 (0.3%)	0	0
Related to study product	626 (88.3%)	165 (56.5%)	159 (51.3%)	26 (22.0%)
Led to study product discontinuation	80 (11.3%)	7 (2.4%)	4 (1.3%)	0
Systemic allergic reaction	67 (9.4%)	11 (3.8%)	27 (8.7%)	2 (1.7%)
Associated with non-study product food	81 (11.4%)	56 (19.2%)	28 (9.0%)	24 (20.3%)
No. (%) subjects with at least 1:				
Serious adverse event	6 (0.8%)	2 (0.7%)	4 (1.3%)	1 (0.8%)
By severity				
Grade 1: Mild	1 (0.1%)	0	0	1 (0.8%)
Grade 2: Moderate	3 (0.4%)	0	2 (0.6%)	0
Grade 3: Severe	1 (0.1%)	1 (0.3%)	2 (0.6%)	0
Grade 4: Life-threatening	1 (0.1%)	0	0	0
Grade 5: Death	0	1 (0.3%)	0	0
By relationship to study product				
Not related	3 (0.4%)	2 (0.7%)	3 (1.0%)	1 (0.8%)
Related	3 (0.4%)	0	1 (0.3%)	0

- Adj: adjusted; IDE: initial dose escalation.

Source: Table 10 in the Summary of Clinical Safety.

Reviewer Comment

It appears that two AEs collected in Study ARC003 that had missing severity grades were re-graded as Grade 3 for the ISS safety analyses, causing some minor discrepancies between Tables 4-5 and Table 6. The two AEs are Rash Maculo-papular (Subject ARC003-(b) (6), Placebo) and Pyrexia (Subject ARC008-(b) (6), Placebo). This does not appear to impact the safety conclusion.

Integrated Safety Population

The overall summary of adverse events for the integrated safety population is consistent with the results for the controlled population. In the integrated safety population, a higher incidence of adverse events of any severity and relationship to study product was

reported during up-dosing (96.9%) compared with all 300 mg/day dosing (81.8%), and initial dose escalation (51.6%). Most adverse events were mild or moderate in severity. A total of 13 subjects (1.6%) had 1 or more serious adverse events: 6 (0.8%) during up-dosing and 8 (1.2%) during all 300 mg/day dosing. Treatment-emergent adverse events are summarized during initial dose escalation, up-dosing, 300 mg/day (any weeks), and overall for the integrated safety population in Table 7.

Table 7. Overall Summary of Treatment-Emergent AEs (Integrated Safety Population)

Period	**IDE (N=812)**	**Up-Dosing (N=794)**	**300 mg/day (any wks) (N=661)**	**Overall (N=812)**
Total no. exposure-years	4.40	334.73	385.75	725.59
Total no. adverse events (exposure-adj)	1124 (255.6)	24271 (72.5)	8548 (22.2)	33943 (46.8)
No. (%) subjects with at least 1:				
Adverse event	419 (51.6%)	769 (96.9%)	541 (81.8%)	802 (98.8%)
By severity				
Grade 1: Mild	374 (46.1%)	364 (45.8%)	344 (52.0%)	321 (39.5%)
Grade 2: Moderate	44 (5.4%)	382 (48.1%)	183 (27.7%)	444 (54.7%)
Grade 3: Severe	1 (0.1%)	22 (2.8%)	14 (2.1%)	36 (4.4%)
Grade 4: Life-threatening	0	1 (0.1%)	0	1 (0.1%)
Grade 5: Death	0	0	0	0
Related to study product	373 (45.9%)	678 (85.4%)	352 (53.3%)	729 (89.8%)
Led to study product discontinuation	15 (1.8%)	73 (9.2%)	7 (1.1%)	94 (11.6%)
Systemic allergic reaction	5 (0.6%)	71 (8.9%)	57 (8.6%)	119 (14.7%)
Associated with non-study product food allergen exposure	2 (0.2%)	95 (12.0%)	56 (8.5%)	137 (16.9%)
No. (%) subjects with at least 1:				
Serious adverse event	0	6 (0.8%)	8 (1.2%)	13 (1.6%)
By severity				
Grade 1: Mild	0	1 (0.1%)	0	0
Grade 2: Moderate	0	3 (0.4%)	4 (0.6%)	7 (0.9%)
Grade 3: Severe	0	1 (0.1%)	4 (0.6%)	5 (0.6%)
Grade 4: Life-threatening	0	1 (0.1%)	0	1 (0.1%)
Grade 5: Death	0	0	0	0
By relationship to study product				
Not related	0	3 (0.4%)	6 (0.9%)	8 (1.0%)
Related	0	3 (0.4%)	2 (0.3%)	5 (0.6%)

