BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125696/247
CBER Received Date	9/28/2023
PDUFA Goal Date	7/26/2024
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Kathleen S. Hise, MD
Review Completion Date / Stamped Date	7/23/2024
Supervisory Concurrence	Rebecca Reindel, MD
Applicant	Aimmune Therapeutics, Inc.
Established Name	Peanut (*Arachis hypogaea*) Allergen Powder
(Proposed) Trade Name	Palforzia
Pharmacologic Class	Allergenic extract
Formulation(s), including Adjuvants, etc.	Powder
Dosage Form(s) and Route(s) of Administration	Capsule/sachet Oral
Dosing Regimen	Once daily
Indication(s) and Intended Population(s)	Mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. For patients ages 1 through 17 years with a confirmed diagnosis of peanut allergy. (This supplement extends age range to 1 through 3 years.)
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
AESI	adverse event of special interest
APAC	Allergenic Products Advisory Committee
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CDER	Center for Drug Evaluation and Research
COVID-19	Coronavirus disease 2019
CP	centralized procedure
DBPCFC	double-blind placebo-controlled food challenge
DRISK	Division of Risk Management
DSMC	Data and Safety Monitoring Committee
EoE	eosinophilic esophagitis
EOP2	End of Phase 2
ETASU	elements to assure safe use
EU	European Union
EU-RMP	European Union risk management plan
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FPIES	food protein-induced enterocolitis syndrome
GI	gastrointestinal
IgE	immunoglobulin E
ITT	intent-to-treat
MHRA	Medicines and Healthcare products Regulatory Agency
NHLBI	National Heart, Lung, and Blood Institute
OBPV	Office of Biostatistics and Pharmacovigilance
OFC	oral food challenge
QoL	quality of life
REMS	risk evaluation and mitigation strategy
PI	prescribing information
PDUFA	Prescription Drug User Fee Act
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PREA	Pediatric Research Equity Act
PT	preferred term
PVP	pharmacovigilance plan
SAE	serious adverse event
sBLA	supplemental Biologics License Application
SOC	system organ class
SPT	skin prick test

1. EXECUTIVE SUMMARY

A supplemental Biologics License Application (sBLA) was submitted by Aimmune Therapeutics to the US Food and Drug Administration (FDA) for Palforzia [peanut (*Arachis hypogaea*) allergen powder-dnfp] on September 28, 2023. The trade name, Palforzia, will be used in this document. Palforzia was initially approved in 2020 for the "mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. Palforzia is approved for use in patients with a confirmed diagnosis of peanut allergy. Initial dose escalation may be administered to patients 4 through 17 years of age. Up-dosing and maintenance may be continued in patients 4 years of age and older." With this supplement, the Applicant proposes to extend the age indication down to patients 1 year of age with a confirmed diagnosis of peanut allergy.

The BLA includes efficacy and safety data from one clinical placebo-controlled study, ARC005. ARC005 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study that evaluated the efficacy and safety of Palforzia in subjects 1 through 3 years of age (N=146). As part of the eligibility criteria, subjects underwent a double-blind placebo-controlled food challenge (DBPCFC) prior to randomization. Subjects were randomized in a 2:1 ratio to receive Palforzia or placebo. The study included 3 dosing phases: initial dose escalation under clinical observation over 1-2 days, up-dosing every 2 weeks, and maintenance dosing of 300 mg Palforzia daily. The primary efficacy endpoint was the proportion of subjects 1 through 3 years of age in the intent-to-treat (ITT) population who tolerated a dose of at least 600 mg of peanut protein with no more than mild symptoms at the exit DBPCFC at the end of the maintenance period. The ARC005 success criterion was met if the lower bound of the 95% CI for the treatment difference between Palforzia and placebo was greater than 15%.

The ARC005 success criterion was met with a treatment difference (efficacy) estimate of 67.2% (95% CI: 50.0, 84.5). Subjects who did not have an exit DBPCFC were analyzed as non-responders for the primary efficacy endpoint. Palforzia recipients also demonstrated statistically significant treatment effect (subjects who tolerated a pre-defined dose of peanut protein with no more than mild symptoms at the exit DBPCFC at the end of the maintenance period) to 300 mg (56.7% (95% CI: 39.8, 73.5) and 1000 mg (64.2% (95% CI: 47.0, 81.4) of peanut protein during a DBPCFC after Palforzia treatment, as well as a reduction in the overall severity of allergic symptoms during a DBPCFC when compared to placebo recipients. A sensitivity analysis evaluating a worst-case scenario (placebo-treated subjects with missing data for the exit DBPCFC were considered as responders and Palforzia-treated subjects with missing data for the exit DBPCFC were considered as nonresponders) continued to demonstrate a statistically significant treatment effect (61.0% (95% CI: 43.7, 78.2). In addition, analyses that factored in medication modification (i.e., extended treatment duration) due to disruptions in clinical study conduct during the COVID-19 pandemic did not demonstrate a negative effect on the primary efficacy endpoint.

In the safety population, Palforzia recipients reported an increased number of allergic reactions, including systemic allergic reactions, compared to placebo recipients. A total of 2 Palforzia recipients had 3 events of systemic allergic reaction during initial dose escalation and up-dosing compared to 0 placebo recipients. In the Palforzia group, 11 subjects (11.2%) used epinephrine at least once, compared to 2 subjects (4.2%) in the placebo group. No Palforzia recipients were diagnosed with eosinophilic esophagitis (EoE) in ARC005. However, in the Palforzia clinical development program (see Table 1); N=1337 in 8 studies), 22 Palforzia recipients developed EoE (1.6%) compared to 0 placebo recipients.

During review of the original BLA, this reviewer, in consultation with Office of Biostatistics and Pharmacovigilance (OBPV) and Division of Risk Management (DRISK) in the Center for Drug Evaluation and Research (CDER) and concurrence from the Center for Biologics Evaluation and Research (CBER) safety working group, recommended that licensure of Palforzia incorporate additional risk mitigation activities as part of a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) to ensure that the benefits of Palforzia outweigh the risks of systemic allergic reactions due to Palforzia. This reviewer recommends that the REMS program remain in place to support safe use of Palforzia in this pediatric subpopulation. The REMS with ETASU is discussed in additional detail in the REMS memorandum. The following items in the REMS with ETASU were recommended and will stay in place:

- Healthcare providers must confirm that any patient prescribed Palforzia has a prescription for injectable epinephrine, has been counseled on the risks of Palforzia, and will maintain a peanut avoidant diet.
- Caregivers/patients must receive counseling from the prescriber on the need to have injectable epinephrine available for immediate use while on Palforzia.
- Physicians must be educated that initial dose escalation and the first dose of each up-dosing level must be administered in a facility capable of treating systemic allergic reactions.

The Pediatric Research Equity Act (PREA) requires that FDA consider the utility of studying Palforzia in pediatric age groups 0 through 16 years of age. At the time of the original BLA approval, a partial waiver from PREA requirements was granted for subjects <1 year of age because per Section 505B(a)(4)(B)(i) of the Federal Food Drug and Cosmetic Act, necessary studies are impossible or highly impracticable due to the small number of patients diagnosed with peanut allergy in this age group, because children <1 year of age are generally fed breast milk or formula milk and then gradually weaned onto age appropriate foods between 6 months and a year. This submission has fulfilled the postmarketing requirement (PMR) to conduct a study in children 1 through 3 years of age evaluating the efficacy and safety of Palforzia. A pregnancy registry study initiated as a postmarketing commitment (PMC) is ongoing.

The data submitted with this sBLA support the approval of Palforzia as a treatment to mitigate allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut in patients 1 through 3 years of age with a confirmed diagnosis of peanut allergy.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

ARC005 included 146 children 1 through 3 years of age, with 98 randomized to Palforzia and 48 to placebo. The median age in both arms was 2.0 years, with balanced representation of the age range. There were slightly more males (58.2% and 58,3%, respectively), and the majority of subjects were non-Hispanic or Latino (76.5% and 64.6%, respectively) and White (67.3% and 66.7%, respectively), followed by Asian (18.4% and 22.9%, respectively) and Black (4.1% and 4.2%, respectively). A slight majority of subjects, 57.5%, resided in the US. Subgroup analysis of non-White subjects was not powered to demonstrate efficacy, however, the data trend toward an efficacious treatment effect (Table 13 under Section 6.1.11.3). Sex and geographic distribution do not appear to affect the treatment effect.

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Immunoglobulin E (IgE)-mediated food allergy is a deleterious immune response to food proteins characterized by acute onset of symptoms generally within 2 hours after ingestion of, or exposure to, the protein (Burks et al., 2012). The clinical presentation includes a range of symptoms from oral pruritus to acute urticaria/angioedema which can progress to more serious sequelae such as anaphylaxis, hypotension, and multiple organ dysfunction syndrome (Burks et al., 2012).

The most common food allergens are peanut, tree nut, milk, egg, soy, wheat, fish, and shellfish (Adkinson et al., 2014; FDA, 2022). As of January 1, 2023, sesame is now required to be labeled as an allergen on packaged foods in addition the eight existing major food allergens (cow's milk, eggs, fish, shellfish, tree nuts, peanuts, wheat, and soybeans) (FDA, 2023a). These constitute the nine major food allergens declared by federal law (FDA, 2023b) and more than 90% of food allergies in children (Sicherer, 2018). Some food allergies (milk, egg, wheat, and soy) have an increased chance of resolving with age whereas others (peanut, tree nut, and shellfish) tend to be persistent over time (Jackson, 2013).

Food allergy affects up to 15 million people in the US, approximately 6 million of whom are children. In 2021, the National Center for Health Statistics reported 5.8% of children 0-17 years of age have a diagnosed food allergy (Zablotsky et al., 2021). Quality of life (QoL) in food-allergic individuals and their caregivers is often adversely affected due to the fear of accidental ingestion as well as the burden of avoiding allergenic foods which is associated with significant anxiety (Yu, 2006).

Peanut allergy is the leading pediatric food allergy and a common cause of anaphylaxis (Warren et al., 2021). Peanut allergy is often diagnosed in childhood when most food allergies develop. The prevalence of peanut allergy in children <5 years of age is estimated to be 0.75-1.3%, and in adults the prevalence is about 0.7% (Sicherer, 2018). Only about 20% of children outgrow a peanut allergy (Sicherer, 2018).

A 3.5-fold increase in peanut allergy prevalence has been reported in recent years, with 1 to 2% of children in Western countries affected (Lange, 2021). A study sponsored by the National Institute of Allergy and Infectious Diseases randomly assigned 640 infants with severe eczema, egg allergy, or both to consume or avoid peanuts until 60 months of age (Du Toit et al., 2015). Results showed that early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts.

For young children with peanut allergies, dietary avoidance is the current standard of care (Jones et al., 2022). Despite peanut avoidance, accidental exposures occur. Two studies estimated that accidental exposures occur at an annual incidence of 12.4% and 14.3% in peanut allergic children (Cherkaoui et al., 2015; Patel et al., 2011). The potential consequences of accidental exposure can be serious and life-threatening. About 50% of cases of anaphylaxis reported by emergency departments are due to a food allergen (Cox, 2011). From 1999 to 2009, hospitalizations due to peanut-related anaphylaxis doubled (from 4% to 7%) (Ma, 2014).

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

Omalizumab, an anti-IgE humanized IgG1 monoclonal antibody, was approved February 16, 2024, for the indication of IgE-mediated food allergy in adult and pediatric patients 1 year of age and older for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods. Omalizumab is to be used in conjunction with food allergen avoidance. The prescribing information (PI) has a boxed warning for anaphylaxis and is contraindicated in individuals with a severe hypersensitivity reaction to omalizumab or to any excipient.

Otherwise, in children 1 through 3 years of age, therapeutic options for mitigating the symptoms of allergic reactions are limited to immediate injection of epinephrine for suspected or confirmed anaphylaxis or with antihistamines for milder symptoms.

2.3 Safety and Efficacy of Pharmacologically Related Products

Palforzia is the only licensed allergen immunotherapy for the treatment of IgE-mediated food allergy. No pharmacologically related products are currently licensed.

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

Palforzia was approved by the FDA on January 31, 2020. It is indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. It is approved for use in patients with a confirmed diagnosis of peanut allergy. Initial dose escalation may be administered to patients 4 through 17 years of age; up-dosing and maintenance may be continued in patients 4 years of age and older (Palforzia PI, 2020). The efficacy in children 4 through 17 years of age was demonstrated with a treatment difference (efficacy) estimate of 63.2% (95% CI: 53.0, 73.3). The main safety concerns associated with oral immunotherapy include allergic reactions including systemic allergic reactions and anaphylaxis, use of

epinephrine (to treat/prevent systemic allergic reactions), and EoE. A higher proportion of Palforzia recipients had adverse events (AEs) of concern with oral immunotherapy, namely systemic allergic reactions and anaphylaxis, epinephrine use to treat/prevent systemic allergic reactions, and EoE.. Twenty-two Palforzia recipients were diagnosed with EoE during both the up-dosing and maintenance periods in the entire clinical development program while no placebo recipients received a diagnosis of EoE. Due to safety concern of anaphylaxis, additional postmarketing risk mitigation via a REMS with ETASU was established in consultation with OBPV and DRISK in CDER, and with concurrence from the CBER safety working group. No new safety signals in the submitted clinical safety data or available postmarketing data from the FDA Adverse Event Reporting System (FAERS) have been identified by the PVP reviewer.

In the European Union (EU), Palforzia was authorized on December 17, 2020 through the centralized procedure (CP) and launched in Germany, Austria, Sweden and France. In the UK, the conversion of the Palforzia EU CP to Great Britain Marketing Authorisation was validated by the Medicines and Healthcare products Regulatory Agency (MHRA) on April 7, 2021. In Switzerland, Palforzia was authorized through national procedure on May 4, 2021. A European Union risk management plan (EU-RMP) was approved December 21, 2020 and updated August 22, 2022 (EMA, 2020) with a summary of safety concerns including important risks(anaphylaxis/systemic allergic reactions, EoE), potential risks (possible rebound after treatment discontinuation) and missing information (use during pregnancy and impact on long-term immune-mediated reactions). Risk minimization procedures in the EU-RMP include product labeling (warnings, precautions, and advice on correct use, in the package leaflet and summary of product characteristics [SmPC]) as well as additional measures that include healthcare professional education materials, patient/parent/caregiver educational materials, and an authorized pack size to ensure a specific amount of medicine is in a prescribed pack as well as different colored capsules to ensure the medication's correct use. No new safety signals were identified in the postmarketing setting through a query of ARGUS, a global pharmacovigilance safety database .

