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Application Type	Biologics License Application Efficacy Supplement
STN	BLA 125696/247
CBER Received Date	09/28/2023
PDUFA Goal Date	07/28/2024
Division / Office	DCTR/OVRR
Committee Chair	Taruna Khurana, PhD
Clinical Reviewer(s)	Kathleen Hise, MD
Project Manager	Girish Ramachandran, PhD Susan DeRocco-Keller, PhD
Priority Review	No
Reviewer Name(s)	Zhong Gao, Ph.D. Mathematical Statistician Therapeutics Evaluation Branch 2, DB/OBPV
Supervisory Concurrence	Lihan Yan, Ph.D. Chief, TEB2/DB/OBPV
Applicant	Aimmune Therapeutics, Inc.
Established Name	Peanut (Arachis hypogaea) Allergen Powder-dnfp
(Proposed) Trade Name	PALFORZIA
Pharmacologic Class	Allergenic extract
Formulation(s), including Adjuvants, etc	Peanut (Arachis hypogaea) Allergen Powder-dnfp
Dosage Form(s) and Route(s) of Administration	Powder for oral administration supplied in 0.5 mg, 1 mg, 10 mg, 20 mg and 100 mg Capsules or 300 mg Sachets.
Dosing Regimen	Administered in three sequential phases: Initial Dose Escalation, Up-Dosing, and Maintenance. Once daily.
Indication(s) and Intended Population(s)	An oral immunotherapy for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. This product was approved for patients 4 through 17 years of age. This submission intends to expand product use to pediatric patients 1 through 3 years of age

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GLOSSARY

COVID-19	Coronavirus Disease 2019
DBPCFC	Double-blind, placebo-controlled food challenge
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
Ig	Immunoglobulin
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
OIT	Oral immunotherapy
PP	Per protocol
PREA	Pediatric Research Equity Act
SPT	Skin prick test
US	United States

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1. Executive Summary

The applicant, Aimmune Therapeutics, submitted a supplement to Biologics License Application (BLA) 125696 for PALFORZIA [Peanut (Arachis hypogaea) Allergen Powder-dnfp]. This submission was also to fulfill the Post-marketing Requirements (PMR) that was established under the Pediatric Research Equity Act (PREA) for Palforzia. PMR #1: Deferred pediatric study under PREA for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut in pediatric patients ages 1 through 3 years. The applicant proposed labeling changes to extend the age indication of PALFORZIA® to patients 1 through 3 years of age based on results from Study ARC005.

Study ARC005 was a Phase 3, randomized, double-blind, placebo-controlled study that evaluated efficacy and safety of AR101 in peanut-allergic children aged 1 through 3 years. The primary efficacy analysis was to evaluate the proportion of subjects who tolerated a single highest dose of at least 600 mg peanut protein (1043 mg cumulative) with no more than mild symptoms at the exit double-blind, placebo-controlled food challenge (DBPCFC). Of 98 subjects in the intent-to-treat (ITT) population who received AR101, the desensitization response rate was 73.5% (95% CI: 63.6, 81.9) compared with 6.3% (95% CI: 1.3, 17.2) for 48 subjects who received placebo. The treatment difference (AR101-placebo) was 67.2% (95% CI: 50.0, 84.5), with the lower limit of 95% CI exceeding the prespecified margin of 15%. The study success criterion was met.

Overall, 75.5% of subjects in the AR101 group and 58.3% in the placebo group had one or more treatment-related adverse events. The most common system organ class of treatment-related adverse events were skin and subcutaneous tissue disorders (49.0% AR101, 37.5% placebo), GI disorders (45.9% AR101, 20.8% placebo), and respiratory, thoracic, and mediastinal disorders (34.7% AR101, 25.0% placebo). Epinephrine was used by 11 (11.2%) AR101-treated subjects for 13 events and 2 (4.2%) placebo-treated subjects for 4 events. A total of 9 serious adverse events were reported in 8 subjects (6 AR101, 6.1%; 2 placebo, 4.2%). No serious adverse events were considered by investigators to be related to study treatment. No subjects died in this study.

As compared with placebo subjects, a higher percentage of subjects receiving AR101 had treatment-related AEs, use of Epinephrine, SAEs, etc. Nevertheless, overall safety profiles of the product do not appear to present major safety signals. I defer to the clinical reviewer for further consideration.

In summary, the Phase 3 study ARC005 met the pre-specified statistical success threshold. The overall safety profiles of the product do not appear to present major safety issues. Therefore, I recommend approval of the application for the proposed indication.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Peanut allergy. For more details, please refer to the clinical review.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Patients with peanut allergy have previously had no treatment options other than avoidance of peanut and treatment of allergic reactions following accidental exposure. In February 2024, FDA approved Xolair (omalizumab) injection for immunoglobulin E-mediated food allergy in certain adults and children 1 year or older for the reduction of allergic reactions (Type I), including reducing the risk of anaphylaxis, that may occur with accidental exposure to one or more foods.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Aimmune Therapeutics, Inc. developed AR101 (brand name PALFORZIA®) using a characterized oral desensitization immunotherapy approach for patients with peanut allergy. AR101 was approved in US on Jan 31, 2020, in Europe on Dec 17, 2020, in the United Kingdom (UK) on Apr 7, 2021, and in Switzerland on May 4, 2021, as oral immunotherapy (OIT) for children aged 4 through 17 years with a confirmed diagnosis of peanut allergy to reduce the incidence and severity of allergic reactions, including anaphylaxis, after accidental exposure to peanut. AR101 is also approved as maintenance of efficacy in patients with peanut allergy who turned age 18 years during therapy. However, AR101 has not been approved for desensitizing patients with peanut allergy aged 1 through 3 years old.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The Food and Drug Administration (FDA) granted fast track designation for AR101 on Sep 5, 2014 for peanut-sensitive adults and children, and breakthrough therapy designation on Jun 15, 2015 for peanut-sensitive children and adolescents aged 4 through 17 years. AR101 was approved in the United States (US) on Jan 31, 2020, as OIT for children aged 4 through 17 years with a confirmed diagnosis of peanut allergy.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission is adequately organized for conducting a complete statistical review.

3.2 Compliance With Good Clinical Practices And Data Integrity

Bioresearch Monitoring (BIMO) inspection identified the following issue in clinical site 008: “the ICF for 6 subjects signatures for both parents were not obtained on the informed consent forms. The institutional review board approval requires the signatures for both parents when obtaining consent. In addition, the signatures for both parents are required but are not present for the COVID-19 addendum to the informed consent form for all enrolled subjects.” The review team considered that this issue would have had no or minimal impact on the data collected from this site.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

N/A

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

This review focuses on Phase 3 Study ARC005 which provides the principal efficacy and safety evaluation of AR101 in children aged 1 through 3 years with peanut allergy.