- Adj: adjusted; IDE: initial dose escalation; wks: weeks.

Source: Table 11 in the Summary of Clinical Safety.

8.2.3 Adverse Events of Special Interest

Systemic Allergic Reaction

In the controlled population during initial dose escalation and up-dosing combined, 81 systemic allergic reactions by any trigger (study product, food allergen, other allergen) were reported in 67 subjects (9.4%) in the AR101 group and 11 were reported in 11 subjects (3.8%) in the placebo group. During daily 300 mg/day dosing in ARC003, 33

systemic allergic reactions were reported in 27 subjects (8.7%) in the AR101 group and 2 were reported in 2 subjects (1.7%) in the placebo group. Most systemic allergic reactions (> 80%) in the AR101 group were considered triggered by study product.

The majority of systemic allergic reactions were mild or moderate in severity: 8.9% of subjects in the AR101 group and 3.8% of subjects in the placebo group during initial dose escalation and up-dosing combined and 8.4% AR101, 1.7% placebo during 300 mg dosing in ARC003. Most subjects with systemic allergic reactions did not have events that reached the level of severity associated with the term anaphylaxis. Anaphylaxis (severe) was reported in 4 subjects (0.6%) in the AR101 group and no subject in the placebo group during up-dosing and 1 AR101 subject (0.3%), no placebo treated subject during 300 mg/day dosing in ARC003.

The overall summary of systemic allergic reactions for the integrated safety population is consistent with the results for the controlled population. A total of 169 events of systemic allergic reaction were reported overall in 118 subjects. Most systemic allergic reactions of any severity and by any trigger (study product, food allergen, other allergen) were reported during up-dosing (85 events, 71 subjects), followed by all 300 mg/day dosing (79 events, 56 subjects) and initial dose escalation (5 events, 5 subjects). Most systemic allergic reactions (139 events) were considered triggered by study product. Anaphylaxis (severe) was reported in 10 subjects (1.2% overall), including no subject during initial dose escalation, 5 subjects (0.6%) during up-dosing, and 5 subjects (0.8%) during all 300 mg/day dosing (0% at 0-13 weeks, 0.2% at 14-26 weeks, 1.4% at 27-52 weeks, and 0% at > 52 weeks).

Epinephrine Use

In the controlled population, 74 subjects (10.4%) in the AR101 group and 14 subjects (4.8%) in the placebo group had at least 1 episode of epinephrine use during initial dose escalation and up-dosing combined. During 300 mg/day dosing in ARC003, 24 subjects (7.7%) in the AR101 group and 4 subjects (3.4%) in the placebo group had at least 1 episode of epinephrine use. Most epinephrine use was associated with mild and moderate adverse events and symptoms (90.5% AR101 and 100% placebo during initial dose escalation and up-dosing combined; 96.6% AR101 and 100% placebo during 300 mg/day dosing in ARC003). During initial dose escalation and up-dosing combined, epinephrine use was associated with 7 (7.4%) severe adverse events in the AR101 group and none in the placebo group. During daily dosing at 300 mg in ARC003, epinephrine use was associated with 1 (3.4%) severe adverse event in the AR101 group and none in the placebo group.