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

The following timeline includes a list of major pre-submission regulatory activity associated with the submission of this sBLA:

- April 12, 2013: The Applicant submitted an initial Phase 2 study (ARC001) to open IND 15463.
- May 10, 2013: A request for Fast Track Designation was granted.
- June 15, 2015: A request for Breakthrough Therapy Designation was granted.
- July 20, 2015: A Type B, End of Phase 2 (EOP2) Meeting was held. CBER requested a more stringent primary endpoint criterion in Phase 3 studies for demonstrating the treatment effect between the Palforzia and placebo groups, ideally with a lower bound of the 95% confidence interval (CI) of about 15% and a longer maintenance dosing period extended from 3 to 6 months to a total of 12 months in the study.
- January 21, 2016: FDA Allergenic Products Advisory Committee (APAC) was convened to obtain advice regarding the design of protocols to evaluate investigational allergenic immunotherapies intended to treat IgE-mediated food allergy.
- January 31, 2017: A teleconference was convened to discuss design elements of Phase 3 studies. The Applicant agreed to revise the primary efficacy endpoint for Study ARC003, to include only pediatric subjects ages 4 to 17 years of age because it was

unlikely the number of adults in the study program (N=56) would be adequate to demonstrate effectiveness of the product in the adult population.
- September 24, 2018: A type B, pre-BLA meeting was held. The format and content of including submission of efficacy and safety datasets was agreed upon for the original BLA evaluating subjects 4 through 17 years of age.
- December 21, 2019: The original BLA was submitted to FDA.
- September 13, 2019: APAC was convened to consider the safety and effectiveness data submitted in support of the requested indication for the age range of 4 through 17 years. The committee voted affirmatively that the available data supported the safety (vote: 8 Yes, 1 No, 0 Abstain) and effectiveness (vote: 7 Yes, 2 No, 0 Abstain) of Palforzia treatment. The committee supported the establishment of a REMS to support the safe use of Palforzia.
- January 31, 2020: Palforzia was approved by the FDA for use in patients with a confirmed diagnosis of peanut allergy, 4 through 17 years of age.
- June 22, 2021: Deferral extension for Study ARC005 was granted due to delays related to the COVID-19 pandemic.

Post submission, a total of 22 amendments were submitted in response to CBER clinical information requests. These amendments satisfactorily addressed all clinical information requests sent during the review period and have been incorporated into this memorandum.

2.6 Other Relevant Background Information

Not applicable.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The application was adequately organized and integrated to accommodate the conduct of a complete clinical review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The Applicant attested that the studies submitted in support of this application were conducted in compliance with Good Clinical Practices.

3.3 Financial Disclosures

Covered clinical study (name and/or number): ARC005
Was a list of clinical investigators provided? Yes
Total number of investigators identified: 235
Number of investigators who are sponsor employees (including both full-time and part-time employees): None
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None

Number of investigators with certification of due diligence (Form FDA 3454, box 3): 234
Is an attachment provided with the reason? Yes

Clinical Reviewer comment: One sub-investigator left the institution (based in the UK) prior to signing a financial disclosure, the site provided this information to the Applicant. Given that the remaining 234 investigators have certification of due diligence for Study ARC005, it is unlikely that this one instance of a missing disclosure from a subinvestigator would affect the data presented in this application.

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

4.1 Chemistry, Manufacturing, and Controls

This submission did not include new CMC data and therefore did not prompt any efficacy or safety concerns. Please see the original CMC review by Drs. Hillyer and Panda for details on CMC considerations.

4.2 Assay Validation

Not applicable.

4.3 Nonclinical Pharmacology/Toxicology

Non-clinical studies including pharmacology and toxicology studies were deemed not to be necessary because Palforzia is a food product.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The precise mechanisms of action of allergen immunotherapy have not been established.

4.4.2 Human Pharmacodynamics (PD)

In ARC005, peanut specific IgE in Palforzia recipients decreased from screening (baseline) to study exit. In the ITT population, the geometric mean (SD) peanut specific IgE of Palforzia recipients was 7.04 (6.712) kUA/L at the screening (n=87) and 3.33 (7.813) kUA/L at exit (n=76). In placebo recipients, peanut specific IgE increased from screening to exit. The geometric mean (SD) peanut specific IgE was 12.26 (8.429) kUA/L at screening (n=45) and 22.52 (6.796) kUA/L at exit (n=38).

In contrast, peanut specific IgG4 increased from screening (baseline) to study exit in Palforzia recipients . The geometric mean (SD) peanut specific IgG4 of the Palforzia recipients was 385.773 (3.8797) mega/L at the screening (n=85) and 3396.998 (4.5179) mgA/L at the exit (n=76). For placebo recipients, the geometric mean (SD) peanut-specific IgG4 was 375.874 (3.9267) mgA/L at the screening (n=45) subjects and 518.675 (4.6027) mgA/L at the exit (n=39).

Clinical Reviewer comment: Increases in specific IgG4 and decreases in specific IgE are known to occur during food allergen specific immunotherapy. This trend is known to occur across

different food allergens and routes of administration. The data from ARC005 are consistent with these trends (Smeekens, 2020).

The mechanism of allergen-specific IgG inhibition of allergic responses is thought to occur through blocking of the activation of IgE-dependent activation of mast cells and basophils (Durham, 2023).

4.4.3 Human Pharmacokinetics (PK)

Not applicable.

4.5 Statistical

A complete statistical review of the clinical studies submitted to the BLA was conducted by Zhong Gao, PhD who verified the safety and efficacy data and conclusions submitted to the BLA.

4.6 Pharmacovigilance

A complete review of the pharmacovigilance plan (PVP) was conducted by Dr. Brendan Day. The Applicant did not propose any major changes to the pre-existing PVP plan or REMS. Per Dr. Day, findings from REMS assessment reports have not resulted in any new REMS modifications. This reviewer determined that, according to the most recently reviewed REMS assessment report (48-month), the Palforzia REMS Program was meeting its goal of mitigating the risk of anaphylaxis. Minor changes to the REMS documented consisted of changes to align the REMS Document and REMS materials with editorial changes in the United States Package Insert (USPI) to improve clarity regarding the first dose of each “new” Up-Dosing level, and to include the different dosing regimen for the younger age group (patients 1 through 3 years of age. No new safety concerns were identified through review of the submitted clinical safety data or review of available postmarketing safety data in FAERS. Please see Dr. Day’s memo for further details.

During the pre-licensure development program, systemic allergic reactions to Palforzia, including anaphylaxis, were observed to occur during all phases of dosing (initial dose escalation, up-dosing, and maintenance), with the highest risk of such reactions associated with the initial dose escalation and up-dosing. During review of the original BLA that led to the licensure of Palforzia in children 4 through 17 years of age, the Applicant instituted a REMS with ETASU (in addition to routine pharmacovigilance) based on numerous collaborative discussions with CBER’s OBPV and CDER’s DRISK, with concurrence from the CBER safety working group

From the original BLA review, the six factors considered, as required by Section 505-1(a)(1) of the FD&C Act, as added by FDAAA, were:

1. The seriousness of any known or potential AEs that may be related to the drug and the background incidence of such events in the population likely to use the drug
2. The expected benefit of the drug with respect to the disease or condition
3. The seriousness of the disease or condition that is to be treated with the drug
4. Whether the drug is a new molecular entity
5. The expected or actual duration of treatment with the drug
6. The estimated size of the population likely to use the drug

In particular, for Palforzia, the main factors contributing to the original decision to require a REMS ETASU were: the imbalance of systemic allergic reactions and epinephrine use as a

rescue medication (factor 1) over the duration of treatment (factor 6) which is likely to be life-long as most children do not grow out of IgE-mediated peanut allergy; the seriousness of IgE-mediated peanut allergy which can be fatal (factor 3); and the benefit of treatment as evidenced by the efficacy Study ARC003 (factor 2).

The REMS includes the following:

- Documentation that any patient prescribed Palforzia has a valid prescription for injectable epinephrine, has been counseled on the risks of Palforzia, and will maintain a peanut avoidant diet.
- Attestation from caregivers/patients to carry injectable epinephrine while on Palforzia.
- Initial dose escalation and the first dose of each up-dosing level must be administered in a certified facility capable of treating systemic allergic reactions.

No substantial changes were made to the REMS which remains in place to ensure the benefits of Palforzia therapy outweigh the risks. For further information, please see the original REMS clinical memo.

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

5.1 Review Strategy

Assessment of the safety and efficacy of Palforzia in children 1 through 3 years of age was based on review of Phase 3 Study ARC005. ARC008 was a Phase 3 uncontrolled follow-on study for eligible participants from all studies in the Palforzia program, including ARC005 (n=72 Palforzia recipients and 40 placebo recipients), that was completed after this sBLA was submitted (CSR submitted to IND15463 in April 2024). CBER requested an updated summary of safety from Study ARC008 be submitted to the sBLA with information pertaining specifically to any ARC005 participants that entered the follow-on study. Throughout the review, the safety and efficacy of Palforzia in subjects 1 through 3 years of age are considered in the context of safety and efficacy data submitted to the original BLA for children 4 through 17 years of age.

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

The following files served as the basis for the clinical review of STN 125696/247:

- STN125696/247.0 :
    - Section 1.2 Cover Letters
    - Section 1.3.4 Financial Certification and Disclosures
    - Section 1.11 Information Not Covered Under Modules 2 to 5
    - Section 1.12 Other Correspondence
    - Section 1.14 Labeling
    - Section 2.2 Introduction
    - Section 2.5 Clinical Overview
    - Section 2.7 Clinical Summary
    - Section 5.2 Tabular Listing of all Clinical Studies
    - Section 5.3 Clinical Study Reports

- STN125696/247.1, Section 1.3.3 Debarment certification
- STN125696/247.3, Section 2.7.4 Revised Summary of Clinical Safety
- STN125696/247.4, Section 1.16 Risk Management Plan
- STN125696/247.8, Section 1.11.3 Clinical Information Amendment
- STN125696/247.9, Section 1.11.3 Clinical Information Amendment
- STN125696/247.11, Section 1.11.3 Clinical Information Amendment

- STN125696/247.13
  - Section 1.11.4 Multiple Module Information Amendment
  - Section 1.14.1 Draft Labeling
- STN125696/247.14
  - Section 1.11.4 Multiple Module Information Amendment
  - Section 1.14.1 Draft Labeling
- STN125696/247.16, Section 1.11.3 Clinical Information Amendment
- STN125696/247.18
  - Section 1.11.3 Clinical Information Amendment
  - Section 5.3 Clinical Study Reports
- STN125696/247.19, Section 1.14.1 Draft Labeling
- STN125696/247.20, Section 1.14.1 Draft Labeling
- STN125696/247.22, Section 1.11.3 Clinical Information Amendment
- STN125696/247.23, Section 1.11.3 Clinical Information Amendment
- STN125696/247.26, Section 1.11.3 Clinical Information Amendment
- STN125696/247.28, Section 1.14.1 Draft Labeling
- STN125696/253.0 Annual report

5.3 Table of Studies/Clinical Trials

Table 1. Summary of Clinical Development

Trial ID *Study Dates (Month/Year)*	**Trial Design**	**Treatment Arms**	**Study Endpoints**	**Treatment Duration**	**N**	**Study Population** (Years of Age)	**Geographic Region** (Number of Sites)
Controlled Study to Support sBLA	--	--	--	--	--	--	--
ARC005 (NCT03736447) *12/18-07/22*	Phase 3, R, DB, PC, MC	300mg Palforzia daily: Placebo (2:1)	Ingestion* of 600mg peanut protein at exit DBPCFC	12 months	146	1-3	US (14), EU (9)
Other Controlled Studies	--	--	--	--	--	--	--
ARC001 (NCT01987817) *2/14-1/15*	Phase 2, R, DB, PC, MC	300mg Palforzia daily: Placebo (1:1)	Ingestion* of 300mg peanut protein at exit DBPCPC	9 months	56	4-26	US (8)
ARC003 (NCT02635776) *12/15-1/16*	Phase 3, R, DB, PC, MC	300mg Palforzia daily: Placebo (3:1)	Ingestion* of 600mg peanut protein at exit DBPCFC	12 months	555	4-55	NA (51), EU (15)
ARC007 (NCT03126227) *5/17-8/18*	Phase 3, R, DB, PC, MC	300mg Palforzia daily: Placebo (2:1)	Safety	6 months	505	4-17	US (59), CA (5)

Trial ID *Study Dates (Month/Year)*	**Trial Design**	**Treatment Arms**	**Study Endpoints**	**Treatment Duration**	**N**	**Study Population** (Years of Age)	**Geographic Region** (Number of Sites)
Uncontrolled Follow-On Studies	--	--	--	--	--	--	--
ARC002 (NCT02198664) *8/14-1/18*	Phase 2, OL, MC, follow-on for ARC001	300mg Palforzia 2000mg Palforzia	Safety	2.7 years	47	4-26	US (8)
ARC004 (NCT02993107) *12/16-5/19*	Phase 3, OL, follow-on for ARC003	300mg Palforzia daily, QOD, BIW, QW, or QOW	Safety	3 years	388	4-55	NA (51), EU (13)
ARC008 (NCT03292484) *11/17-4/23*	Phase 3, OL, follow-on for all Palforzia studies	300mg Palforzia daily, QOD, BIW, QW, or QOW	Safety	3 years	911	4-55	US (61), CA (5), EU (18)
ARC011 (NCT03337542) *10/17-9/19*	Phase 3, OL, follow-on for ARC007	300mg Palforzia daily	Safety	6 months	243	4-17	NA (63)

Source: FDA-generated table
Abbreviations: ID=identification; R=randomized; DB=double-blind; PC=placebo-controlled; MC=multi-center; OL=open label;; DBPCFC=double-blind placebo-controlled food challenge; BIW=twice weekly; QOD=every other day; QOW=every other week; QW=once weekly; US=United States; CA=Canada; NA=North America; EU=European Union

5.4 Consultations

None.

5.4.1 Advisory Committee Meeting (if applicable)

Not applicable

5.4.2 External Consults/Collaborations

None.

5.5 Literature Reviewed

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study ARC005

NCT03736447
Title: “Peanut oral immunotherapy study of early intervention for desensitization (POSEIDON)”

6.1.1 Objectives (Primary, Secondary, etc.)

Primary

- Efficacy of Palforzia treatment in peanut allergic subjects 1 through 3 years of age, assessed by tolerability of a single dose of 600 mg peanut protein in a DBPCFC

Secondary

- Safety and tolerability of study treatment
- Efficacy of Palforzia, assessed by tolerability of single doses of 300 mg and 1000 mg 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 Palforzia in peanut-allergic children 1 through 3 years of age. Subjects were randomly assigned 2:1 to blinded treatment with Palforzia or placebo. Randomization was stratified by geographic region (North America [n=14 sites], Europe [n=9 sites]).