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

- STN 125696/247 Module 2.5. Clinical Overview
- STN 125696/247 Module 2.7.3. Summary of Clinical Efficacy
- STN 125696/247 Module 2.7.4. Summary of Clinical Safety
- STN 125696/247 Module 5.3.5.1. Study ARC005

5.3 Table of Studies/Clinical Trials

The applicant conducted a Phase 3 study ARC005 to evaluate safety and efficacy of the product for toddlers aged 1 through 3 years (Table 1). The subjects in Study ARC005 were also invited to participate in a long-term follow-up study (ARC008) along with subjects from other studies. Study ARC008 was ongoing and not submitted to the BLA at the time of submission.

Table 1. Summary of individual clinical studies

Study ID	Study Design Study Treatment (Randomization)	Subject Population Age Range	Dosing Regimen	Planned, Actual Enrollment Treated, Completed
ARC005	Phase 3, randomized, double-blind, placebo-controlled AR101 or placebo (2:1)	Peanut allergic children 1-3 years	Initial dose escalation: 2 days, 0.5-3 mg Up-dosing: ~24-40 weeks, 1-300 mg/day Maintenance: ~12-24 weeks, 300 mg/day Exit DBPCFC: Single challenge doses up to 2000 mg (4043 mg cumulative)	Planned, 132; Actual, 146 Treated, 146 (98 AR101, 48 placebo) Completed, 128 (83 AR101, 45 placebo)

Source: adapted from Table 1 in Summary of Clinical Safety

5.4 Consultations

N/A

5.5 Literature Reviewed (if applicable)

N/A

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study ARC005

Title: Peanut Oral Immunotherapy Study of Early Intervention for Desensitization (POSEIDON)

6.1.1 Objectives

Primary Objective:

- Efficacy of AR101 treatment in peanut-allergic subjects aged 1 through 3 years, assessed by tolerability of specified doses of peanut protein in a DBPCFC

Secondary Objectives:

- Safety and tolerability of study treatment
- Efficacy of AR101, assessed by tolerability of other specified single doses of peanut protein in a DBPCFC
- Maximum severity of allergy symptoms in a DBPCFC

6.1.2 Design Overview

This Phase 3, randomized, double-blind, placebo-controlled study evaluated efficacy and safety of AR101 in peanut-allergic children aged 1 through 3 years (Figure 1). Eligible subjects who developed age-appropriate dose-limiting allergy symptoms after consuming single doses of peanut protein > 3 mg to ≤ 300 mg in a screening DBPCFC was randomly assigned 2:1 to blinded treatment with AR101 or placebo. Randomization was stratified by geographic region (North America, Europe).

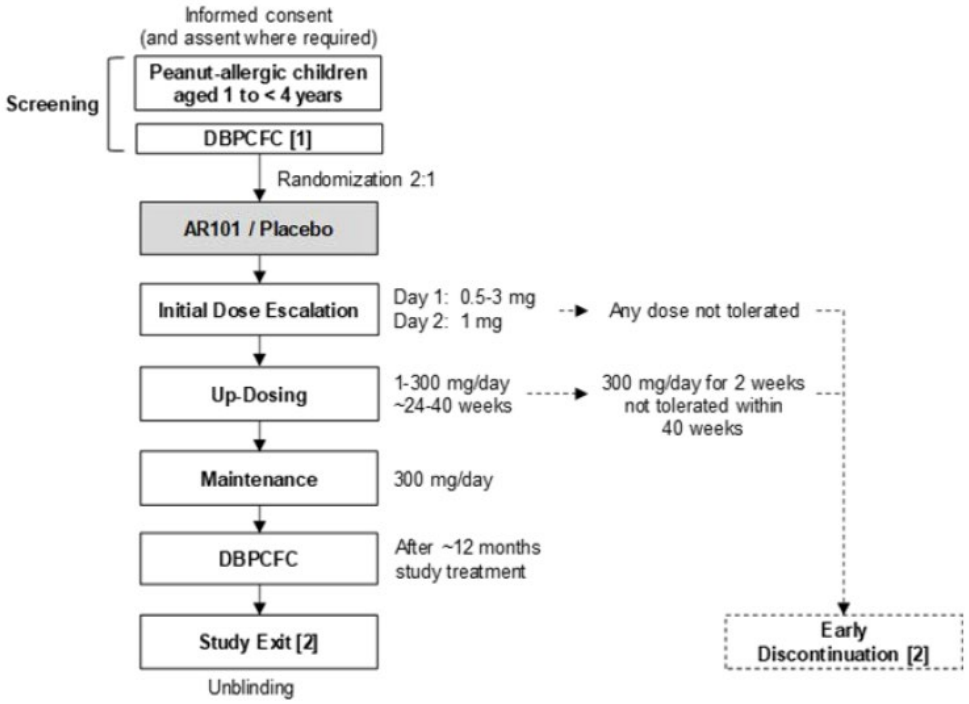
Initial dose escalation period: Subjects began initial dose escalation on day 1 with a stepwise dose escalation of study product (up to 4 single doses of 0.5, 1, 1.5, and 3 mg) administered at 20- to 30-minute intervals as tolerated. Subjects who tolerated the 3 mg dose on day 1 returned on day 2 for a single 1 mg dose. Subjects who tolerated the 1 mg dose with no more than mild allergy symptoms that were not dose-limiting began the up-dosing period. Subjects who did not tolerate any dose on day 1 or day 2 discontinued early from the study.

Up-dosing period: This period was approximately 6 months (maximum 40 weeks), with dose escalation approximately every 2 weeks. Daily doses of study product during up-dosing were 1, 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, and 300 mg/day. Subjects who tolerated the 300 mg/day dose for 2 weeks within 40 weeks began the maintenance period. Subjects who were unable to tolerate the 300 mg/day dose for 2 weeks within 40 weeks of up-dosing discontinued early from the study.

Maintenance period: Subjects who began maintenance treatment continued daily dosing with study product at 300 mg/day for an overall total of approximately 12 months of treatment, with study site visits every 4 weeks. The duration of maintenance treatment could vary from a minimum of 12 weeks to a maximum of 24 weeks depending on the up-dosing interval (24-40 weeks). After the end of maintenance, subjects had an exit

DBPCFC up to a single highest challenge dose of 2000 mg peanut protein (4043 mg cumulative). The 300 mg daily dose of study product had to be tolerated for at least 2 consecutive weeks before having the DBPCFC. Subjects who completed both days of the exit DBPCFC completed the study.

Figure 1. Study Scheme



Note:
[1] Eligible subjects had age-appropriate dose-limiting allergy symptoms after consuming single doses of peanut protein > 3 mg to ≤ 300 mg in the screening DBPCFC.
[2] Subjects with unresolved adverse events or who had gastrointestinal adverse events of interest had safety follow-up.
Source: Figure 1 in Study ARC005 CSR

6.1.3 Population

- Peanut-allergic children aged 1 through 3 years.
- Sensitivity to peanut, defined as one of the following:
    - No known history of peanut ingestion and has serum IgE to peanut ≥ 5 kUA/L within 12 months before randomization.
    - Documented history of physician-diagnosed IgE-mediated peanut allergy that includes the onset of characteristic signs and symptoms of allergy within 2 hours of known oral exposure to peanut or peanut-containing food, and has a mean wheal diameter on skin prick test (SPT) to peanut of at least 3 mm greater than the negative control (diluent) or serum IgE to peanut ≥ 0.35 kUA/L, obtained within 12 months before randomization.