The use of epinephrine as a rescue medication for the integrated safety population is consistent with the results for the controlled population. In the integrated safety population, the incidence of at least 1 episode of epinephrine use was lowest during initial dose escalation (2.0%) and highest during up-dosing (9.9%); the incidence was 8.2% during all 300 mg/day dosing. For episodes of epinephrine use associated with adverse events and symptoms, most were associated with events of mild and moderate severity (93.8% initial dose escalation, 88.6% up-dosing, and 94.5% all 300 mg/day

dosing). Epinephrine use was associated with 1 (6.3%) severe adverse event during initial dose escalation, 8 (8.2%) during up-dosing, and 4 (5.5%) during all 300 mg/day dosing.

Accidental Food Allergen Exposure

In the controlled population, 102 accidental exposures to any food allergen were reported in the AR101 group and 65 in the placebo group during initial dose escalation and up-dosing combined. During daily dosing at 300 mg in ARC003, 37 accidental exposures to any food allergen were reported in the AR101 group and 25 in the placebo group. Of these, most accidental food allergen exposures were to nonpeanut allergens.

The overall summary of accidental food allergen exposures for the integrated safety population is consistent with the results for the controlled population. Most accidental food allergen exposures to any food were reported during up-dosing (123 exposures), followed by all 300 mg/day dosing (78 exposures) and initial dose escalation (2 exposures). Of these, most accidental food allergen exposures were to nonpeanut allergens.

Chronic/Recurrent GI AEs

In the controlled population, 55 subjects (7.8%) in the AR101 group and 3 subjects (1.0%) in the placebo group had 1 or more adverse events in the GI disorders system organ class that led to discontinuation of study product during initial dose escalation and up-dosing combined. Of these, 36 subjects (all in the AR101 group) discontinued from the study due to chronic or recurrent GI adverse events. No subject discontinued due to chronic/recurrent GI adverse events during 300 mg/day dosing in ARC003.

In the integrated safety population, 62 subjects (7.6%) had 1 or more adverse events in the GI disorders system organ class that led to discontinuation of study product. Of these, more than half (36 subjects) discontinued from the study due to chronic or recurrent GI adverse events. For subjects who discontinued due to chronic or recurrent GI adverse events, 20 subjects had at least 1 GI adverse event during initial dose escalation, 36 subjects during up-dosing, and no subject during all 300 mg/day dosing.

Eosinophilic Esophagitis

In the controlled population, EoE was diagnosed in 3 of 693 AR101-treated subjects (0.4%) during up-dosing and no subject during dosing with 300 mg/day in ARC003. In the integrated safety population of 812 subjects, EoE was diagnosed in 1 additional AR101-treated subject during up-dosing for an overall incidence of 0.5%. EoE was considered treatment related in 2 of the subjects (0.2% overall). The severity of EoE was considered mild in 2 subjects (0.2%), moderate in 1 subject (0.1%), and severe in 1 subject (0.1%). All 4 subjects with EoE discontinued from the study, including 1 who was discontinued due to no longer meeting eligibility criteria.

8.3 Additional Safety Evaluations

8.3.1 Subgroup Analyses

The impact of demographic subgroups of age (4-11 years, 12-17 years), sex (male, female), race (white, nonwhite), and history of allergic rhinitis, systemic allergic reaction, atopic dermatitis, and asthma (yes, no) on the safety of AR101 was evaluated for the controlled population and the integrated safety population. The extent of exposure to AR101 was generally consistent across subgroups.

8.3.2 Safety Update

On April 23, 2019, Aimmune submitted a safety update with the cutoff date of December 21, 2018, which provided data for an additional 5 months of exposure to AR101 from the ongoing open-label studies. There was no change in the numbers of subjects overall with serious adverse events, severe or life-threatening adverse events, or deaths. One new event of anaphylaxis (severe systemic allergic reaction or anaphylactic reaction) and 1 new case of eosinophilic esophagitis (moderate severity) were reported during the additional maintenance treatment. Epinephrine use was similar to that reported in the original Summary of Clinical Safety (SCS). Overall, no new safety concerns were identified in the 812 subjects treated with AR101 (any dose, any period) for a median of approximately 50 weeks compared with a median of approximately 45 weeks in the original SCS (43.8% were treated for ≥ 1 year compared with 31.2% in the original SCS).