Prior to enrollment, subjects underwent a DBPCFC with up to 300 mg peanut protein and with placebo to confirm true peanut allergy. 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 were enrolled. The food challenge was considered positive and halted if ≥1 major criteria or ≥2 minor criteria were present. Specific dose limiting symptoms under major and minor criteria are presented in Table 2 criteria below:

Table 2. Food Challenge Stopping Criteria for Subjects 1 through 3 Years of Age

Major Criteria (stop food challenge if ≥1 criteria are present)	**Minor Criteria (stop food challenge if ≥2 criteria are present)**
• Confluent erythematous, pruritic rash • ≥3 urticarial lesions • ≥1 site of angioedema • Respiratory (at least 1 of the following): – Wheezing – Repetitive cough – Difficulty breathing or increased work of breathing – Stridor – Dysphonia – Aphonia • Hypotension for age not associated with vasovagal episode • Evidence of severe abdominal pain (e.g., abnormal stillness, inconsolable crying, doubling over/drawing legs up to the abdomen) persisting ≥3 minutes	• Vomiting (except gag reflex-induced vomiting during feeding) • Diarrhea • Persistent rubbing of nose or eyes ≥3 minutes • Persistent rhinorrhea ≥3 minutes • Persistent scratching ≥3 minutes

Source: Applicant ARC005 protocol v4, Appendix 1, Table 2. Adapted from the LEAP study protocol and guidelines from the AAAAI Adverse Reactions to Foods Committee (Bird, 2017; Du Toit, 2015).
Notes: Symptoms should be of new onset and must occur within 2 hours after the last dose. Quantitative criteria (e.g., persistent scratching ≥3 minutes) are continuous, not cumulative during the entire double-blind, placebo-controlled food challenge. The food challenge will be considered positive if ≥1 major criteria or ≥2 minor criteria are present. The food challenge will be considered indeterminate if 1 minor criterion is present at the time the food challenge is stopped (i.e., onset of the first minor symptom does not meet the food challenge stopping rules). The food challenge will be considered negative if both major and minor criteria are absent.

Table 3. Guide for Assessment of Allergic Reaction Symptom Severity by Organ System

Organ System	**Mild Symptoms**	**Moderate Symptoms**	**Severe Symptoms**
Skin	Limited (few) or localized hives, swelling (e.g., mild lip edema), skin flushing (e.g., few areas of faint erythema) or pruritus (mild, e.g., causing occasional scratching)	Systemic hives (e.g., numerous or widespread hives), swelling (e.g., significant lip or face edema), pruritus causing protracted scratching, more than a few areas of erythema or pronounced erythema	Severe generalized urticaria/ angioedema/ erythema
Respiratory	Rhinorrhea (e.g., occasional sniffling or sneezing), nasal congestion, occasional cough, throat discomfort	Throat tightness without hoarseness, persistent cough, wheezing without dyspnea	Laryngeal edema, throat tightness with hoarseness, wheezing with dyspnea, stridor
Gastrointestinal	Mild abdominal discomfort (including mild nausea), minor vomiting (typically a single episode), and/or a single episode of diarrhea	Persistent moderate abdominal pain/ cramping/ nausea, more than a single episode of vomiting and/or diarrhea	Severe abdominal pain/ cramping/ repetitive vomiting and/or diarrhea
Cardiovascular/ Neurologic	Subjective response (weak, dizzy), or tachycardia	Moderate drop in blood pressure and/or >20% from baseline, or significant change in mental status	Cardiovascular collapse, signs of impaired circulation (unconscious)

Source: Applicant ARC005 protocol v4, Appendix 1, Table 3. Adapted from Practical Allergy (PRACTALL) guidelines (Sampson, 2012).

After randomization, subjects began initial dose escalation under medical supervision at the study site 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. When multiple symptoms were present, the severity of the most severe symptom was used to determine tolerability. Mild symptoms were not considered dose limiting if they met the following tolerability criteria:

- Isolated to a single organ system
- Resolved with no medications or with ≤2 doses of oral H1 antihistamine
- Did not require administration of epinephrine
- Does not worsen in intensity or distribution over time
- Resolved or showed definite signs of resolving in under 1 hour
- Did not include objective wheezing

Subjects who did not tolerate any dose on Day 1 or Day 2 discontinued early from the study.

The up-dosing period was approximately 6 months (maximum 40 weeks), with daily dose escalation approximately every 2 weeks over the following 12 steps: 1, 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, and 300 mg/day. The first dose of study product at each new step was administered under medical supervision at the study site; the subsequent remaining doses at each step were administered daily at home as tolerated. Tolerability (i.e., absence of dose-limiting symptoms) was assessed throughout the study. Dose adjustments were allowed. 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.

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 underwent an exit DBPCFC (conducted over two days, with one day with escalating doses of peanut and another day placebo administered over the same number of steps) to assess efficacy for the primary endpoint. Single doses of 3, 10, 30, 100, 300, 600, 1000, and 2000 mg peanut protein or placebo (4043 mg cumulative) were evaluated in the exit DBPCFC. Subjects were considered responders for the primary endpoint if 600 mg of peanut protein was ingested with no or only mild symptoms (see tolerability criteria above). The 300 mg daily dose of study product had to be tolerated for at least 2 consecutive weeks (e.g., no dose interruptions or dose changes/decreases due to allergic reactions) before having the DBPCFC. Eligible subjects had the option to enroll in an open-label, follow-on Study ARC008 to receive Palforzia treatment.

6.1.3 Population

Inclusion Criteria

1. Aged 1 through 3 years at randomization.

2. Written informed consent from the legal guardian/parent (or both parents where required by local authorities). Provide assent where required and as appropriate per local requirements.
3. Sensitivity to peanut, defined as one of the following:
    a. No known history of peanut ingestion and has serum IgE to peanut ≥5 kUA/L within 12 months before randomization.
    b. 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 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.

*Characteristic signs and symptoms of IgE-mediated allergic reactions are generally objective and affect the target organs of skin, GI tract, upper/lower respiratory tract, cardiovascular system, or a combination of target organs as follows:

- Cutaneous: Pruritus, erythema/flushing, urticaria, angioedema, contact urticaria
- Ocular: Pruritus, tearing, conjunctival injection, periorbital edema
- Upper respiratory tract: Pruritus, nasal congestion, rhinorrhea, sneezing, hoarseness, laryngeal edema
- Lower respiratory tract: Cough, wheezing, dyspnea, chest tightness/pain
- Gastrointestinal (GI): Oral pruritus, oral angioedema (lips, tongue, or palate), colicky abdominal pain, nausea, emesis, diarrhea
- Cardiovascular: Tachycardia, dizziness, hypotension, loss of consciousness/fainting

4. Development of age-appropriate dose-limiting allergy symptoms after consuming single doses of peanut protein >3 mg to ≤300 mg in a screening DBPCFC.
5. A palatable vehicle food to which the subject is not allergic must be available for administering study product.

Exclusion Criteria

1. History of severe or life-threatening anaphylaxis any time before the screening DBPCFC.
2. History of hemodynamically significant cardiovascular or renovascular disease, including uncontrolled or inadequately controlled hypertension.
3. History of biopsy-confirmed diagnosis of EoE; other eosinophilic GI disease; chronic, recurrent, or severe gastroesophageal reflux disease (GERD); or symptoms of dysphagia (e.g., difficulty swallowing, food “getting stuck”).
4. Recurrent GI symptoms considered clinically significant in the opinion of the investigator.
5. History of a mast cell disorder including mastocytosis, urticaria pigmentosa, chronic idiopathic or chronic physical urticaria beyond simple dermatographism (e.g., cold urticaria, cholinergic urticaria), and hereditary or idiopathic angioedema.
6. Moderate or severe persistent asthma (criteria steps 3-6; National Heart, Lung, and Blood Institute [NHLBI], 2007).
7. Mild asthma (criteria steps 1-2; NHLBI, 2007) that is uncontrolled or difficult to control based on NHLBI 2007 criteria.
8. History of high-dose corticosteroid use (e.g., 1-2 mg/kg prednisone or equivalent for 3 days) by any route of administration as defined by any of the following:
    - Steroid administered daily for >1 month within 1 year before screening
    - One steroid course within 6 months before screening
    - More than 2 steroid courses ≥1 week in duration within 1 year before screening

9. History of food protein-induced enterocolitis syndrome (FPIES) within 12 months before screening.
10. Recurrent urticaria.
11. History of failure to thrive or any other form of abnormal growth, or developmental or speech delay that precludes age-appropriate communication.
12. History of chronic disease (except mild intermittent asthma, mild persistent asthma that is controlled, atopic dermatitis, or allergic rhinitis) that is or is at significant risk of becoming unstable or requiring a change in a chronic therapeutic regimen.
13. Unable to discontinue antihistamines and other medications that could interfere with the assessment of an allergic reaction for 5 half-lives of the medication before the screening SPT, first day of dose escalation, and DBPCFCs.
14. Use or anticipated use of a prohibited medication (e.g., beta blockers [oral], angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, or tricyclic antidepressants), monoclonal antibody, or any other immunomodulatory therapy (including immunosuppressive medications).
15. Treatment with any form of immunotherapy for any food allergy any time before screening.
16. Participation in another clinical trial within 30 days or 5 half-lives of the investigational product, whichever is longer, before screening.
17. Allergy to oat or rice.
18. Hypersensitivity to epinephrine or any of the excipients in the epinephrine auto-injector.
19. Parent/caregiver unable or unwilling to use epinephrine auto-injectors.
20. Unable to follow the protocol requirements.
21. Any other condition (concurrent disease, infection, comorbidity, or psychiatric or psychological disorders) or reason that may interfere with the ability to participate in the study, cause undue risk, or complicate the interpretation of data, in the opinion of the investigator or medical monitor.
22. Resides at the same place as another subject in any Palforzia interventional trial.
23. Lives in the same household and/or is a family member of a sponsor employee or site staff involved in conducting this study.

Clinical Reviewer comment: The enrollment criteria in ARC005 appropriately define a peanut-allergic population for evaluating the efficacy and safety of Palforzia by use of an entry oral food challenge (OFC) to determine true peanut allergy. The criteria for a positive OFC are similar those used in ARC003 (a Phase 3 study that evaluated the safety and efficacy of Palforzia in children 4 through 17 years of age). The upper limit of the entry DBPCFC was raised from 100 mg in ARC003 to 300 mg in ARC005 in a subsequent protocol revision; however, none of the enrolled subjects with a confirmatory OFC reached the 300 mg dose.

ARC005 excluded subjects who had a higher risk of a serious allergic reaction to the study product such as those with a history of severe or life-threatening anaphylaxis, those taking beta blockers, those with uncontrolled asthma and those with a history of eosinophilic gastrointestinal disease including EoE. Those with a history of failure to thrive or developmental delay that precluded age-appropriate communication and a history of FPIES were also excluded because these conditions could confound the safety assessment.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The products administered in this study were either Palforzia or placebo that contained excipients color-matched to the Palforzia to maintain treatment blinding. The Palforzia active pharmaceutical ingredient was initially sourced as raw peanuts, *Arachis hypogaea*, and was

processed into food-grade, (b) (4) defatted, roasted peanut flour that contained approximately (b) (4) peanut protein (b) (4). The drug product was encapsulated in hydroxypropyl methyl cellulose (HPMC) or filled in foil-laminate sachets and supplied in color-coded pull-apart capsules at 5 dosage strengths (0.5, 1, 10, 20, and 100 mg) and 300 mg sachets. Placebos were provided as matching capsules and sachets identical to the Palforzia-containing capsules and sachets.

6.1.5 Directions for Use

Procedures for preparation and administration were the same at the study site and at home. Capsules or sachets containing Palforzia or placebo were emptied into and mixed with a vehicle food (e.g., applesauce, yogurt, pudding, or other age-appropriate semisolid matrix food). The volume of the vehicle food was to be such that the entire dose could be consumed in a few spoonfuls/mouthfuls in one sitting. The study product was to be consumed as promptly after mixing as practicable and as part of a meal for dosing at home. The study product could be stored for up to 24 hours under conditions appropriate for the food matrix in which it was prepared. For delays longer than 24 hours, the study product was to be discarded and a new study product dose mixed and consumed. It was recommended that each dose of study product was to be consumed at a consistent time (within 4 hours) each day, with an interval of at least 8 hours between doses.

Subjects were instructed to have other food (besides the matrix vehicle used to prepare the dose) in the stomach before taking the dose. In addition, subjects were cautioned against activities that increase the likelihood of allergic reactions (e.g., exercising or taking hot baths within 3 hours after ingestion). Dosing was to be delayed until signs of a hypermetabolic state (e.g., flushing, sweating, rapid breathing, and/or rapid heart rate) resolved. Ingestion was not to occur within 2 hours of bedtime. In case of illness, the parent/caregiver was advised to withhold the dose of study product from the subject and notify the study site of the symptoms and for possible dose adjustments.

6.1.6 Sites and Centers

This study was conducted in 4 countries at 14 study sites in the US and 9 in Europe (France, Germany, United Kingdom [UK]).