- Development of age-appropriate dose-limiting allergy symptoms after consuming single doses of peanut protein > 3 mg to ≤ 300 mg in a screening DBPCFC.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study products administered in this study were AR101 and placebo that contained excipients color-matched to the AR101 study product.

6.1.6 Sites and Centers

This study was conducted at 14 study sites in North America and 9 in Europe.

6.1.7 Surveillance/Monitoring

Please refer to the clinical review memo.

6.1.8 Endpoints and Criteria for Study Success

The applicant included different sets of primary and secondary endpoints for their respective regulatory submissions in North America and Europe regions. This review focuses on the pre-specified primary and secondary endpoints.

- Primary efficacy endpoint: Proportion of subjects treated with AR101 compared with placebo who tolerated a single dose of at least 600 mg of peanut protein with no more than mild symptoms during the exit DBPCFC. The primary efficacy objective would be considered met if the lower bound of the 95% CI of the difference (AR101-Placebo) is greater than the prespecified margin of 0.15.

- Secondary efficacy endpoints:
  - Desensitization response rate at a single dose of 300 mg peanut protein. The proportion of subjects who tolerated a single dose of at least 300 mg single dose of peanut protein (443 mg cumulative) with no more than mild allergy symptoms at the exit DBPCFC.
  - Desensitization response rate at a single dose of 1000 mg peanut protein. The proportion of subjects who tolerate a single dose of at least 1000 mg single dose of peanut protein (2043 mg) with no more than mild allergy symptoms at the exit DBPCFC.
  - The maximum severity of symptoms that occurred at any challenge dose of peanut protein during the exit DBPCFC.

6.1.9 Statistical Considerations & Statistical Analysis Plan

- Blinding

This was a double-blind study. All subjects, study site personnel (including investigators), and sponsor staff and its representatives were blinded to treatment identity, except the designated unblinded person who accessed the interactive response system to obtain the randomization order for the peanut protein and placebo challenge days and prepare the DBPCFC material. In addition, the peanut and placebo food challenges were conducted in a double-blind manner.

- Randomization

Randomization was central and treatment allocation was 2:1 (AR101 or placebo). Randomization was stratified by geographic region (North America, Europe); at least 30% of subjects were planned to be enrolled in Europe.

- Definitions of analysis populations
  - ITT population: All subjects who received any part of 1 dose of study product. Subjects were evaluated based on randomized treatment. The ITT population was used as primary analysis population for all efficacy endpoints.
  - Completer population: All subjects in the ITT population who completed treatment and had an evaluable exit DBPCFC.
  - PP population: The subset of the completer population that included subjects who had no major protocol deviations that may have influenced the desensitization response. Exclusions to the PP population were determined by blinded review before database lock and study unblinding.
  - Safety population: All subjects who received any randomized study treatment (i.e., who receive any part of 1 dose of study product and complete 1 study visit). Subjects were evaluated based on treatment received.

- Sample size planning

The applicant indicated that the sample size of this study (approximately 132 subjects randomly assigned 2:1 to AR101 or placebo) would provide 85% power to demonstrate a significantly higher desensitization response rate with AR101 compared with placebo with an at least 15% margin for the primary efficacy endpoint of the proportion of subjects tolerating an at least 600 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC. The sample size calculations were based on the Farrington and Manning method for the difference in proportions and a two-side 0.05 level test, assuming a desensitization rate based on the DBPCFC of 55% in AR101-treated subjects, and a maximum desensitization rate of 15% in placebo-treated subjects, conducted in the ITT population.

- Statistical Analysis for Primary Efficacy Endpoint

Desensitization response rates and associated 95% CIs were to be presented for each treatment group using exact Clopper-Pearson CIs. The 95% CI for the treatment difference (desensitization rate for AR101 treatment minus desensitization rate for placebo) was based on the Farrington-Manning method. The primary efficacy endpoint for North America will be considered met if the lower bound of the 95% CI is greater than the prespecified margin of 0.15. The ITT population was to be used for these analyses. Subjects tolerating a single dose of at least 600 mg peanut protein were to be considered as responders; otherwise as nonresponders. Nonresponders also included subjects who withdrew consent or discontinued early any time before the exit DBPCFC.

- Statistical Analysis for Secondary Efficacy Endpoints
  - The proportion of subjects who tolerated an at least 300 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC: this analysis was to be conducted using the ITT population.

Desensitization response rates and associated 95% CIs were to be presented for each treatment group using exact Clopper-Pearson CIs. The 95% CI for the treatment difference (desensitization rate for AR101 treatment minus desensitization rate for placebo) was based on the Farrington-Manning method.

- The proportion of subjects who tolerate an at least 1000 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC: the methods were same as those for the 1st secondary endpoint.
- The maximum severity of allergy symptoms after consuming peanut protein during the exit DBPCFC: assessed by tabulating the number and percentage of subjects in the ITT population by maximum severity of allergy symptoms at the exit DBPCFC and by treatment group. The Cochran-Mantel-Haenszel statistics with equally spaced scores stratified by geographic region was used to test for a treatment difference.

- Multiplicity adjustment

Secondary efficacy endpoints were assessed in hierarchical order if the primary efficacy endpoint analysis was significant at the 0.05 level. Each endpoint was evaluated for statistical significance (2-sided, $p < 0.05$) only if all preceding in the hierarchy and the primary analysis of the primary efficacy endpoint were statistically significant in favor of AR101.

- Missing data handling

For the primary and secondary endpoints involving desensitization rates, if a subject discontinued prior to the exit DBPCFC, they were to be considered as non-responders. As one of sensitivity analyses to determine the impact of missing data on the robustness of the study results, the primary efficacy endpoint was to be analyzed using a worst-case approach to missing data imputation. Specifically, placebo subjects who had missing data (i.e., did not have an Exit DBPCFC) for the primary efficacy endpoint for any reason would be considered as responders while AR101 subjects would be considered as non-responders if they had missing data for the endpoint. Sensitivity analyses based on the PP and completer populations were also planned.

For the secondary endpoint of maximum severity of allergy symptoms, if a subject discontinued prior to the exit DBPCFC, the maximum severity of symptoms during the exit DBPCFC were to be imputed using the maximum severity of symptoms during the screening DBPCFC.

- Statistical Methods for Safety Analyses

The safety population was used to summarize all adverse event data, unless otherwise specified. Statistical methods for safety analysis were to be mainly descriptive.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics and Baseline Characteristics

Overall, the baseline demographic characteristics were similar between the treatment groups (Table 2).