8.4 Safety Conclusions

No new safety concerns were identified in this larger combined analysis. It was concluded by the applicant that the adverse event profile reflects that expected with desensitization treatment, as AR101 is a peanut-based treatment containing the allergen to which the enrolled peanut-allergic subjects were highly sensitized.

Reviewer Comment
I agree with the applicant's conclusion that no new safety concerns were identified in the ISS analyses. The safety profile in the ISS was largely consistent with that observed in ARC003 and ARC007. I defer to the clinical reviewer regarding the acceptability of the applicant's conclusion that the safety profile of AR101 reflects that expected of desensitization treatment.

9. Additional Statistical Issues

9.1 Analyses Excluding Dr. Baker's Site (009)

A Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) was issued in March 2018 to Dr. Baker, M.D. of Portland, Oregon, and he was fully disqualified as a clinical investigator as of May 1, 2018. Studies ARC003 and ARC007 were completed on December 21, 2017 and August 31, 2018, respectively, and Dr. Baker participated in both studies (in addition to follow-on studies ARC004 and ARC008). An IR was sent to Aimmune under IND on September 20, 2018 requesting

additional information. In the September 28, 2018 IR response submitted to IND 15463.162, Aimmune provided numbers of subjects consented, withdrawn, completed, included in the safety analyses as well as the efficacy analyses. Aimmune also concluded that neither the overall integrity of data at the site nor subject safety were compromised.

During the BLA review, Office of Compliance and Biologics Quality (OCBQ) expressed concerns over several observations that were the same or similar in nature to the violations included in the disqualification of Dr. Baker. Therefore, an IR was communicated to Aimmune on August 13, 2019, requesting efficacy and safety sensitivity analyses for studies ARC003 and ARC007, excluding subjects recruited at Dr. Baker's site (Site 009). The sensitivity analysis results are briefly summarized in this subsection.

9.1.1 Sensitivity analysis for efficacy (ARC003)

Sixteen subjects (12 AR101, 4 placebo) were enrolled at site 009 in study ARC003, all of which were 4 to 17 years of age. No subject aged 18 to 55 years was enrolled at site 009; thus, no sensitivity analysis of the fourth key secondary endpoint of desensitization response in adult subjects was performed.

The treatment difference for the primary efficacy endpoint (tolerating 600 mg peanut protein) was 63.1% (95% CI: 52.7%, 73.4%). The treatment differences were 68.6% (95% CI: 58.5%, 78.7%) and 47.5% (95% CI: 37.5%, 57.5%) for the key secondary endpoints of tolerating 300 mg and 1000 mg peanut protein, respectively. For the key secondary endpoint of the maximum severity of symptoms at any challenge dose, the percentages of subjects experiencing none, mild, moderate, and severe or higher symptoms were 37.2%, 32.8%, 24.7%, and 5.3%, respectively, for AR101 subjects, and 2.5%, 27.5%, 59.2%, and 10.8%, respectively for placebo subjects. The difference between the sensitivity analysis results and the original results were all less than 1%. The applicant concluded that the sensitivity analyses of the primary and key secondary endpoints excluding subjects enrolled at Site 009 were consistent with the pre-specified analyses.

9.1.2 Sensitivity analyses for safety (ARC003 and ARC007)

Twenty-three subjects (17 AR101, 6 placebo) at site 009 received study product in studies ARC003 and ARC007 during initial dose escalation and up-dosing, and 12 subjects (9 AR101, 3 placebo) received study product during 300 mg/day dosing.