6.1.7 Surveillance/Monitoring

Table 4. Study Schedule of Activities: Treatment (Initial Dose Escalation, Up-Dosing, and Maintenance), Study ARC005

Initial Dose Escalation Day 1[1]	Initial Dose Escalation Day 2[2]	Up-Dosing (every 2 wks up to 40 wks), ±3-day window	Up-Dosing 80 mg and 300 mg varies, ±3-day window	Maintenance (every 4 wks for 12-24 wks[5]) varies, ±3-day window)	Unscheduled[3]	ED/ Exit[4] varies, ±5-day window
• Randomization • Weight, height • Vital signs[7] • Complete physical examination[11] • Diet/food allergen exposure review • Food allergy instruction[12] • AEs review[13] • Concomitant medications review & instruction[14] • Study product administration[15]	• Weight, height • Vital signs[7] • Symptom-directed physical examination[11] • Diet/food allergen exposure review • Food allergy instruction[12] • AEs review[13] • Concomitant medications review & instruction[14] • Study product administration[15] • Study product dispensing[16] • Telephone call[17]	• Weight, height • Vital signs[7] • Symptom-directed physical examination[11] • Diet/food allergen exposure review • Food allergy instruction[12] • AEs review[13] • Concomitant medications review & instruction[14] • Study product administration[15] • Study product dispensing[16] • Study product accountability • Telephone call[17]	• TRACK[6] • Weight, height • Vital signs[7] • Asthma evaluation[8] • EASI score[9] • Complete physical examination[11] • Diet/food allergen exposure review • Food allergy instruction[12] • AEs review[13] • Concomitant medications review & instruction[14] • Study product administration[15] • Study product dispensing[16] • Study product accountability • Telephone call[17]	• TRACK[6] • Weight, height • Vital signs[7] • Asthma evaluation[8] • Complete physical examination[11] • Diet/food allergen exposure review • Food allergy instruction[12] • AEs review[13] • Concomitant medications review & instruction[14] • Study product administration[15] • Study product dispensing[16] • Study product accountability • Telephone call[17]	• TRACK (opt)[6] • Weight, height • Vital signs[7] • Asthma evaluation (opt)[8] • EASI score (opt)[9] • Symptom-directed physical examination[11] • Complete physical examination (opt)[11] • Diet/food allergen exposure review • Food allergy instruction (opt)[12] • AEs review[13] • Concomitant medications review & instruction[14] • Study product administration (opt)[15] • Study product dispensing (opt)[16] • Study product accountability (opt) • Telephone call (opt)[17]	• TRACK[6] • Weight, height • Vital signs[7] • Asthma evaluation[8] • EASI score[9,10] • Complete physical examination[11] • Diet/food allergen exposure review • Food allergy instruction[12] • AEs review[13] • Concomitant medications review & instruction[14] • Study product accountability • Telephone call[17] • Skin prick test to peanut extract[10] • Palatability survey • DBPCFC[18] • Hematology, immunology[20,10] • Blood sample for evaluation of cellular responses to peanut antigen (opt, certain study sites only)[10]

Source: Applicant ARC005 Protocol Amend 4.0, pgs. 109-110, Adapted from Appendix 5

Abbreviations: DBPCFC=double-blind, placebo-controlled food challenge; EASI=Eczema Area and Severity Index; ED=early discontinuation; GI=gastrointestinal; Ig=immunoglobulin; na=not applicable; NHLBI=National Heart, Lung, and Blood Institute; opt=optional; TRACK=Test for Respiratory and Asthma Control in Kids; wks=weeks; AE=adverse event; PI=prescribing information.

Notes:

1. Day 1 activities must begin within 42 days after obtaining signed consent and assent (where required) and within 10 days after the second day of the screening DBPCFC. The timing of Day 1 study product administration, vital signs, and assessment of allergic reactions for initial dose escalation is presented in Applicant Protocol Amendment 4.0, March 17, 2021, pg. 29, Table 2.

2. Day 2 should be the next consecutive day after Day 1. Day 2 may be delayed up to 7 days after Day 1 if unexpected circumstances (e.g., an intercurrent illness) create a safety risk.
3. Anytime necessary to assess or follow up AEs, at the request of the parent/caregiver, or per investigator decision. Perform procedures as appropriate.
4. Early discontinuation: For subject who discontinues treatment early; approximately 14 days after the last dose.
5. Exit: For subject who completes initial dose escalation, up-dosing, and maintenance for an overall total of approximately 12 months of treatment, and both days of the exit DBPCFC. If the follow-on study is not yet available at the study site, blinded study treatment may continue and the visit schedule will be every 4 weeks until the follow-on study is available.
6. For subject not enrolling in the follow-on study, the exit visit is approximately 14 days after the last dose.
7. The first maintenance visit will occur after 300 mg/day is tolerated for 2 weeks during up-dosing. Maintenance treatment will continue daily for an overall total of approximately 12 months of treatment. The duration of maintenance treatment may vary from a minimum of 12 weeks to a maximum of 24 weeks depending on the up-dosing interval (24-40 weeks).
8. For subject with asthma. Instruct parent/caregiver to complete TRACK at the start of the visit before other procedures and before the DBPCFC on both days of the DBPCFC.
9. Vital signs include blood pressure, heart rate, temperature, respiratory rate, and oxygen saturation level. Measure pre-dose, at 15-30 minutes post-dose, and every approximately 30 minutes thereafter (until at least 90 minutes post-dose or end of observations for allergy symptoms, whichever is last). During maintenance treatment, the post-dose observation period may be shortened to approximately 30 minutes if no allergy symptoms occurred during the previous 3 maintenance visits.
10. For subject with asthma. Evaluate asthma severity per 2007 NHLBI criteria. Evaluate asthma before the DBPCFC on both days of the DBPCFC.
11. For subject with eczema or atopic dermatitis. Assess eczema or atopic dermatitis.
12. Perform/collect at early discontinuation visit or before the exit DBPCFC begins (same day or any previous day within the exit visit window are acceptable).
13. Symptom-directed: Assess systems per standard of care at the study site or as clinically indicated by symptoms.
14. Complete: Assess systems (e.g., general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal).
15. Instruct that subject is to avoid peanut during the study. Provide food/peanut allergy education (including recognition of an allergic reaction, symptoms of anaphylaxis, administration of epinephrine auto-injector, anaphylaxis action plan, ways to minimize accidental exposure to peanut) per standard of care at the study site.
16. Include review of symptoms recorded in subject diary. For subject with GI AEs of interest, instruct parent/caregiver to complete the PEESS v2.0 questionnaire while subject is symptomatic, at early discontinuation or study exit, and during safety follow-up. Subject with unresolved AEs at early discontinuation or exit and subject with GI AEs of interest will have safety follow-up per Appendix 6.
17. Review medications since previous visit. Instruct that subject is to discontinue antihistamines and other medications that could interfere with the assessment of an allergic reaction 5 half-lives of the medication before initial dose-escalation day 1, skin prick tests, and the exit DBPCFC. Review the PI to determine the half-life of each medication for the subject's relevant age group.
18. Administer study product at the study site per the dose-escalation schedules and dose modification guidelines. Measure vital signs and assess signs/symptoms of allergic reaction at 15-30 minutes post-dose and every approximately 30 minutes thereafter (until at least 90 minutes post-dose or end of observations for allergy symptoms, whichever is last). During maintenance treatment, the post-dose observation period may be shortened to approximately 30 minutes if no allergy symptoms occurred during the previous 3 maintenance visits.
19. Review instructions for administration of study product at home. Instruct that subject withhold study product when it will be administered at the study site and on the days of the exit DBPCFC.
20. Contact parent/caregiver by telephone for AEs review and to inquire about compliance with study product dosing on the day after initial dose-escalation Day 2, up-dosing visits, maintenance visits, and the exit DBPCFC. Remind parent/caregiver to record symptoms in the diary (except after completion of the exit DBPCFC).
21. For subject who completes an overall total of approximately 12 months of treatment and tolerates the 300 mg daily dose of study product for at least 2 consecutive weeks before having the exit DBPCFC. Conduct on 2 separate days within 7 days.
22. Refer to the laboratory manual for sample collection and processing.
23. Complete blood count with differential. Total, peanut-specific, and peanut component-specific IgE. Peanut-specific and peanut component-specific IgG4.

Study Monitoring
Table 4 above summarizes the schedule of activities for Study ARC005. For this study, two site audits were conducted. Study monitors contacted and visited the study sites regularly to inspect the study records. The study monitors inspected the case report forms and verified adherence to the protocol and the completeness, correctness, and accuracy of all case report form entries. They had access to laboratory test results and any other source records and data needed to verify the entries on the case report forms. The investigators agreed to cooperate with the study monitors to ensure that any problems detected during these monitoring visits were resolved. A sponsor medical monitor or clinical research associate attended several monitoring visits to randomly monitor work conducted by the contract research organization. When restrictions due to COVID-19 and associated challenges prevented the conduct of study site visits, study monitoring was conducted remotely until onsite study monitoring visits could resume.

Safety Monitoring
Diaries were used to document daily dosing and any reaction to home administration of study product. Study product compliance was monitored at study visits by comparing the returned unused study product with the daily dosing diary records. The diaries were also used to record lost or destroyed doses of study product at home. All unused study product and used capsules/sachets were to be returned to the study site at each visit, subjects or parents/caregiver of subjects were questioned about AEs and use of concomitant medications since their last visit, and diaries were reviewed.

Subjects who discontinued early were to return for early discontinuation procedures 14 days after the last dose of study product. Subjects were to be monitored for safety until the early discontinuation visit. Subjects with ongoing AEs were to have safety follow-up for at least 30 days or until the AEs resolved or stabilized (whichever was last), or until consent for follow-up was withdrawn.

Subjects who had GI AEs of interest were to have safety follow-up for at least 6 months or until consent for follow-up was withdrawn. For chronic or recurrent GI symptoms persisting after 6 months, follow-up was to continue for up to 1 year or until chronic or recurrent GI symptoms resolve or consent for follow-up was withdrawn, whichever was first.

The Data and Safety Monitoring Committee (DSMC) met periodically to review accruing safety data. The independent committee consisted of 3 clinicians and 1 biostatistician with relevant experience in adult and pediatric peanut allergy, and in the conduct and monitoring of randomized clinical trials. Committee members were not involved in the conduct of the study.

Efficacy Monitoring
The primary objective of Study ARC005 was to determine the efficacy of Palforzia through increasing threshold reactivity based on exit DBPCFCs, which occurred over two days (one day with peanut and one day with placebo). Compared to screening DBPCFC, the exit challenge included 3 additional peanut protein doses of 600 mg, 1000 mg and 2000 mg.

The DBPCFC followed procedures adapted for young children based on PRACTALL guidelines and guidelines from the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma, and Immunology workgroup (Bird, 2017; Sampson, 2012) (see Table 5 below).

Table 5. Modified PRACTALL Guidelines for Screening and Exit DBPCFCs

Timing	Peanut Protein Dose (mg)	Cumulative Peanut Protein (mg) Screening	Cumulative Peanut Protein (mg) Exit
Screening	1	1	0 (or 1)[a]
Screening/Exit	3	4	3 (or 4)
Screening/Exit	10	14	13 (or 14)
Screening/Exit	30	44	43 (or 44)
Screening/Exit	100	144	143 (or 144)
Screening/Exit	300	444	443 (or 444)
Exit	600	-	1043 (or 1044)
Exit	1000	-	2043 (or 2044)
Exit	2000	-	4043 (or 4044)

Source: Applicant CSR, ARC005, pg. 29, Table 4
Abbreviations: DBPCFC=double-blind, placebo-controlled food challenge
Notes:
a. The 1 mg challenge dose may be administered at the exit DBPCFC per investigator decision.

Before the DBPCFC, subjects were assessed to ensure they were at baseline health and that those with concurrent asthma and chronic atopic diseases were adequately controlled. Antihistamines and other medications that could interfere with the assessment of an allergic reaction were required to be discontinued for approximately 5 half-lives of the medication before the DBPCFC. DBPCFCs were performed under medical supervision at the study site and followed established procedures with emergency medications and trained staff immediately available. Vital signs were measured before each challenge dose of the DBPCFC; if the interval between challenge doses was prolonged, vital signs were measured at approximately 15-minute intervals post-dose.

Dose-limiting symptoms were assessed during the DBPCFC by the study physician blinded to treatment assignment, and who was not involved directly in the oversight of study product dosing or the assessment or management of AEs. The same study physician was to oversee the screening and exit DBPCFC for any given subject as practicable.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint (North America)

The primary efficacy endpoint is the proportion of subjects treated with Palforzia compared with placebo who tolerate an at least 600 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC. Subjects who tolerated 600 mg were considered responders for the primary efficacy endpoint. The primary efficacy estimate was calculated as the difference in the rate of responders in the Palforzia group relative to the placebo group. The pre-specified success criterion for efficacy was a lower bound of the 95% CI for the primary efficacy estimate was greater than 15%.

Clinical Reviewer comment: The pre-specified criterion for success was the same as the criterion utilized to determine efficacy of Palforzia in ARC003 which, in consideration of the risks and benefits, led to the licensure of Palforzia in children 4 through 17 years of age. This criterion was originally agreed upon between CBER and the Applicant at the EOP2 meeting. The lower bound of 15% (of the 95% CI) was determined to represent a clinically meaningful benefit based on the results of early phase studies. The ability to tolerate a single dose of 600 mg peanut protein with no more than mild symptoms was considered to translate into protection against accidental exposure to approximately 2 peanut kernels. Protection against a serious allergic reaction upon accidental exposure is as important in children 1 through 3 years of age as it is for

older children. A recent study of bakery items purchased in two major cities showed that some baked goods were cross-contaminated with 0.07 mg to 474.5 mg of peanut protein consumption per single eating episode based on National Health and Nutrition Examination Survey (NHANES) average consumption estimates (Miller et al., 2022).

The primary efficacy analyses were conducted using the ITT population. Subjects who withdrew consent or discontinued early at any time before the exit DBPCFC were also considered nonresponders in the ITT population. The number and percentage of responders (those able to ingest the 600 mg dose of peanut protein with no more than mild symptoms) were reported by treatment group.

Key Secondary Efficacy Endpoints
These endpoints were assessed in hierarchical order:

1. The proportion of subjects who tolerate at least 300 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC
2. The proportion of subjects who tolerate at least 1000 mg single dose of peanut protein with no more than mild allergy symptoms during the exit DBPCFC
3. The maximum severity of allergy symptoms after consuming peanut protein during the exit DBPCFC

Safety Endpoints
1. Overall summary of adverse events
2. Incidence of all nonserious and serious adverse events (SAEs)
3. Incidence of adverse events by severity grade
4. Incidence of adverse events during up-dosing and maintenance
5. Incidence and severity of treatment-related adverse events
6. Incidence of treatment-related adverse events during up-dosing and maintenance
7. Incidence of dose modifications
8. Exposure-adjusted event rates for the most frequent adverse events (i.e., adverse events in ≥ 5% of the safety population)
9. Exposure-adjusted event rates for the most frequent treatment-related adverse events (i.e., adverse events in ≥ 5% of the safety population)
10. Incidence of early treatment discontinuation due to adverse events and due to chronic or recurrent GI adverse events
11. Separate summaries for anaphylaxis, allergic reaction adverse events, use of epinephrine, and accidental/nonaccidental food allergen exposure

Exploratory Endpoints
1. Change from baseline in peanut-specific and peanut component-specific serum immunoglobulins
2. Change from baseline in mean wheal diameter and mean erythema diameter on SPT to peanut
3. Change from baseline in TRACK and EASI scores
4. Palatability of study treatment assessed using a palatability survey
5. Proportion of subjects who tolerate a single highest dose of 2000 mg peanut protein (4043 mg cumulative) during the exit DBPCFC
6. Change from baseline in the single highest tolerated dose of peanut protein at the exit DBPCFC

7. Maximum dose of peanut protein reached with no more than mild allergy symptoms at the exit DBPCFC

6.1.9 Statistical Considerations & Statistical Analysis Plan

The target sample size of approximately 105 subjects was selected to provide ARC005 over 90% power to detect at least a 35% absolute difference in the proportion of subjects tolerating at least a single dose of 600 mg of peanut protein with no more than mild allergy symptoms between the Palforzia and placebo groups. This power calculation was based on the assumption that 60% of the Palforzia group and 25% of the placebo group would be responders.