Table 2. Baseline Demographics Characteristics (ITT Population)

Characteristic	**AR101 (N = 98)**	**Placebo (N = 48)**
Age (Years)		
Median	2.0	2.0
Min, max	1, 3	1, 3
Age category (years)		
1 - <2	33 (33.7%)	16 (33.3%)
2 - <3	35 (35.7%)	15 (31.3%)
3 - <4	30 (30.6%)	17 (35.4%)
Sex		
Male	57 (58.2%)	28 (58.3%)
Female	41 (41.8%)	20 (41.7%)
Ethnicity		
Hispanic or Latino	5 (5.1%)	3 (6.3%)
Not Hispanic or Latino	75 (76.5%)	31 (64.6%)
Not collected	18 (18.4%)	14 (29.2%)
Race*		
American Indian or Alaska Native	0	0
Asian	16 (16.3%)	8 (16.7%)
Black or African American	3 (3.1%)	2 (4.2%)
Native Hawaiian or Other Pacific Islander	0	1 (2.1%)
White	65 (66.3%)	28 (58.3%)
Other	8 (8.2%)	2 (4.2%)
Multiple Races Reported	2 (2.0%)	4 (8.3%)
Not collected	4 (4.1%)	4 (8.3%)
Country		
United States	56 (57.1%)	28 (58.3%)
United Kingdom	29 (29.6%)	12 (25.0%)
Germany	9 (9.2%)	5 (10.4%)
France	4 (4.1%)	3 (6.3%)

Source: Table 12 in Study ARC005 CSR.
* The applicant's response to CBER IR #16 Table 14.1.3.1 – ir16.

However, both the baseline median peanut-specific IgE and Ara h 2 IgE were lower in the AR101 group (6.8 kUA/L and 5.190 kUA/L, respectively) compared with the placebo group (30.0 kUA/L and 14.200 kUA/L). On the other hand, another marker of clinical response to peanut, the median mean wheal diameter in the screening skin prick test to peanut, was similar between the 2 groups, 9.0 mm (range, 4-36 mm) for the AR101 group and 9.75 mm (range, 2-26.5 mm) for the placebo group (Table 3).

Table 3. Baseline Immunoglobulin Values and Skin Prick Test (ITT Population)

Characteristic	AR101 (N = 98)	Placebo (N = 48)
Total IgE (IU/mL)		
n	86	45
Median	162.5	175.0
Q1, Q3	52.0, 453.0	41.0, 343.0
Min, max	5, 3324	9, 5508
Peanut-specific IgE (kUA/L)		
n	87	45
Median	6.80	30.00
Q1, Q3	2.28, 33.50	2.12, 69.70
Min, max	0.01, 100.0	0.06, 100.0
Peanut-specific IgG4 (mgA/L)		
n	85	45
Median	370.0	360.0
Q1, Q3	120.0, 910.0	100.0, 790.0
Min, max	70, 16900	70, 8880
Peanut-specific IgE/IgG4 ratio		
n	85	45
Median	0.019	0.040
Q1, Q3	0.008, 0.050	0.013, 0.137
Min, max	0.00, 0.32	0.00, 1.43
Skin prick test mean wheal diameter (mm)		
n	95	48
Median	9.00	9.75
Q1, Q3	7.00, 13.50	6.75, 13.00
Min, max	4.0, 36.0	2.0, 26.5
Ara h 2 IgE (kUA/L)		
n	86	45
Median	5.190	14.200
Q1, Q3	1.260, 25.400	1.790, 54.700
Min, max	0.01, 100.00	0.05, 100.00
Ara h 2 IgG4 (mgA/L)		
n	85	45
Median	0.070	0.060
Q1, Q3	0.020, 0.260	0.010, 0.200
Min, max	0.01, 1.71	0.01, 2.44
Ara h 2 IgE/IgG4 ratio		
n	85	45
Median	77.519	142.857
Q1, Q3	21.500, 234.500	43.290, 418.571
Min, max	0.56, 2000.00	4.33, 10000.00

Source: Table 13 in Study ARC005 CSR

Reviewer Comment: *I discussed with the clinical reviewer on whether the IgE imbalance at baseline could affect interpretation of efficacy outcomes. In the clinical setting, higher IgEs give clinicians more reassurance for correctly diagnosing a patient with peanut allergy when combined with a positive clinical history. It will not predict how much peanut protein they react to or how severe the reactions are. This study included an oral food challenge as the gold standard at baseline, every subject's threshold sensitivity to peanut protein was examined (Table 4). Those threshold sensitivities showed some imbalance between the treatment groups, especially at the level of 100mg peanut protein. Please see additional evaluation of the baseline imbalance in Reviewer's Comment in Section 6.1.11.1.*

Table 4. Single Highest Tolerated Dose of Peanut Protein at Screening DBPCFC (ITT Population)

Single Highest Tolerated Dose of Peanut Protein at Screening DBPCFC	**AR101 (N = 98)**	**Placebo (N = 48)**
1 mg	1 (1.0%)	1 (2.1%)
3 mg	13 (13.3%)	8 (16.7%)
10 mg	17 (17.3%)	10 (20.8%)
30 mg	32 (32.7%)	17 (35.4%)
100 mg	35 (35.7%)	12 (25.0%)
300 mg	0	0

Source: Table 14 in Study ARC005 CSR

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 5 summaries peanut allergy history for the subjects in the safety population. Overall, peanut allergy history appears to be similar between the AR101 and Placebo group.

Table 5. Peanut Allergy History (Safety Population)

	AR101 (N = 98)	Placebo (N = 48)
Months since peanut allergy diagnosis		
n	98	48
Mean (SD)	15.52 (10.224)	15.69 (10.944)
Median	14.55	13.14
Q1, Q3	6.94, 22.88	6.93, 28.43
Min, max	0.6, 39.9	0.1, 36.5
No. anaphylactic reactions for peanut in lifetime		
0	62 (63.3%)	31 (64.6%)
1	34 (34.7%)	15 (31.3%)
2	2 (2.0%)	1 (2.1%)
3	0	1 (2.1%)
> 3	0	0
Months since most recent allergic reaction to peanut		
n	49	21
Mean (SD)	11.11 (9.051)	12.61 (7.682)
Median	8.96	10.58
Q1, Q3	3.83, 15.21	8.89, 15.14
Min, max	0.5, 33.4	0.7, 31.5
Symptoms during the most recent peanut exposure (≥ 5% total subjects) *		
Hives	57 (58.2%)	26 (54.2%)
Vomiting	21 (21.4%)	13 (27.1%)
Rash (non-specific)	15 (15.3%)	10 (20.8%)
Facial swelling	14 (14.3%)	6 (12.5%)
Cough	11 (11.2%)	5 (10.4%)
Itching	9 (9.2%)	6 (12.5%)
Wheezing	7 (7.1%)	6 (12.5%)
Angioedema	10 (10.2%)	2 (4.2%)
Skin flushing	6 (6.1%)	5 (10.4%)