One subject (AR101) at site 009 experienced a serious adverse event during up-dosing (grade 4 acute lymphocytic leukemia considered not related to study product by the investigator). No subject experienced a systemic allergic reaction. One subject (AR101) used epinephrine (2 episodes) for grade 1 adverse events at the study site during up-dosing. No subject was diagnosed with eosinophilic esophagitis.

The clinical safety summary including and excluding data from subjects at site 009 is consistent for both the controlled and integrated safety populations.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The main clinical study supporting clinical efficacy was the Phase 3, international, randomized, double-blind, placebo-controlled pivotal study ARC003. An additional Phase 3, randomized, double-blind, placebo-controlled study, ARC007, evaluated safety during the up-dosing period.

Efficacy

In Study ARC003, treatment with AR101 resulted in a statistically significant treatment effect in the proportion of subjects aged 4 to 17 years who tolerated a single highest dose of at least 600 mg peanut protein with no more than mild symptoms at the exit double-blind, placebo-controlled food challenge (DBPCFC).

In Study ARC003, the desensitization response rate for the primary efficacy endpoint was 67.2% (95% CI: 62.3, 71.8) in the AR101 group compared with 4.0% (95% CI: 1.7, 9.1) in the placebo group. The treatment difference (AR101-placebo) was 63.2% (95% CI: 53.0, 73.3; $p < 0.0001$), with the lower bound of the 95% CI exceeding the prespecified margin of 15%. The primary objective was met. Favorable treatment effects of AR101 compared with placebo were also observed for the key secondary endpoints in the age group of 4-17 years. The key secondary endpoint of tolerating 600 mg peanut protein in the adult group (18-55 years of age) was not met, likely due to small sample size and high discontinuation rate.

Safety

The safety profile of AR101 was based on 4 clinical studies involving 812 subjects aged 4 to 17 years who received at least 1 dose of AR101. The studies included the 2 completed, randomized, double-blind, placebo-controlled, phase 3 studies, ARC003 and ARC007, and their respective ongoing, uncontrolled, follow-on studies, ARC004 and ARC011.

In the controlled population of the ISS, 626 (88.3%) AR101-treated subjects and 165 (56.5%) placebo-treated subjects had one or more treatment-related AEs during the initial dose escalation and up-dosing combined period, and 159 (51.3%) AR101-treated subjects and 26 (22.0%) placebo-treated subjects had one or more treatment-related AEs during 300 mg/day maintenance dosing. Seventy-four subjects (10.4%) in the AR101 group and 14 subjects (4.8%) in the placebo group had at least 1 episode of epinephrine use during initial dose escalation and up-dosing combined. During 300 mg/day dosing in ARC003, 24 subjects (7.7%) in the AR101 group and 4 subjects (3.4%) in the placebo group had at least 1 episode of epinephrine use.

The overall summary of adverse events for the integrated safety population is consistent with the results for the controlled population. A total of 373 (45.9%), 678 (85.4%), and 352 (53.3%) AR101-treated subjects had one or more treatment-related AEs during IDE, up-dosing, and 300 mg/day maintenance dosing, respectively. Anaphylaxis (severe) was reported in 10 subjects (1.2% overall), including no subject during initial dose escalation,

5 subjects (0.6%) during up-dosing, and 5 subjects (0.8%) during all 300 mg/day dosing. The incidence of at least 1 episode of epinephrine use was lowest during initial dose escalation (2.0%) and highest during up-dosing (9.9%); the incidence was 8.2% during all 300 mg/day dosing.

10.2 Conclusions and Recommendations

In summary, the primary efficacy endpoint for study ARC003 met its pre-specified success criterion. Favorable treatment effects of AR101 compared with placebo were also observed for the key secondary endpoints in the age group of 4-17 years. On the other hand, a higher risk of allergic reactions was observed in AR101-treated subjects, and more subjects required the use of epinephrine to treat allergic reaction across studies as compared to placebo-treated subjects. I defer to the clinical reviewer regarding the overall benefit-risk assessment of AR101.