Unless otherwise stated in the review, all statistical tests were conducted at $\alpha = 0.05$ (2-sided) level. The primary and key secondary endpoints were tested in a stepwise procedure, starting with the former. Statistical significance in the primary endpoint was required for subsequent testing of the 4 key secondary efficacy endpoints in ascending order (see Section 6.1.8).

Please see the statistical review for a detailed description of the statistical analysis plan for ARC005.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The following analysis populations will be defined for this study.

Intent-To-Treat (ITT) Population
The ITT population (i.e., full analysis set) was defined as all subjects who receive any part of 1 dose of study product. This population was used for all efficacy analyses unless otherwise specified and analyzed according to randomized treatment. Some sensitivity analyses were performed using the ITT population. All subjects received the correct study treatment at randomization. The ITT and safety populations are the same.

Completer Population
The completer population was defined as all subjects in the ITT population who completed study treatment and had an evaluable exit DBPCFC (completion of at least the peanut food challenge day). Sensitivity analyses and supportive analyses of the primary endpoint and secondary endpoints were performed using the completer population.

Per Protocol (PP) Population
The per protocol (PP) population may be defined if it is sufficiently different from the completer population. The PP population differs from the Completer population only in that it excludes subjects who may have undergone the exit DBPCFC despite having major protocol deviations that may influence the desensitization response. Analyses of the primary and all secondary efficacy endpoints were performed using the PP population if results differed from the completer population by more than 5% in either treatment group.

Safety Population
The safety population was defined as all subjects who received any randomized study treatment (i.e., who received any part of 1 dose of study product and completed 1 study visit). The safety population was used for all safety analyses and analyzed according to treatment received. All subjects received the correct study treatment at randomization.

6.1.10.1.1 Demographics

Table 6. Demographics and Baseline Characteristics, ITT Population, Study ARC005

Characteristic	Palforzia (N=98)	Placebo (N=48)	Total (N=146)
Age[a]	--	--	--
Median	2.0	2.0	2.0
Min, max	1, 3	1, 3	1, 3
Age category	--	--	--
1 - <2	33 (33.7%)	16 (33.3%)	49 (33.6%)
2 - <3	35 (35.7%)	15 (31.3%)	50 (34.2%)
3 - <4	30 (30.6%)	17 (35.4%)	47 (32.2%)
Sex	--	--	--
Male	57 (58.2%)	28 (58.3%)	85 (58.2%)
Female	41 (41.8%)	20 (41.7%)	61 (41.8%)
Ethnicity	--	--	--
Hispanic or Latino	5 (5.1%)	3 (6.3%)	8 (5.5%)
Non-Hispanic or non-Latino	75 (76.5%)	31 (64.6%)	106 (72.6%)
Not collected	18 (18.4%)	14 (29.2%)	32 (21.9%)
Race[b]	--	--	--
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	16 (16.3%)	8 (16.7%)	24 (16.4%)
Black or African American	3 (3.1%)	2 (4.2%)	5 (3.4%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	65 (66.3%)	28 (58.3%)	93 (63.7%)
Other	8 (8.2%)	2 (4.2%)	10 (6.8%)
Multiple Races Reported[c]	2 (2.0%)	4 (8.3%)	6 (4.1%)
Not collected	4 (4.1%)	4 (8.3%)	8 (5.5%)
Body mass index (kg/m^2)	--	--	--
N	95	48	143
Median	16.18	16.06	16.13
Min, max	12.9, 24.1	13.6, 21.8	12.9, 24.1
Country	--	--	--
United States	56 (57.1%)	28 (58.3%)	84 (57.5%)
United Kingdom	29 (29.6%)	12 (25.0%)	41 (28.1%)
Germany	9 (9.2%)	5 (10.4%)	14 (9.6%)
France	4 (4.1%)	3 (6.3%)	7 (4.8%)

Source: Applicant CSR ARC005, p. 55-56, Table 14.1.3.2
Abbreviations: ITT=intent-to-treat; Min, max=minimum, maximum.
a. Calculated relative to the date of informed consent.
b. Subjects could be included in more than 1 category.
c. Includes subjects where multiple race categories were marked on the case report form.

Clinical Reviewer comment: The study population in ARC005 is primarily White (63.7%) and non-Hispanic (72.6%) with more than half of subjects from the US (57.5%). Regrettably, substantially lower enrollment from racial groups other than White limits the interpretation of treatment differences by race and ethnicity. However, the clinical diagnosis of IgE-mediated food allergy is unlikely to differ by race and ethnicity and, therefore, it is likely that all patients in these subpopulations would benefit from the treatment effect of Palforzia.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The median time since peanut allergy diagnosis was 14 months. Of the 146 subjects, 93 (63.7%) had no history of systemic allergic reactions to peanut, 49 (33.6%) had one, 3 (2.1%) had two, and 1 (0.7%) had three prior reactions. No subject had more than 3 reactions. Most subjects had a food allergy other than peanut (71.2%). Other common atopic conditions included allergic rhinitis (15.8%), asthma (8.2%), and atopic dermatitis (62.3%). These conditions were balanced across treatment groups. All subjects reacted at 100 mg or less of peanut protein during entry DBPCFC and the proportion of subjects who reacted at a particular dose (subjects who reacted at 1, 3, 10, 30, or 100 mg peanut protein) were balanced across treatment groups (see table below).

Table 7. Single Highest Tolerated Dose of Peanut Protein at Screening DBPCFC, ITT Population, Study ARC005

Single Highest Tolerated Dose of Peanut Protein at Screening DBPCFC	Palforzia (N=98)	Placebo (N=48)	Total (N=146)
None	0	0	0
1 mg[a]	1 (1.0%)	1 (2.1%)	2 (1.4%)
3 mg	13 (13.3%)	8 (16.7%)	21 (14.4%)
10 mg	17 (17.3%)	10 (20.8%)	27 (18.5%)
30 mg	32 (32.7%)	17 (35.4%)	49 (33.6%)
100 mg	35 (35.7%)	12 (25.0%)	47 (32.2%)
300 mg	0	0	0

Source: Applicant CSR ARC005, pg. 58, Table 14; Table 14.1.3.2
Abbreviations: DBPCFC=double-blind, placebo-controlled food challenge; ITT=intent-to-treat
Notes:
a. Subjects had no dose limiting symptoms at the 3 mg dose and met the protocol inclusion criteria based on dose-limiting symptoms; concurrent medications were given at later doses in the screening DBPCFC.

Clinical Reviewer comment: The statistical reviewer, Dr. Gao, noted an imbalance between Palforzia and the placebo group with respect to the single highest tolerance dose at screening, especially at the level of 100 mg of peanut protein (Table 7, above). Dr. Gao conducted an "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)." Dr. Gao concluded that there is no impact of the observed imbalance on the conclusion of the positive treatment effect. This reviewer agrees with Dr. Gao's assessment.

6.1.10.1.3 Subject Disposition

The table below outlines subject disposition in Study ARC005.

Table 8. Subject Disposition, All Subjects, Study ARC005

Disposition	Palforzia	Placebo	Total
Number of subjects randomized	98	48	146
Safety population[a]	98 (100%)	48 (100%)	146 (100%)
ITT population[b]	98 (100%)	48 (100%)	146 (100%)
Completer population[c]	83 (84.7%)	45 (93.8%)	128 (87.7%)
PP population[d]	74 (75.5%)	42 (87.5%)	116 (79.5%)
Entered initial escalation period	98 (100%)	48 (100%)	146 (100%)
Entered up-dosing period	98 (100%)	48 (100%)	146 (100%)
Entered maintenance period	87 (88.8%)	45 (93.8%)	132 (90.4%)
Completed all dosing as defined in the protocol	--	--	--
Yes	83 (84.7%)	45 (93.8%)	128 (87.7%)
No	15 (15.3%)	3 (6.3%)	18 (12.3%)

Source: Original sBLA STN125696_247; CSR ARC005, p.210
Abbreviations: DBPCFC=double-blind placebo-controlled food challenge; GI=gastrointestinal; ITT=intent-to-treat; PP=per-protocol.
Notes: Denominators for percentages were based on total subjects screened for screen failure and based on number of randomized subjects for all other percentages.
a. Safety population included all subjects who received at least 1 dose of randomized study treatment. Treatment group assignment was based on the treatment actually received.
b. ITT population included all subjects who received at least 1 dose of randomized study treatment. Treatment group assignment was based on the randomized treatment assignment.
c. Completer population included all ITT subjects who completed treatment and had an evaluable exit DBPCFC.
d. PP population included all subjects in the completer population who had no major protocol deviations that may have influenced the desensitization response.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary efficacy assessment was the proportion of subjects 1 through 3 years of age in the ITT population who tolerated a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild allergy symptoms at the exit DBPCFC. Subjects who tolerated 600 mg were considered responders for the primary efficacy endpoint. Subjects who did not tolerate a single dose of at least 600 mg peanut protein were considered nonresponders. Nonresponders also included subjects who withdrew consent or discontinued early any time before the exit DBPCFC. The primary efficacy endpoint was calculated as the treatment difference in the responder rate relative to placebo (% of Palforzia recipients who tolerated at least 600 mg of peanut protein minus the % of placebo recipients who tolerated at least 600 mg of peanut protein). The pre-specified criterion for efficacy was demonstrated if the lower bound of the corresponding 95% CI for the point estimate of the treatment difference exceeded 15%.

Table 9. Overall Summary of Primary Efficacy Endpoint for North America Estimands, ITT Population, Study ARC005

North America Estimands	Palforzia (N=98)	Placebo (N=48)	Treatment Difference (Palforzia-placebo) [95% CI][b]	P-value[b]
Primary Efficacy Endpoint	--	--	--	--
Response rate: proportion of subjects who tolerated 600 mg peanut protein (95% CI)[a]	73.5% (63.6, 81.9)	6.3% (1.3, 17.2)	67.2% (50.0, 84.5)	<0.0001

Source: Adapted from Applicant CSR ARC005, pg.73, Table 23
Abbreviations: DBPCFC=double-blind, placebo-controlled food challenge; ITT=intent-to-treat
Notes: Subjects without an exit DBPCFC were counted as nonresponders.
a. Response rate was based on exact Clopper-Pearson intervals.
b. Based on the Farrington-Manning confidence limits.
c. Subjects without an exit DBPCFC were assigned the maximum severity during the screening DBPCFC (no change from screening).
d. No subject had symptoms considered life-threatening or fatal.
e. Tested using the Cochran-Mantel-Haenszel statistic (with equally spaced scores) stratified by geographic region (North America, Europe).

Clinical Reviewer comment: The primary efficacy analysis met the pre-specified criterion for success, supporting the effectiveness of Palforzia in children 1 through 3 years of age. As discussed in an earlier reviewer comment, the ability to tolerate a single dose of 600 mg peanut protein with no more than mild symptoms is considered to translate into protection of individuals against a serious allergic reaction elicited by accidental exposure to up to peanut protein contained in 2 peanut kernels. Protection against serious allergic reactions after consumption of food items containing trace or small amounts of peanut protein is a clinically meaningful goal for children 1 through 3 years of age because toddlers cannot communicate the nature of their disease to responsible adults or understand the inherent risks of their peanut allergy. The risk of accidental exposure is ever-present, whether due to mislabeling of packaged foods, cross contamination, or accidental consumption of foods and can happen in virtually any setting - the home and neighborhood environment, preschool, restaurants, parties, religious and other social gatherings where exposure to peanut allergen, despite best precautions, may occur.

An additional analysis of the primary endpoint in the completer population which contained only subjects who had an evaluable exit DBPCFC (i.e., completion of at least the peanut food challenge day), was supportive of the findings from the primary efficacy analysis with a treatment difference compared to placebo of 86.7% (95% CI: 77.5%, 93.2%).

Sensitivity Analyses of the Primary Efficacy Endpoint

Sensitivity analyses of the primary efficacy endpoint was conducted by the Applicant to evaluate the impact of missing data. These analyses included using a worst-case scenario for missing data imputation and analyses to assess the impact of restrictions due to the COVID-19 pandemic. This included a subgroup analysis that only included subjects who were on study treatment for up to 64 weeks (maximal allowable duration of up to 40 weeks of up-dosing and 24 weeks of maintenance per the protocol prior to the onset of the pandemic), and a subgroup analysis that excluded subjects who had >24 weeks of maintenance (maximal allowable duration of maintenance therapy prior to the exit DBPCFC per the protocol prior to the onset of the pandemic).

Table 10. Summary of Sensitivity Analyses to the Primary Efficacy Endpoint for North America Estimand, Study ARC005

North America Estimands	Palforzia	Placebo	Treatment Difference (95% CI)[c]	P-value[c]
Worst-case imputation[a]	N=98	N=48	--	--
Response rate (95% CI), ITT Population[b]	73.5% (63.6, 81.9)	12.5% (4.7, 25.2)	61.0% (43.7, 78.2)	<0.0001
Inclusion of subjects with treatment up to 64 weeks due to COVID-19 restrictions	N=17	N=15	--	--
Response rate (95% CI), ITT Population[b]	88.2% (63.6, 98.5)	13.3% (1.7, 40.5)	74.9% (40.3, 100.0)	<0.0001
Exclusion of subjects with more than 24 weeks of maintenance treatment due to COVID-19 restrictions	N=39	N=14	--	--
Response rate (95% CI), ITT Population[b]	51.3% (34.8, 67.6)	7.1% (0.2, 33.9)	44.1% (14.3, 74.0)	<0.0038

Source: Applicant CSR ARC005, pg. 77, Table 25
Abbreviations: DBPCFC=double-blind, placebo-controlled food challenge; ITT=intent-to-treat.
Notes: Treatment difference is Palforzia-placebo.
a. Palforzia-treated subjects without an exit DBPCFC were counted as nonresponders and placebo-treated subjects without an exit DBPCFC were counted as responders.
b. Based on exact Clopper-Pearson intervals.
c. Based on the Farrington-Manning confidence limits

Clinical Reviewer comment: ARC005 was conducted, in part, during the COVID-19 pandemic. Due to restrictions imposed during the pandemic, some subjects were on study treatment for up to 64 weeks because of delays in clinic study visits required for up-dosing and study conduct due to regional restrictions. Analysis of subjects who underwent treatment for longer than the maximum allowable prior to the onset of the pandemic (40 weeks of up-dosing and 24 weeks of maintenance per the protocol) demonstrates that Palforzia treatment is durable even when up-dosing is prolonged. All three sensitivity analyses support the robustness of the treatment effect demonstrated by Palforzia in this study.