* Subjects could be included in more than 1 category.
Source: Table 17 in Study ARC005 CSR

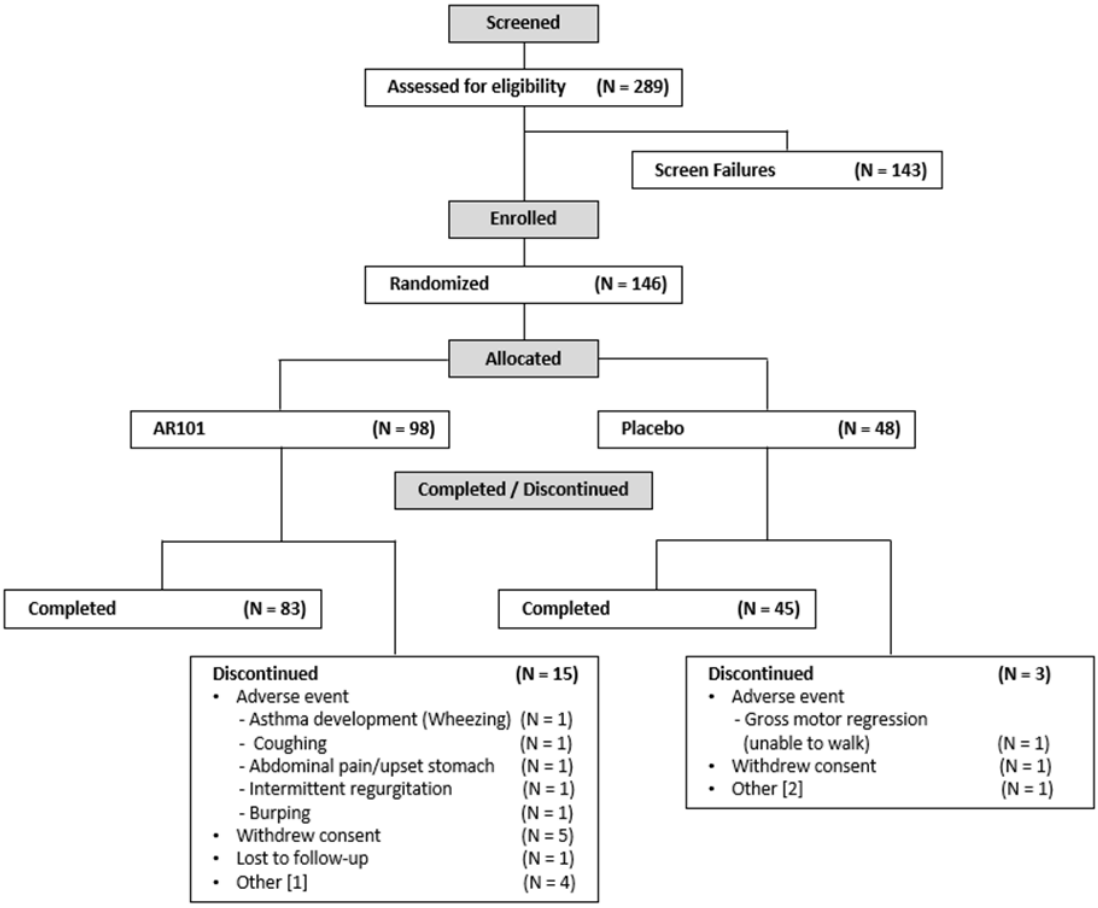
6.1.10.1.3 Subject Disposition

A total of 289 subjects aged 1 through 3 years were screened and 146 were randomly assigned to study treatment (98 to AR101 and 48 to placebo). Of these, 83 of 98 (84.7%) subjects in the AR101 group and 45 of 48 (93.8%) subjects in the placebo group completed the study (Figure 2).

The primary reason for subjects not being randomized was for not meeting the screening DBPCFC criterion. As shown in Figure 2, the most common reasons for study discontinuation in the AR101 group were subject withdrew consent (5, 5.1%) and adverse

event (5, 5.1%). Other reasons for study treatment discontinuation were reported for 4 (4.1%) or fewer subjects in either treatment group.

Figure 2. Subject Disposition Flow Chart (All Subjects)



Note: [1] Reasons included 1 investigator's decision due to noncompliance, and 3 subjects' decision due to continued commitment to study treatment. [2] One subject discontinued due to taste aversion to study product.

Source: Figure 2 in Study ARC005 CSR

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

The primary efficacy analysis was to evaluate the proportion of subjects who tolerated a single highest dose of at least 600 mg peanut protein (1043 mg cumulative) with no more than mild symptoms at the exit DBPCFC. Of 98 subjects in the ITT population who received AR101, the desensitization response rate was 73.5% (95% CI: 63.6, 81.9) compared with 6.3% (95% CI: 1.3, 17.2) for 48 subjects who received placebo. The treatment difference (AR101-placebo) was 67.2% (95% CI: 50.0, 84.5), with the lower

limit of 95% CI exceeding the prespecified margin of 15% (Table 6). The primary efficacy endpoint analysis met the study success criterion.

Table 6. Primary Efficacy Endpoint Analysis Result (ITT Population)

Primary Efficacy Endpoint	**AR101 (N = 98)**	**Placebo (N = 48)**
Response rate: proportion of subjects who tolerated 600 mg peanut protein (95% CI)	73.5% (63.6, 81.9)	6.3% (1.3, 17.2)
Treatment difference (AR101-placebo) [95% CI]	67.2% (50.0, 84.5)	

Source: Adapted from Table 23 in Study ARC005 CSR

Reviewer Comment*:*

- *My analysis verified the applicant's primary efficacy analysis result based on the pre-specified analysis method.*
- *In Section 6.1.10.1.1, I discussed the imbalance between the AR101 and placebo group in single highest tolerance dose at screening, especially at the level of 100mg of peanut protein (Table 4). I conducted additional analysis on the primary efficacy endpoint adjusting for the single highest tolerance dose at baseline (dichotomized to two categories: <100mg vs. ≥100mg), using logistic regression. The results showed statistically significant treatment effect ($p < 0.0001$) while the baseline tolerance level effect was not statistically significant ($p= 0.125$). I conclude that there is no impact of the observed imbalance on the conclusion of the positive treatment effect.*

The sensitivity analysis with the Completer population showed that, of 83 subjects in the Completer population who received AR101, the desensitization response rate was 86.7% (95% CI: 77.5, 93.2) compared with 6.7% (95% CI: 1.4, 18.3) for 45 subjects who received placebo; the treatment difference (AR101-placebo) was 80.1% (95% CI: 62.2, 98.0). Another sensitivity analysis with the PP population showed that, of 74 subjects in the PP population who received AR101, the desensitization response rate was 87.8% (95% CI: 78.2, 94.3) compared with 7.1% (95% CI: 1.5, 19.5) for 42 subjects who received placebo; the treatment difference (AR101-placebo) was 80.7% (95% CI: 62.0, 99.3). These analysis results were similar with the primary efficacy analysis on the ITT population.