6.1.11.2 Analyses of Secondary Endpoints

Key secondary analyses include:

1. The proportion of subjects 1 through 3 years of age who tolerate a single highest dose of at least 300 mg (443 mg cumulative) of peanut protein with no more than mild symptoms at the exit DBPCFC
2. The proportion of subjects 1 through 3 years of age who tolerate a single highest dose of at least 1000 mg (2043 mg cumulative) of peanut protein with no more than mild symptoms at the exit DBPCFC
3. The maximum severity of symptoms in subjects 1 through 3 years of age occurring at any challenge dose of peanut protein during the exit DBPCFC

The key secondary endpoints were tested sequentially and required that the primary endpoint analysis was significant in order for additional statistical testing to occur (see Sections 6.1.8 and 6.1.9). Below are the results of the key secondary endpoints in tabular format.

Table 11. Overall Summary of Key Secondary Efficacy Endpoints for North America Estimands, ITT Population, Study ARC005

North America Estimands	Palforzia (N=98)	Placebo (N=48)	Treatment Difference (Palforzia-placebo) [95% CI][b]	P-value[b]
Key Secondary Efficacy Endpoints	--	--	--	--
Response rate: proportion of subjects who tolerated 300 mg peanut protein (95% CI)[a]	79.6% (70.3, 87.1)	22.9% (12.0, 37.3)	56.7% (39.8, 73.5)	<0.0001
Response rate: proportion of subjects who tolerated 1000 mg peanut protein (95% CI)[a]	68.4% (58.2, 77.4)	4.2% (0.5, 14.3)	64.2% (47.0, 81.4)	<0.0001
Max severity of symptoms at any challenge dose[c]	--	--	--	<0.0001
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)[d]	2 (2.0%)	2 (4.2%)	--	--

Source: Adapted from Applicant CSR ARC005, pg.73, Table 23
Abbreviations: DBPCFC=double-blind, placebo-controlled food challenge; ITT=intent-to-treat
Notes: Subjects without an exit DBPCFC were counted as nonresponders.
a. Response rate was based on exact Clopper-Pearson intervals.
b. Based on the Farrington-Manning confidence limits.
c. Subjects without an exit DBPCFC were assigned the maximum severity during the screening DBPCFC (no change from screening).
d. No subject had symptoms considered life-threatening or fatal.
e. Tested using the Cochran-Mantel-Haenszel statistic (with equally spaced scores) stratified by geographic region (North America, Europe).

Clinical reviewer comment: The data presented in Table 12 demonstrate a consistent treatment response. As expected, the response rate decreases with ingestion of increasing amounts of peanut protein during the DBPCFC. However, it is encouraging that the majority of Palforzia-treated subjects could ingest 1000 mg of peanut protein with no more than mild symptoms, suggesting that these individuals will experience a protective effect against accidental exposures to peanut protein contained in approximately 3 peanut kernels.

Another interesting finding is that despite tolerating the daily maintenance dose of 300 mg of peanut protein, some Palforzia recipients were not able to ingest 300 mg of peanut protein during the exit DBPCFC with no more than mild symptoms. This may be due to the fact that during the OFC, the cumulative dose of peanut protein is greater than 300 mg (total of 444 mg peanut protein). In addition, the multiple escalating doses rather than a one-time dose may lower the threshold for allergic responsiveness for some. Furthermore, an individual's reactivity to allergens can vary from day to day based on many factors including concurrent illness, stress, or increased metabolic rate.

6.1.11.3 Subpopulation Analyses

Table 12. Subpopulation Desensitization Response Rates, Tolerating 600 mg at the Exit DBPCFC, Subjects 1 to <4 Years of Age, ITT Population, Study ARC005

Subpopulation Category	Palforzia N % Responders (95% CI)[1]	Placebo N % Responders (95% CI)[1]	% Treatment Difference (Palforzia-Placebo) (95% CI)[2]	P-value[2]
Geographic region	--	--	--	--
North America	56 76.8% (63.6%, 87.0%)	28 3.6% (0.1%, 18.3%)	73.2% (50.6%, 95.9%)	<0.0001
Europe	42 69.0% (52.9%, 82.4%)	20 10.0% (1.2%, 31.7%)	59.0% (32.4%, 85.7%)	<0.0001
Age	--	--	--	--
1 - <2 Years	33 81.8% (64.5%, 93.0%)	16 12.5% (1.6%, 38.3%)	69.3% (40.0%, 98.7%)	<0.0001
2 - <3 Years	35 65.7% (47.8%, 80.9%)	15 6.7% (0.2%, 31.9%)	59.0% (28.8%, 89.3%)	0.0001
3 - <4 Years	30 73.3% (54.1%, 87.7%)	17 0.0% (0.0%, 19.5%)	73.3% (43.6%, 100.0%)	<0.0001
Sex	--	--	--	--
Male	57 70.2% (56.6%, 81.6%)	28 3.6% (0.1%, 18.3%)	66.6% (44.0%, 89.2%)	<0.0001
Female	41 78.0% (62.4%, 89.4%)	20 10.0% (1.2%, 31.7%)	68.0% (41.5%, 94.6%)	<0.0001
Race	--	--	--	--
Asian	16 75.0% (47.6%, 92.7%)	8 0.0% (0.0%, 36.9%)	75.0% (32.6%, 100.0%)	0.0005
Black or African American	3 33.3% (0.8%, 90.6%)	2 0.0% (0.0%, 84.2%)	33.3% (-38.2%, 100.0%)	0.3613
White	65 73.8% (61.5%, 84.0%)	28 10.7% (2.3%, 28.2%)	63.1% (41.1%, 85.2%)	<0.0001
Other	8 62.5% (24.5%, 91.5%)	2 0.0% (0.0%, 84.2%)	62.5% (-15.0%, 100.0%)	0.1138
Multiple Races Reported	2 100.0% (15.8%, 100.0%)	4 0.0% (0.0%, 60.2%)	100.0% (20.0%, 100.0%)	0.0143
Not collected	4 100.0% (39.8%, 100.0%)	4 0.0% (0.0%, 60.2%)	100.0% (30.7%, 100.0%)	0.0047

Subpopulation Category	Palforzia N % Responders (95% CI)[1]	Placebo N % Responders (95% CI)[1]	% Treatment Difference (Palforzia-Placebo) (95% CI)[2]	P-value[2]
Ethnicity	--	--	--	--
Hispanic or Latino	5 80.0% (28.4%, 99.5%)	3 0.0% (0.0%, 70.8%)	80.0% (8.4%, 100.0%)	0.0285
Not Hispanic or Latino	75 74.7% (63.3%, 84.0%)	31 6.5% (0.8%, 21.4%)	68.2% (47.4%, 89.0%)	<0.0001
Not collected	18 66.7% (41.0%, 86.7%)	14 7.1% (0.2%, 33.9%)	59.5% (25.2%, 93.8%)	0.0007
Asthma history	--	--	--	--
Yes	10 70.0% (34.8%, 93.3%)	4 0.0% (0.0%, 60.2%)	70.0% (12.0%, 100.0%)	0.0180
No	88 73.9% (63.4%, 82.7%)	44 6.8% (1.4%, 18.7%)	67.0% (49.0%, 85.1%)	<0.0001
Baseline peanut specific-IgE	--	--	--	--
PS IgE ≤100 (kUA/L)	77 77.9% (67.0%, 86.6%)	37 8.1% (1.7%, 21.9%)	69.8% (50.3%, 89.3%)	<0.0001
PS IgE >100 (kUA/L)	10 40.0% (12.2%, 73.8%)	8 0.0% (0.0%, 36.9%)	40.0% (1.3%, 78.7%)	0.0425
Missing	11 72.7% (39.0%, 94.0%)	3 0.0% (0.0%, 70.8%)	72.7% (9.6%, 100.0%)	0.0241
Baseline Ara h 2 IgE	--	--	--	--
Ara h 2 IgE ≤2 (kUA/L)	27 88.9% (70.8%, 97.6%)	12 25.0% (5.5%, 57.2%)	63.9% (32.5%, 95.3%)	<0.0001
Ara h 2 IgE >2 (kUA/L)	59 66.1% (52.6%, 77.9%)	33 0.0% (0.0%, 10.6%)	66.1% (45.0%, 87.2%)	<0.0001
Missing	12 75.0% (42.8%, 94.5%)	3 0.0% (0.0%, 70.8%)	75.0% (13.0%, 100.0%)	0.0177
Baseline Total IgE	--	--	--	--
Total IgE ≤100 (IU/L)	29 82.8% (64.2%, 94.2%)	16 18.8% (4.0%, 45.6%)	64.0% (34.1%, 93.9%)	<0.0001
Total IgE >100 (IU/L)	57 68.4% (54.8%, 80.1%)	29	68.4% (46.2%, 90.7%)	<0.0001
Missing	12	3	75.0% (13.0%, 100.0%)	0.0177

Source: IR #9, 1/24/2024, Seq. #219, Table 14.2.2.15, pg. 3
Abbreviations: DBPCFC=double-blind placebo-controlled food challenge; ITT=intent-to-treat; ps=peanut-specific
Notes: Subjects who do not have an exit DBPCFC were counted as non-responders.
1. The 95% CIs for each treatment group are based on exact Clopper-Pearson intervals.
2. The 95% CIs for difference in binomial proportions and corresponding p-values are based on the Farrington-Manning confidence limits.

Clinical Reviewer comment: Subgroup analyses of the primary efficacy endpoint by geographic region, years of age, sex, race, and ethnicity, asthma history, baseline total IgE, baseline peanut-specific serum IgE, and baseline Ara h2-specific IgE yield estimates of treatment difference similar to the ITT population. While this study was not powered to show a difference between these groups and the analyses were not adjusted for multiplicity, many of the subgroup comparisons had a lower bound which exceeded 15% with p values ≤0.0001.

Interestingly, subgroup analyses of the primary efficacy endpoint by baseline peanut-specific serum IgE and baseline Ara h2-specific IgE appear to suggest that individuals with lower levels of either of these laboratory studies (peanut-specific serum IgE ≤100kUA/L and/or Ara h2-specific IgE ≤2 kUA/L) may be more likely to respond to Palforzia than to those with more elevated markers of sensitization. Studies designed to evaluate different cohorts of peanut-allergic individuals defined by the degree of sensitization based on serology would be informative for clinicians to counsel parents and caregivers as well as patients who may be worried about the chance of treatment failure.

6.1.11.4 Dropouts and/or Discontinuations

Table 13. Overview of AEs Leading to Discontinuation, Study ARC005

Study ARC005	Palforzia (N=98)	Placebo (N=48)
Completed	83	45
Discontinued	15	3
Adverse Event	--	--
Asthma development (wheezing)	1	0
Coughing	1	0
Abdominal pain / upset stomach	1	0
Intermittent regurgitation	1	0
Burping	1	0
Gross motor regression (unable to walk)	--	1
Withdrew Consent	5	1
Lost to Follow-up	1	0
Other[a,b]	4	1

Source: Adapted from Figure 2, pg. 52, Applicant CSR ARC005
a. Reasons included 1 investigator decision due to noncompliance, and 3 subjects' decision due to continued commitment to study treatment.
b. One subject discontinued due to taste aversion to study product.

Clinical Reviewer comment: Palforzia recipients discontinued the study at a higher rate compared to placebo recipients (Palforzia 15.3% vs placebo 6.7%). This trend is consistent with the discontinuation rate observed in the original BLA review in children 4-17 years and adults 18-55 years of age due to the reactogenic nature of peanut OIT. It is reasonable to infer that most patients who experience intolerable effects of Palforzia treatment will, with their medical provider via shared decision making, choose to discontinue treatment. In addition, drop-outs are accounted for in the primary efficacy endpoint calculation because they are considered non-responders.

6.1.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.1.12 Safety Analyses

6.1.12.1 Methods

A total of 146 subjects (98 Palforzia recipients, 48 placebo recipients) were included in the safety population used in the safety analyses presented in this section. All subjects received the correct study treatment at randomization; the ITT and safety populations are the same.

AEs were assessed by their severity and relation to the study treatment. In regard to allergic events, the CoFAR severity grading scale (Sampson et al, 2019), shown in Table 14, was used for coding allergic reactions. For allergic reactions that met criteria for a systemic allergic reaction or anaphylaxis (criteria presented below; Sampson, 2006), the severity was graded using the Muraro scale, shown in Table 15.

1. Acute onset of an illness (minutes to hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips/tongue/uvula) and at least 1 of the following:
   - Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, hypoxemia)
   - Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for the subject (minutes to hours):
   - Involvement of the skin/mucosal tissue (e.g., generalized hives, itch/flush, swollen lips/tongue/uvula)
   - Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, hypoxemia)
   - Reduced blood pressure or associated symptoms (e.g., hypotonia, syncope, incontinence)
   - Persistent GI symptoms (e.g., nausea, crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to a known allergen for the subject (minutes to hours) as follows:
   - Infants and children: >30% decrease from baseline in systolic blood pressure or low systolic blood pressure in children defined as follows:
     i. Aged 1 month to 1 year: <70 mm Hg
     ii. Aged >1 to 10 years: <(70 mm Hg + [2 × age])

Table 14. CoFAR Severity Grading System for Allergic Reactions, Study ARC005

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-Threatening	Grade 5 Death
Transient or mild discomforts (<48 hours), no or minimal medical intervention/ therapy required.	Symptoms that produce mild to moderate limitation in activity, some assistance may be needed; no or minimal intervention/ therapy is required. Hospitalization is possible.	Marked limitation in activity, some assistance usually required; medical intervention/ therapy required, hospitalization is possible. Parenteral medication(s) are usually indicated.	Extreme limitation in activity, significant assistance required; significant medical/ therapy. Intervention is required; hospitalization is probable.	Death
Symptoms may include pruritus, swelling or rash, abdominal discomfort, or other transient symptoms.	Symptoms may include persistent hives, wheezing without dyspnea, abdominal discomfort/ increased vomiting, or other symptoms.	Symptoms may include bronchospasm with dyspnea, severe abdominal pain, throat tightness with hoarseness, transient hypotension, or other symptoms.	Symptoms may include persistent hypotension and/or hypoxia with resultant decreased level of consciousness associated with collapse and/or incontinence, or other life-threatening symptoms.	--

Source: Applicant CSR, ARC005, pg. 35, Table 8; Adapted from Burks, 2012; Consortium of Food Allergy Research (CoFAR)

Table 15. Modified EAACI Severity Grading System for Anaphylactic Reactions

Severity Grade	Description	Symptoms
1 – Mild	Involves skin and subcutaneous tissues, gastrointestinal, and/or mild respiratory	Flushing; urticaria; periorbital edema or facial angioedema; mild dyspnea, wheezing, or upper respiratory symptoms; mild abdominal pain and/or emesis
2 – Moderate	Involves mild symptoms and features suggesting moderate respiratory, cardiovascular, or gastrointestinal symptoms	Marked dysphagia, hoarseness, and/or stridor; shortness of breath, wheezing, and retractions; crampy abdominal pain, recurrent vomiting, and/or diarrhea; and/or mild dizziness
3 – Severe	Involves hypoxia, hypotension, or neurologic compromise	Cyanosis or SpO_2 ≤92% at any stage, hypotension[a], confusion, collapse, loss of consciousness, or incontinence

Source: Applicant CSR, ARC005, pg. 34, Table 7; Adapted from Muraro, 2007.
a. Systolic blood pressure: <70 mm Hg in subjects 1 month to 1 year of age, <(70 mm Hg + [2 × age]) in subjects >1 to 10 years of age. EAACI, European Academy of Allergy and Clinical Immunology.