The applicant also conducted sensitivity analysis to evaluate the impact of missing data on the robustness of the results using a worst-case approach to missing data imputation. Of 98 subjects in the ITT population who received AR101, the desensitization response rate for the proportion of subjects who tolerated a single highest dose of 600 mg peanut protein with no more than mild symptoms at the exit DBPCFC using the worst-case imputation method was 73.5% (95% CI: 63.6, 81.9) compared with 12.5% (95% CI: 4.7, 25.2) for 48 subjects who received placebo. The treatment difference (AR101-placebo) was 61.0% (95% CI: 43.7, 78.2).

Reviewer Comment: *The applicant performed multiple sensitivity analyses including analyses based on the completer population and per-protocol population, and worst-case*

imputation for missing data. The results of these analyses showed the similar trend as the primary analysis. Overall, the sensitivity analyses were supportive of the primary efficacy analysis.

6.1.11.2 Analyses of Secondary Endpoints

Table 7 summarizes the results of the key secondary endpoint analyses.

Table 7 Summary of Key Secondary Efficacy Endpoints for (ITT Population)

Key Secondary Efficacy Endpoints	**AR101 (N = 98)**	**Placebo (N = 48)**
Response rate: proportion of subjects who tolerated 300 mg peanut protein (95% CI)	79.6% (70.3, 87.1)	22.9% (12.0, 37.3)
Treatment difference (AR101-placebo) [95% CI]	56.7% (39.8, 73.5)	
Response rate: proportion of subjects who tolerated 1000 mg peanut protein (95% CI)	68.4% (58.2, 77.4)	4.2% (0.5, 14.3)
Treatment difference (AR101-placebo) [95% CI]	64.2% (47.0, 81.4)	
Max severity of symptoms at any challenge dose		
None	50 (51.0%)	2 (4.2%)
Mild	29 (29.6%)	23 (47.9%)
Moderate	17 (17.3%)	21 (43.8%)
Severe or higher (life-threatening or fatal)	2 (2.0%)	2 (4.2%)
P-value	< 0.0001	

Source: adapted from Table 23 in Study ARC005 CSR

- Proportion of subjects who tolerated at least 300 mg peanut protein

As shown in Table 7, of 98 subjects in the ITT population who received AR101, the desensitization response rate was 79.6% (95% CI: 70.3, 87.1) compared with 22.9% (95% CI: 12.0, 37.3) for 48 subjects who received placebo. The treatment difference (AR101-placebo) was 56.7% (95% CI: 39.8, 73.5). The results showed that treatment with AR101 resulted in a statistically significant treatment effect over placebo in the proportion of subjects who tolerated a single highest dose of at least 300 mg peanut protein (443 mg cumulative) with no more than mild symptoms at the exit DBPCFC.

- Proportion of subjects who tolerated at least 1000 mg peanut protein

Of 98 subjects in the ITT population who received AR101, the desensitization response rate was 68.4% (95% CI: 58.2, 77.4) compared with 4.2% (95% CI: 0.5, 14.3) for 48 subjects who received placebo. The treatment difference (AR101-placebo) was 64.2% (95% CI: 47.0, 81.4) (Table 7). The results showed that treatment with AR101 resulted in a statistically significant treatment effect over placebo in the proportion of subjects who tolerated a single highest dose of at least 1000 mg peanut protein (2043 mg cumulative) with no more than mild symptoms at the exit DBPCFC.

- Maximum Severity of Symptoms

The maximum severity of symptoms was none for 51.0% of subjects in the AR101 group and 4.2% of subjects in the placebo group. The maximum severity of symptoms was mild

for 29.6% and 47.9% of subjects, moderate for 17.3% and 43.8%, and severe for 2.0% and 4.2%, for AR101 and placebo respectively (Table 7). The p-value was < 0.0001 for the treatment difference in maximum severity of symptoms at any challenge dose. The results showed that treatment with AR101 resulted in a statistically significant effect over placebo in the maximum severity of symptoms at any challenge dose at the exit DBPCFC.

Reviewer Comment:
The applicant used CMH to evaluate the maximum severity of symptoms (none, mild, moderate, and severe or higher) between AR101 and placebo group. I conducted additional analyses with combining the severity categories into 2×2 tables, i.e., None vs. Mild+Moderate+Severe or higher, None+Mild v.s. Moderate+Severe or higher, and None+Mild+Moderate v.s. Severe or higher. For None vs. Mild+Moderate+Severe or higher and None+Mild v.s. Moderate+Severe or higher, statistical analysis showed that treatment effect was statistically significant (Chi-square test: p value < 0.05). On the other hand, the analyses for None+Mild+Moderate v.s. Severe or higher showed that treatment effect was not statistically significant (Chi-square test: p value 0.46) due to very few subjects in the severe category.

6.1.11.3 Subpopulation Analyses

The subgroup analyses of the primary efficacy endpoint by region, sex, race, and ethnicity showed similar trends of treatment difference. It's noted that, however, the treatment difference in the European subgroup appears to be numerically smaller than that in the North American subgroup (Table 8).

Table 8. Subpopulation Desensitization Response Rates, Tolerating 600 mg at the Exit DBPCFC, Subjects 1 - 3 Years of Age (ITT Population)