6.1.12.2 Overview of Adverse Events

A total of 3340 AEs were reported in 146 subjects 1 through 3 years of age. Of those, 98.0% of subjects in the treatment group and 97.9% of subjects in the placebo group experienced AEs. A

majority of these were mild (51% treatment, 60.4% placebo) to moderate (41.8% treatment, 33.3% placebo).

The tables below (Tables 16, 17, and 18) summarize AEs in the safety population by dosing periods (initial dose escalation, up-dosing, and maintenance/overall).

Table 16. Summary of TEAEs, Initial Dose Escalation, Palforzia and Placebo, Safety Population, Study ARC005

Initial Dose Escalation	Palforzia (N=98)	Placebo (N=48)
Total exposure (years)	0.55	0.26
Total AEs	49	16
Total SAEs	0	0
Subjects with at least 1 AE	21 (21.4%)	10 (20.8%)
By maximum severity[a]	--	--
Grade 1: Mild	20 (20.4%)	10 (20.8%)
Grade 2: Moderate	1 (1.0%)	0
Grade ≥3: Severe or higher	0	0
By relationship to study product[b]	--	--
Not related	6 (6.1%)	7 (14.6%)
Related	15 (15.3%)	3 (6.3%)
AEs leading to study product discontinuation	0	0
AEs requiring dose interruption of study product	0	0
AEs requiring dose reduction of study product	0	0
Anaphylactic reaction[c]	0	0
Hypersensitivity event[d]	15 (15.3%)	3 (6.3%)
AE associated with food allergen exposure	2 (2.0%)	1 (2.1%)
Subjects with at least 1 SAE	0	0
SAEs by relationship to study product[b]	--	--
Not related	0	0
Related	0	0

Source: Adapted from Applicant CSR ARC005 p. 122, Table 43
Abbreviations: AEs=adverse events; SAEs=serious adverse events; TEAEs=treatment emergent adverse events
a. Subjects with more than 1 AE were counted only once using the maximum severity.
b. Subjects with more than 1 AE were counted only once using the closest relationship to study product.
c. None of the reported reactions were classified as severe.
d. Defined as AEs that were considered by investigators to be allergic reactions.
e. Defined as the total number of events divided by the total number of subject-years at risk during the period.

Table 17. Summary of TEAEs, Up-Dosing, Palforzia and Placebo, Safety Population, Study ARC005

Up-Dosing	Palforzia (N=98)	Placebo (N=48)
Total exposure (years)	51.71	26.87
Total AEs	1637	682
Total SAEs	3	0
Subjects with at least 1 AE	96 (98.0%)	47 (97.9%)
By maximum severity[a]	--	--
Grade 1: Mild	64 (65.3%)	38 (79.2%)
Grade 2: Moderate	30 (30.6%)	9 (18.8%)
Grade ≥3: Severe or higher	2 (2.0%)	0
By relationship to study product[b]	--	--
Not related	29 (29.6%)	20 (41.7%)
Related	67 (68.4%)	27 (56.3%)
AEs leading to study product discontinuation	5 (5.1%)	0
AEs requiring dose interruption of study product	53 (54.1%)	25 (52.1%)

Up-Dosing	Palforzia (N=98)	Placebo (N=48)
AEs requiring dose reduction of study product	14 (14.3%)	4 (8.3%)
Anaphylactic reaction[c]	2 (2.0%)	2 (4.2%)
Hypersensitivity event[d]	69 (70.4%)	32 (66.7%)
AE associated with food allergen exposure	32 (32.7%)	15 (31.3%)
Subjects with at least 1 SAE	3 (3.1%)	0
SAEs by relationship to study product[b]	--	--
Not related	3 (3.1%)	0
Related	0	0

Source: Adapted from Applicant CSR ARC005 p. 122, Table 43
Abbreviations: AEs=adverse events; SAEs=serious adverse events; TEAEs=treatment emergent adverse events
a. Subjects with more than 1 AE were counted only once using the maximum severity.
b. Subjects with more than 1 AE were counted only once using the closest relationship to study product.
c. None of the reported reactions were classified as severe.
d. Defined as AEs that were considered by investigators to be allergic reactions.
e. Defined as the total number of events divided by the total number of subject-years at risk during the period.

Table 18. Summary of TEAEs, Maintenance and Overall, Palforzia and Placebo, Safety Population, Study ARC005

Maintenance and Overall	Maintenance Palforzia (N=87)	Maintenance Placebo (N=45)	Overall Palforzia (N=98)	Overall Placebo (N=48)
Total exposure (years)	46.16	25.25	98.42	52.38
Total AEs	694	262	2380	960
Total SAEs	4	2	7	2
Subjects with at least 1 AE	79 (90.8%)	41 (91.1%)	96 (98.0%)	47 (97.9%)
By maximum severity[a]				
Grade 1: Mild	55 (63.2%)	29 (64.4%)	50 (51.0%)	29 (60.4%)
Grade 2: Moderate	21 (24.1%)	10 (22.2%)	41 (41.8%)	16 (33.3%)
Grade ≥3: Severe or higher	3 (3.4%)	2 (4.4%)	5 (5.1%)	2 (4.2%)
By relationship to study product[b]	--	--	--	--
Not related	49 (56.3%)	34 (75.6%)	22 (22.4%)	19 (39.6%)
Related	30 (34.5%)	7 (15.6%)	74 (75.5%)	28 (58.3%)
AEs leading to study product discontinuation	2 (2.3%)	0	6 (6.1%)	0
AEs requiring dose interruption of study product	45 (51.7%)	23 (51.1%)	68 (69.4%)	31 (64.6%)
AEs requiring dose reduction of study product	7 (8.0%)	1 (2.2%)	18 (18.4%)	5 (10.4%)
Anaphylactic reaction[c]	6 (6.9%)	2 (4.4%)	8 (8.2%)	4 (8.3%)
Hypersensitivity event[d]	45 (51.7%)	23 (51.1%)	80 (81.6%)	36 (75.0%)
AE associated with food allergen exposure	22 (25.3%)	13 (28.9%)	41 (41.8%)	22 (45.8%)
Subjects with at least 1 SAE	3 (3.4%)	2 (4.4%)	6 (6.1%)	2 (4.2%)
SAEs by relationship to study product[b]	--	--	--	--
Not related	3 (3.4%)	2 (4.4%)	6 (6.1%)	2 (4.2%)
Related	0	0	0	0

Source: Adapted from Applicant CSR ARC005 p. 122, Table 43
Abbreviations: AEs=adverse events; SAEs=serious adverse events; TEAEs=treatment emergent adverse events
a. Subjects with more than 1 AE were counted only once using the maximum severity.
b. Subjects with more than 1 AE were counted only once using the closest relationship to study product.
c. None of the reported reactions were classified as severe.
d. Defined as AEs that were considered by investigators to be allergic reactions.
e. Defined as the total number of events divided by the total number of subject-years at risk during the period.

Clinical Reviewer comment: During the two-day initial dose escalation, more Palforzia-treated subjects reported hypersensitivity AEs that were related to the study product. No anaphylactic reactions were reported. During the up-dosing period, more Palforzia treated subjects reported AEs related to the study product and reported slightly more hypersensitivity AEs. Two anaphylactic reactions were reported in each group. Five of these subjects discontinued. In the maintenance period, a similar proportion of study subjects in both treatment groups reported hypersensitivity AEs. However, those treated with Palforzia reported more anaphylactic reactions related to Palforzia and two of these subjects discontinued. No SAEs were related to the study product. Overall, Palforzia treated subjects reported more hypersensitivity AEs than placebo recipients. Most of these reactions were mild to moderate. However, parents and caregivers of young children are routinely instructed to immediately treat allergic symptoms upon recognition before a reaction progresses to a severe, life-threatening stage. Please see Section 6.1.12.5 below for a more granular discussion on AESIs which include anaphylaxis.

Common Adverse Events

The most common system organ classes (SOCs) represented in common AEs (≥20% of subjects in either treatment group with ≥5% higher incidence in the Palforzia group) were GI disorders (83.7% Palforzia, 64.6% placebo), respiratory, thoracic and mediastinal disorders (78.6% Palforzia, 68.8% placebo), and general disorders and administration site conditions (62.2% Palforzia, 52.1% placebo). The most common AEs by preferred term (PT) were cough (53.1% Palforzia, 43.8% placebo), vomiting (53.1% Palforzia, 31.3% placebo), pyrexia (51.0% Palforzia, 41.7% placebo), rhinorrhea (42.9% Palforzia, 31.3% placebo), upper respiratory tract infection (35.7% Palforzia, 27.1% placebo), diarrhea (34.7% Palforzia 27.1% placebo), and abdominal pain (23.5% Palforzia , 12.5% placebo).

Table 19 presents common AEs by PT during the up-dosing and maintenance periods, which comprised all but two days (for initial dose escalation) of the duration of safety data collection for ARC005.

Table 19. TEAEs in at Least 5% of Subjects in Either Treatment Group Overall by System Organ Class (SOC) and Preferred Term, Safety Population, Study ARC005

SOC Preferred Term	IDE Palforzia (N=98)	IDE Placebo (N=48)	Up-Dosing Palforzia (N=98)	Up-Dosing Placebo (N=48)	Maintenance Palforzia (N=87)	Maintenance Placebo (N=45)	Overall Palforzia (N=98)	Overall Placebo (N=48)
Vomiting	0	1 (2.1%)	41 (41.8%)	11 (22.9%)	25 (28.7%)	7 (15.6%)	52 (53.1%)	15 (31.3%)
Diarrhea	2 (2.0%)	1 (2.1%)	31 (31.6%)	11 (22.9%)	10 (11.5%)	3 (6.7%)	34 (34.7%)	13 (27.1%)
Abdominal pain	0	1 (2.1%)	21 (21.4%)	5 (10.4%)	7 (8.0%)	3 (6.7%)	23 (23.5%)	6 (12.5%)
Abdominal pain upper	1 (1.0%)	0	10 (10.2%)	2 (4.2%)	4 (4.6%)	2 (4.4%)	14 (14.3%)	4 (8.3%)
Oral pruritus	0	0	7 (7.1%)	2 (4.2%)	4 (4.6%)	0	10 (10.2%)	2 (4.2%)
Flatulence	0	0	4 (4.1%)	0	1 (1.1%)	0	5 (5.1%)	0
Lip swelling	0	0	2 (2.0%)	0	3 (3.4%)	0	5 (5.1%)	0
Upper respiratory tract infection	0	2 (4.2%)	24 (24.5%)	10 (20.8%)	20 (23.0%)	8 (17.8%)	35 (35.7%)	13 (27.1%)

SOC Preferred Term	IDE Palforzia (N=98)	IDE Placebo (N=48)	Up-Dosing Palforzia (N=98)	Up-Dosing Placebo (N=48)	Maintenance Palforzia (N=87)	Maintenance Placebo (N=45)	Overall Palforzia (N=98)	Overall Placebo (N=48)
Rhinitis	0	1 (2.1%)	15 (15.3%)	5 (10.4%)	11 (12.6%)	3 (6.7%)	20 (20.4%)	8 (16.7%)
Ear infection	0	0	6 (6.1%)	2 (4.2%)	5 (5.7%)	0	11 (11.2%)	2 (4.2%)
Gastroenteritis viral	0	0	6 (6.1%)	0	4 (4.6%)	1 (2.2%)	8 (8.2%)	1 (2.1%)
Influenza	0	0	2 (2.0%)	0	3 (3.4%)	0	5 (5.1%)	0
Lower respiratory tract infection	0	0	5 (5.1%)	0	0	0	5 (5.1%)	0
Urinary tract infection	0	0	4 (4.1%)	0	2 (2.3%)	0	5 (5.1%)	0
Perioral dermatitis	1 (1.0%)	0	11 (11.2%)	1 (2.1%)	7 (8.0%)	3 (6.7%)	17 (17.3%)	4 (8.3%)
Dry skin	0	0	6 (6.1%)	0	2 (2.3%)	2 (4.4%)	8 (8.2%)	2 (4.2%)
Swelling face	0	0	5 (5.1%)	0	0	1 (2.2%)	5 (5.1%)	1 (2.1%)
Cough	2 (2.0%)	0	43 (43.9%)	15 (31.3%)	25 (28.7%)	15 (33.3%)	52 (53.1%)	21 (43.8%)
Rhinorrhea	3 (3.1%)	3 (6.3%)	29 (29.6%)	11 (22.9%)	15 (17.2%)	6 (13.3%)	42 (42.9%)	15 (31.3%)
Wheezing	0	0	11 (11.2%)	4 (8.3%)	4 (4.6%)	1 (2.2%)	14 (14.3%)	4 (8.3%)
Asthma	0	0	9 (9.2%)	2 (4.2%)	5 (5.7%)	5 (11.1%)	11 (11.2%)	7 (14.6%)
Pyrexia	0	0	40 (40.8%)	19 (39.6%)	23 (26.4%)	10 (22.2%)	50 (51.0%)	20 (41.7%)
Headache	0	0	8 (8.2%)	1 (2.1%)	4 (4.6%)	0	10 (10.2%)	1 (2.1%)
Irritability	1 (1.0%)	0	6 (6.1%)	0	2 (2.3%)	1 (2.2%)	6 (6.1%)	1 (2.1%)
Decreased appetite	0	0	3 (3.1%)	0	2 (2.3%)	0	5 (5.1%)	0

Source: Adapted from Applicant CSR, ARC005, pg. 125, Table 44
Abbreviations: SOC=System Organ Class; AE=adverse event; TEAE=treatment emergent adverse event
Notes: At each level of summarization (any event, system organ class, and preferred term), subjects with more than 1 AE were counted only once within each study period.
Shaded cells indicate AEs and symptoms with ≥5% higher incidence in the Palforzia group compared with the placebo group.