Subpopulation	Category	Treatment Group	N	% Responders (95% CI)	% Treatment Difference (AR101-Placebo) (95% CI)
Geographic region	North America	AR101	56	76.8% (63.6%, 87.0%)	73.2% (50.6%, 95.9%)
		Placebo	28	3.6% (0.1%, 18.3%)	
	Europe	AR101	42	69.0% (52.9%, 82.4%)	59.0% (32.4%, 85.7%)
		Placebo	20	10.0% (1.2%, 31.7%)	
Age	1 - <2 Years	AR101	33	81.8% (64.5%, 93.0%)	69.3% (40.0%, 98.7%)
		Placebo	16	12.5% (1.6%, 38.3%)	
	2 - <3 Years	AR101	35	65.7% (47.8%, 80.9%)	59.0% (28.8%, 89.3%)
		Placebo	15	6.7% (0.2%, 31.9%)	
	3 Years	AR101	30	73.3% (54.1%, 87.7%)	73.3% (43.6%, 100.0%)
		Placebo	17	0% (0.0%, 19.5%)	
Sex	Male	AR101	57	70.2% (56.6%, 81.6%)	66.6% (44.0%, 89.2%)
		Placebo	28	3.6% (0.1%, 18.3%)	
	Female	AR101	41	78.0% (62.4%, 89.4%)	68.0% (41.5%, 94.6%)
		Placebo	20	10.0% (1.2%, 31.7%)	
Race	Asian	AR101	16	75.0% (47.6%, 92.7%)	75.0% (32.6%, 100.0%)
		Placebo	8	0.0% (0.0%, 36.9%)	
	Black or African American	AR101	3	33.3% (0.8%, 90.6%)	33.3% (-38.2%, 100%)
		Placebo	2	0.0% (0.0%, 84.2%)	
	White	AR101	65	73.8% (61.5%, 84.0%)	63.1% (41.1%, 85.2%)
		Placebo	28	10.7% (2.3%, 28.2%)	
	Other	AR101	8	62.5% (24.5%, 91.5%)	62.5% (-15.0%, 100.0%)
		Placebo	2	0.0% (0.0%, 84.2%)	
	Multiple Races Reported	AR101	2	100.0% (15.8%, 100.0%)	100.0% (20.0%, 100.0%)
		Placebo	4	0.0% (0.0%, 60.2%)	
	Not collected	AR101	4	100.0% (39.8%, 100.0%)	100.0% (30.7%, 100.0%)
		Placebo	4	0.0% (0.0%, 60.2%)	
Ethnicity	Hispanic or Latino	AR101	5	80.0% (28.4%, 99.5%)	80.0% (8.4%, 100.0%)
		Placebo	3	0.0% (0.0%, 70.8%)	
	Not Hispanic or Latino	AR101	75	74.7% (63.3%, 84.0%)	68.2% (47.4%, 89.0%)
		Placebo	31	6.5% (0.8%, 21.4%)	
	Not collected	AR101	18	66.7% (41.0%, 86.7%)	59.5% (25.2%, 93.8%)
		Placebo	14	7.1% (0.2%, 33.9%)	

Source: adapted from Table 14.2.2.15 in the applicant's response to FDA IR #9 (dated Jan 24, 2024), Table 14.2.2.17 – IR16 in the applicant's response to CBER IR #16

6.1.11.4 Dropouts and/or Discontinuations

Please refer to Section 6.1.10.1.3 "Subject Disposition" and Section 6.1.9 "Statistical Considerations & Statistical Analysis Plan" – Missing Data Handling.

6.1.12 Safety Analyses

The median exposure was 2.0 days during initial dose escalation in each treatment groups of AR101 and placebo. During up-dosing period, the median exposure was 177.5 days (range, 4-529 days) for AR101 and 185.5 (range, 126-336 days) days for placebo. The median exposure during maintenance was 188.0 days (range, 9-406 days) for the AR101 group and 187.0 days (range, 109-346 days) for the placebo group (Table 9).

The maximum dose of 300 mg/day was reached by 88 AR101-treated subjects (89.8%) and 45 placebo-treated subjects (93.8%) during up-dosing and was continued by 86 AR101-treated subjects (98.9%) and 45 placebo-treated subjects (100%) during maintenance (Table 9).

Table 9. Extent of Exposure (Safety Population)

Parameter	Initial Dose Escalation AR101 (N = 98)	Initial Dose Escalation Placebo (N = 48)	Up-Dosing AR101 (N = 98)	Up-Dosing Placebo (N = 48)	Maintenance AR101 (N = 87)	Maintenance Placebo (N = 45)
Duration of exposure (months)						
n	98	48	98	48	87	45
Mean (SD)	0.07 (0.000)	0.07 (0.000)	6.34 (2.310)	6.73 (1.846)	6.37 (2.248)	6.74 (1.906)
Median	0.07	0.07	5.84	6.10	6.18	6.15
Q1, Q3	0.07, 0.07	0.07, 0.07	5.26, 7.11	5.28, 7.37	5.33, 6.88	5.72, 7.34
Min, max	0.1, 0.1	0.1, 0.1	0.1, 17.4	4.1, 11.1	0.3, 13.4	3.6, 11.4
Duration of exposure (days)						
n	98	48	98	48	87	45
Mean (SD)	2.0 (0.00)	2.0 (0.00)	192.7 (70.24)	204.5 (56.12)	193.8 (68.35)	204.9 (57.95)
Median	2.0	2.0	177.5	185.5	188.0	187.0
Q1, Q3	2.0, 2.0	2.0, 2.0	160.0, 216.0	160.5, 224.0	162.0, 209.0	174.0, 223.0
Min, max	2, 2	2, 2	4, 529	126, 336	9, 406	109, 346
Maximum dose reached (mg/day)						
n	98	48	98	48	87	45
Mean (SD)	6.0 (0.00)	6.0 (0.00)	273.0 (82.66)	290.4 (42.87)	300.7 (6.43)	300.0 (0.00)
Median	6.0	6.0	300.0	300.0	300.0	300.0
Q1, Q3	6.0, 6.0	6.0, 6.0	300.0, 300.0	300.0, 300.0	300.0, 300.0	300.0, 300.0
Min, max	6, 6	6, 6	1, 300	40, 300	300, 360	300, 300
Maximum dose reached by category (mg/day)						
0.5	0	0	0	0	0	0
1	0	0	1 (1.0%)	0	0	0
1.5	0	0	0	0	0	0
3	0	0	0	0	0	0
6	98 (100.0%)	48 (100.0%)	6 (6.1%)	0	0	0
12	0	0	0	0	0	0
20	0	0	0	0	0	0
40	0	0	1 (1.0%)	1 (2.1%)	0	0
80	0	0	1 (1.0%)	0	0	0
160	0	0	0	1 (2.1%)	0	0
200	0	0	1 (1.0%)	0	0	0
240	0	0	0	1 (2.1%)	0	0
300	0	0	88 (89.8%)	45 (93.8%)	86 (98.9%)	45 (100.0%)
360	0	0	0	0	1 (1.1%)	0

Source: adapted from Table 42 in Study ARC005 CSR

Overall, in the safety population (98 AR101, 48 placebo), 98.0% of subjects in the AR101 group and 97.9% of subjects in the placebo group had 1 or more adverse events.

Most adverse events were of mild or moderate intensity (severity) (92.8% in AR101 group and 93.7% in placebo). Seventy-four (74) subjects (75.5%) in AR101 group had treatment-related AEs while 28 placebo subjects (58.3%) had treatment-related AEs. Six subjects (6.1%) in the AR101 group and 2 subjects (4.2%) in placebo group had at least one serious adverse event (SAEs); none were considered by investigators to be related to the study product. No subject had an adverse event that was life-threatening or resulted in death.

Table 10 summarizes the safety profiles between AR101 and Placebo group across initial dose escalation, up-dosing, and maintenance stages. At the initial dosing period, subjects receiving AR101 had higher percentage of treatment-related AEs (15.3%) than placebo subjects (6.3%). During the up-dosing period, a higher percentage of subjects in AR101 group had AEs with moderate intensity (30.6%) than placebo subjects (18.8%); a higher percentage of subjects in AR101 group (68.4%) had treatment-related AEs than those in placebo group (56.3%); a higher percentage of subjects in AR101 group (5.1%) had AEs leading to early discontinuation than those in placebo group (0%); 3 subjects in AR101 group (3.1%) experienced SAEs while no subject in placebo group had a SAE. During the maintenance period, a higher percentage of subjects in AR101 group (34.5%) had treatment-related AEs than those in placebo group (15.6%); a higher percentage of subjects in AR101 group (2.3%) had AEs leading to early discontinuation than those in placebo group (0%).

Table 10. Overall Summary of Treatment-Emergent Adverse Events (Safety Population)

Parameters	**Initial Dose Escalation AR101 (N = 98)**	**Initial Dose Escalation Placebo (N = 48)**	**Up-Dosing AR101 (N = 98)**	**Up-Dosing Placebo (N = 48)**	Maintenance **AR101 (N = 87)**	Maintenance **Placebo (N = 45)**
Total adverse events	49	16	1637	682	694	262
Total serious adverse events	0	0	3	0	4	2
Subjects with at least 1 adverse event	21 (21.4%)	10 (20.8%)	96 (98.0%)	47 (97.9%)	79 (90.8%)	41 (91.1%)
By maximum severity						
Grade 1: Mild	20 (20.4%)	10 (20.8%)	64 (65.3%)	38 (79.2%)	55 (63.2%)	29 (64.4%)
Grade 2: Moderate	1 (1.0%)	0	30 (30.6%)	9 (18.8%)	21 (24.1%)	10 (22.2%)
Grade ≥ 3: Severe or higher	0	0	2 (2.0%)	0	3 (3.4%)	2 (4.4%)
By relationship to study product						
Not related	6 (6.1%)	7 (14.6%)	29 (29.6%)	20 (41.7%)	49 (56.3%)	34 (75.6%)
Related	15 (15.3%)	3 (6.3%)	67 (68.4%)	27 (56.3%)	30 (34.5%)	7 (15.6%)
Adverse events leading to study product discontinuation	0	0	5 (5.1%)	0	2 (2.3%)	0
Adverse events requiring dose interruption of study product	0	0	53 (54.1%)	25 (52.1%)	45 (51.7%)	23 (51.1%)
Adverse events requiring dose reduction of study product	0	0	14 (14.3%)	4 (8.3%)	7 (8.0%)	1 (2.2%)
Anaphylactic reaction	0	0	2 (2.0%)	2 (4.2%)	6 (6.9%)	2 (4.4%)
Hypersensitivity event [4]	15 (15.3%)	3 (6.3%)	69 (70.4%)	32 (66.7%)	45 (51.7%)	23 (51.1%)
Adverse event associated with food allergen exposure	2 (2.0%)	1 (2.1%)	32 (32.7%)	15 (31.3%)	22 (25.3%)	13 (28.9%)
Subjects with at least 1 serious adverse event	0	0	3 (3.1%)	0	3 (3.4%)	2 (4.4%)
Serious adverse events by maximum severity						
Grade 1: Mild	0	0	0	0	1 (1.1%)	0
Grade 2: Moderate	0	0	1 (1.0%)	0	0	0
Grade ≥ 3: Severe or higher	0	0	2 (2.0%)	0	2 (2.3%)	2 (4.4%)
Serious adverse events by relationship to study product						
Not related	0	0	3 (3.1%)	0	3 (3.4%)	2 (4.4%)
Related	0	0	0	0	0	0

Source: adapted from Table 43 in Study ARC005 CSR

Epinephrine was used by 11 AR101-treated subjects (11.2%) for 13 events and 2 placebo-treated subjects (4.2%) for 4 events. Most episodes of epinephrine use were associated with mild or moderate adverse events; 2 events in AR101 group and 1 event in placebo group were severe. None of the severe reactions treated with epinephrine were related to study therapy. Two events associated with use of epinephrine in the AR101 group and 1 event in the placebo group were serious. None of the serious events associated with epinephrine use was allergic in nature.

6.1.12.1 Methods

Descriptive methods were used for safety analysis.

6.1.12.3 Deaths

No subject died in this study.

6.1.12.4 Nonfatal Serious Adverse Events

Eight subjects (6 in AR101 group and 2 in Placebo group) experienced a total of 9 serious adverse events. The events were considered by investigators to be unrelated to study treatment.

6.1.12.5 Adverse Events of Special Interest (AESI)

N/A

6.1.12.6 Clinical Test Results

N/A

6.1.12.7 Dropouts and/or Discontinuations

Six subjects overall (6 AR101, 6.1%; 0 placebo) discontinued from the study due to 1 or more adverse events; 5 (5.1%) during up-dosing and 2 (2.3%) during maintenance; 1 subject had an event during both up-dosing and maintenance. One subject had an event during both up-dosing and maintenance.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

To support proposed indication, the applicant provided the following evidence from Study ARC005, a Phase 3, randomized, double-blind, placebo-controlled study that evaluated efficacy and safety of AR101 in peanut-allergic children aged 1 through 3 years of age:

Efficacy:

The primary efficacy endpoint analysis was to evaluate the proportion of subjects who tolerated a single highest dose of at least 600 mg peanut protein (1043 mg cumulative) with no more than mild symptoms at the exit DBPCFC. Of 98 subjects in the ITT population who received AR101, the desensitization response rate was 73.5% (95% CI: 63.6, 81.9) compared with 6.3% (95% CI: 1.3, 17.2) for 48 subjects who received placebo. The treatment difference (AR101-placebo) was 67.2% (95% CI: 50.0, 84.5), with the lower limit of 95% CI exceeding the prespecified margin of 15%. The primary efficacy endpoint analysis met the pre-specified study success criterion.

Safety:

Overall, 75.5% of subjects in the AR101 group and 58.3% in the placebo group had 1 or more treatment-related adverse events. The most common system organ class of treatment-related adverse events were skin and subcutaneous tissue disorders (49.0%

AR101, 37.5% placebo), GI disorders (45.9% AR101, 20.8% placebo), and respiratory, thoracic, and mediastinal disorders (34.7% AR101, 25.0% placebo).

Epinephrine was used by 11 AR101-treated subjects (11.2%) for 13 events and 2 placebo-treated subjects (4.2%) for 4 events. Most episodes of epinephrine use were associated with mild or moderate adverse events. A total of 9 serious adverse events were reported in 8 subjects (6 AR101, 6.1%; 2 placebo, 4.2%). No serious adverse events were considered by investigators to be related to study treatment. No subjects died in this study.

As compared with the placebo subjects, a higher percentage of subjects receiving AR101 had treatment-related AEs, use of Epinephrine, SAEs, etc. Nevertheless, overall safety profiles of the product appear to be acceptable from the statistical perspectives. I defer to the clinical reviewer for further consideration.

10.2 Conclusions and Recommendations

Overall, the Phase 3 study ARC005 met the statistical success threshold for efficacy. The treatment effect was robust and internally consistent across subgroups. The overall safety profiles of the product do not appear to present major safety issues. Therefore, I recommend approval of the application for the proposed indication.