Table 20 below presents the most common adverse reactions (treatment related events) in subjects treated with Palforzia (incidence ≥5%). These were gastrointestinal, respiratory, and skin symptoms commonly associated with allergic reactions.

Table 20. Treatment-Emergent Adverse Reactions in ≥5% of Palforzia-Treated Subjects in Any Dosing Phase and Overall (1 through 3 Years of Age)

SOC / PT[a]	IDE Palforzia (N=98)	IDE Placebo (N=48)	Up-Dosing Palforzia (N=98)	Up-Dosing Placebo (N=48)	300 mg Palforzia (N=87)	300 mg Placebo (N=45)	Overall Palforzia (N=98)	Overall Placebo (N=48)
Respiratory, thoracic and mediastinal disorders	--	--	--	--	--	--	--	--
Cough	2 (2.0%)	0	17 (17.3%)	2 (4.2%)	4 (4.6%)	0	20 (20.4%)	2 (4.2%)
Sneezing	4 (4.1%)	0	14 (14.3%)	5 (10.4%)	2 (2.3%)	2 (4.4%)	19 (19.4%)	4 (8.3%)
Rhinitis[b]	3 (3.1%)	1 (2.1%)	9 (9.2%)	1 (2.1%)	5(5.7%)	0	15 (15.3%)	(4.2%)
Nasal congestion	4 (4.1%)	0	3 (3.1%)	0	0	0	6 (6.1%)	0 (0.0%)
Throat irritation	1 (1.0%)	1 (2.1%)	4 (4.1%)	1 (2.1%)	3 (3.4%)	0	5 (5.1%)	2 (4.2%)
Wheezing[c]	0	0	4 (4.1%)	1 (2.1%)	1 (1.1%)	0	5 (5.1%)	1 (2.1%)
GI disorders	--	--	--	--	--	--	--	--
Abdominal pain[d]	0	1 (2.1%)	15 (15.3%)	2 (4.2%)	7 (8.0%)	1 (2.2%)	19 (19.4%)	4 (8.3%)
Vomiting[e]	0	0	13 (13.3%)	0	4(4.6%)	0	16 (16.3%)	0 (0.0%)
Diarrhea[f]	1 (1.0%)	1 (2.1%)	9 (9.2%)	5 (10.4%)	3 (3.4%)	0	11 (11.2%)	5 (10.4%)
Oral pruritus[g]	0	0	4 (4.1%)	1 (2.1%)	7 (8.0%)	0	9 (9.2%)	1 (2.1%)
Oropharyngeal pain[h]	1 (1.0%)	0	3 (3.1%)	0	1 (1.1%)	0	5 (5.1%)	0 (0.0%)
Skin and subcutaneous tissue disorders	--	--	--	--	--	--	--	--
Urticaria[i]	5 (5.1%)	1 (2.1%)	27 (27.6%)	13 (27.1%)	9 (10.3%)	2 (4.4%)	31 (31.6%)	14 (29.2%)
Rash[j]	2 (2.0%)	2 (4.2%)	26 (26.5%)	11 (22.9%)	7 (8.0%)	1 (2.2%)	30 (30.6%)	11 (22.9%
Pruritus[k]	2 (2.0%)	0	14 (14.3%)	12 (25.0%)	2 (2.3%)	1 (2.2%)	14 (14.3%)	12 (25.0%)
Perioral dermatitis	1 (1.0%)	0	6 (6.1%)	0	4 (4.6%)	0	9 (9.2%)	0 (0.0%)

Source: Adapted from Applicant CSR

Abbreviations: SOC=system organ class; PT=preferred term; IDE=initial dose escalation; GI=gastrointestinal

Notes: At each level of summarization (any event, system organ class, and preferred term), subjects with more than 1 adverse reaction were counted only once within study period.

a. Adverse reactions were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.1.
b. Includes preferred terms of rhinorrhea, rhinitis and rhinitis allergic.
c. Includes preferred terms of wheezing and stridor.
d. Includes preferred term of abdominal pain, abdominal pain upper, and abdominal discomfort.
e. Includes preferred terms of vomiting and regurgitation.
f. Includes preferred terms of diarrhea and frequent bowel movements.
g. Includes preferred terms of oral pruritus, tongue pruritis, and lip pruritus.
h. Includes preferred terms of oropharyngeal pain, oral discomfort, odynophagia, and oral pain.
i. Includes preferred terms of urticaria and urticaria papular.
j. Includes preferred terms of rash, rash erythematous, rash generalized, rash macular, rash papular, rash pruritic, eczema, erythema, and papule.
k. Includes preferred terms of pruritus, pruritus generalized, ear pruritus, eye pruritus, and nasal pruritus.

6.1.12.3 Deaths

No deaths occurred.

6.1.12.4 Nonfatal Serious Adverse Events

SAEs of systemic allergic reactions and anaphylaxis are discussed in Section 6.1.12.5 below. Eight subjects (6 in the Palforzia group and 2 in the placebo group), experienced a total of 9 SAEs during up-dosing and maintenance periods. In the Palforzia group, the SAEs included asthma (2), enterovirus infection (1), influenza (1), RSV bronchiolitis/status asthmaticus (1), and viral infection (1). None of these were considered related. In the placebo group these included asthma (1) and carbon monoxide poisoning (1) which were considered not related.

Clinical Reviewer comment: This reviewer independently assessed the relatedness of the SAEs to the study product based on reviews of the individual subject narratives submitted to the sBLA. This reviewer agrees with the Applicant's assessment that the 9 SAEs were unrelated to study treatment.

One event of asthma in the Palforzia group occurred in a 1-year-old male on maintenance immunotherapy of Palforzia who received a dose in the morning, despite having symptoms of a URI. A family member also had similar symptoms. Later that day, he had an asthma exacerbation that led to hospital admission. Study product was interrupted during the event, but the subject was able to complete the study. A second event of asthma occurred in a 2-year-old female during up-dosing (6 mg Palforzia) 4 hours after ingestion of the study material. The subject had wheezing, was administered epinephrine, and taken to an urgent care where a workup for infection was unrevealing. The subject was admitted to the hospital for treatment for 3 days for wheezing and increased work of breathing. The illness resolved after 8 days; she was permanently discontinued from study treatment. The clinical histories (viral illness and number of days with continued wheezing despite study treatment being withheld) suggest that these two episodes were unrelated to the study treatment.

None of the SAEs were anaphylaxis. Please see Section 6.1.12.5 for a discussion of events of anaphylaxis in ARC005 which are considered AESIs.

ARC008, a Phase 3 open label follow on study for all studies in the Palforzia clinical developmental program, was recently completed (April 2024). A total of 112 subjects from ARC005 were enrolled (72 Palforzia recipients, 40 placebo recipients) in ARC008. Subjects already on Palforzia maintenance therapy continued maintenance. Placebo recipients initiated Palforzia with the initial dose escalation, up-dosing, to maintenance as tolerated. A total of 6 SAEs were reported for these 112 subjects, none of which were considered related to Palforzia. This reviewer independently assessed the relatedness of the SAEs to the study product based on review of the individual subject narratives and agrees that none of the SAEs were related.

6.1.12.5 Adverse Events of Special Interest (AESIs)

Pre-specified adverse events of special interest (AESIs) included anaphylaxis, GI AEs that resulted in prolonged dose interruption (>7 consecutive days) or that resulted in early discontinuation, accidental and nonaccidental food allergen exposure, severe AEs, and use of epinephrine. Allergic reactions during DBPCFCs were expected to occur among the peanut-allergic children, therefore they were not reported as AESIs.

Anaphylaxis (Anaphylactic Reaction) and Systemic Allergic Reactions

All cases occurred during the up-dosing and maintenance periods. Palforzia recipients reported similar rates of systemic allergic reactions or anaphylaxis (8.2%; 8/98) compared to placebo recipients (8.3%; 4/48). One subject had 2 events of anaphylaxis while the remaining subjects reported 1 event. None of the systemic reactions or anaphylaxis were graded as severe. Two Palforzia recipients (2.0%) had mild systemic allergic reactions and 6 Palforzia recipients (6.1%) had moderate allergic reactions. Two placebo recipients (4.2%) had mild allergic reactions, and 2 placebo recipients (4.2%) had moderate allergic reactions.

Table 21. Summary of Treatment-Emergent Systemic Allergic Reaction (MedDRA Preferred Term Anaphylactic Reaction) Episodes by Study Period, Safety Population, Study ARC005

Treatment-Emergent Systemic Allergic Reaction Episodes	Up-Dosing Palforzia (N=98)	Up-Dosing Placebo (N=48)	Maintenance Palforzia (N=87)	Maintenance Placebo (N=45)	Overall Palforzia (N=98)	Overall Placebo (N=48)
Subjects with an anaphylactic reaction	--	--	--	--	--	--
1 event	1 (1.0%)	2 (4.2%)	6 (6.9%)	2 (4.4%)	7 (7.1%)	4 (8.3%)
2 events	1 (1.0%)	0	0	0	1 (1.0%)	0
3 events	0	0	0	0	0	0
>3 events	0	0	0	0	0	0
Subjects with an anaphylactic reaction by maximum severity[1]	--	--	--	--	--	--
Mild	0	1 (2.1%)	2 (2.3%)	1 (2.2%)	2 (2.0%)	2 (4.2%)
Moderate	2 (2.0%)	1 (2.1%)	4 (4.6%)	1 (2.2%)	6 (6.1%)	2 (4.2%)
Severe	0	0	0	0	0	0
Subjects with a serious anaphylactic reaction	0	0	0	0	0	0
Subjects with an anaphylactic reaction requiring epinephrine use	1 (1.0%)	1 (2.1%)	4 (4.6%)	1 (2.2%)	5 (5.1%)	2 (4.2%)
Subjects with an anaphylactic reaction requiring epinephrine use by location of epinephrine use	--	--	--	--	--	--
Location other than study site	1 (1.0%)	1 (2.1%)	3 (3.4%)	0	4 (4.1%)	1 (2.1%)
Study site	0	0	1 (1.1%)	1 (2.2%)	1 (1.0%)	1 (2.1%)
Number of anaphylactic reactions	3	2	6	2	9	4
Number of anaphylactic reactions by trigger	--	--	--	--	--	--
Study product	3	0	0	0	3	0
Peanut or peanut containing food	0	0	0	0	0	0
Other food allergen	0	2	6	2	6	4
Other	0	0	0	0	0	0

Treatment-Emergent Systemic Allergic Reaction Episodes	Up-Dosing Palforzia (N=98)	Up-Dosing Placebo (N=48)	Maintenance Palforzia (N=87)	Maintenance Placebo (N=45)	Overall Palforzia (N=98)	Overall Placebo (N=48)
Common symptoms in subjects with an anaphylactic reaction [2]	--	--	--	--	--	--
Cough	0	0	4 (4.6%)	2 (4.4%)	4 (4.1%)	2 (4.2%)
Urticaria	0	0	4 (4.6%)	1 (2.2%)	4 (4.1%)	1 (2.1%)
Throat irritation	1 (1.0%)	0	2 (2.3%)	0	3 (3.1%)	0
Wheezing	2 (2.0%)	0	1 (1.1%)	1 (2.2%)	3 (3.1%)	1 (2.1%)
Vomiting	0	2 (4.2%)	1 (1.1%)	1 (2.2%)	1 (1.0%)	3 (6.3%)

Source: ARC005 Applicant CSR, pg. 153, Table 54; Table 14.3.7.3.1
Notes:
1. Severity was graded on a 3-point scale (mild, moderate, severe) according to the European Academy of Allergy and Clinical Immunology (EAACI) grading system (adapted from Muraro, 2007) . None of the reported reactions were classified as severe.
2. In at least 2 subjects overall in either treatment group.

Clinical Reviewer comment: Three events of systemic allergic reaction/anaphylaxis (2 events occurring in one subject) related to study treatment occurred in Palforzia recipients during up-dosing. Two of these events were mild and one was a moderate systemic allergic reaction. Epinephrine was used for one of the moderate events. None of these events were considered SAEs. The rest of these events were due to accidental food allergen exposures to foods other than peanut. None of these subjects discontinued the study due to the event. It is encouraging that none of the allergic reaction events were severe, which suggests that parents and caregivers of young study participants were appropriately counseled on how to recognize and treat an allergic reaction early, thereby preventing progression in severity).

During the original BLA review, in pivotal Phase 3 study ARC003, Palforzia recipients 4 through 17 years of age reported more systemic allergic reactions (14.2%) compared to placebo (3.2%). In ARC003 Palforzia recipients, 88.7% of these events were considered related to study treatment. It appears that older children (≥4 years of age) experience a higher rate of systemic reactions to Palforzia therapy than younger children/toddlers. It is not clear why this may be occurring. This result may be a combination of immune plasticity and/or that children between 1 and 3 years of age cannot verbally express that they are experiencing the early symptoms of an allergic reaction (e.g., itching), though it would be expected that symptoms would become objective if an allergic reaction were to progress.

Of the ARC005 participants (N=112) who entered follow-on Study ARC008, two Palforzia recipients experienced two systemic allergic reactions/anaphylaxis due to Palforzia while continuing maintenance therapy in ARC008. These were mild events that did not require auto-injectable epinephrine. Three placebo recipients experienced a total of 11 anaphylactic reactions during up-dosing and maintenance. These events were mild to moderate. Five of these events were treated with epinephrine.

These events highlight the need for ongoing vigilance for systemic reactions as well as the necessity of readily available auto-injectable epinephrine for patients on long-term therapy.

Use of Epinephrine
In the Palforzia group 11 subjects (11.2%) versus 2 (4.2%) subjects in the placebo group used epinephrine at least once. Most of these episodes occurred outside of the study site (84.6% Palforzia vs. 75% placebo) and were associated with mild to moderate AEs. Two events associated with use of epinephrine in the Palforzia group and 1 event in the placebo group were

serious. None of the serious reactions treated with epinephrine were considered related to study therapy. Overall, one subject discontinued due an AE that required epinephrine, however, this treatment was used in the context of an asthma exacerbation and not an acute allergic reaction. No epinephrine use was reported during the initial dose escalation; therefore, this row is not shown in Table 22.

Table 22. Use of Epinephrine as Rescue Medication Excluding DBPCFCs, Safety Population, Study ARC005

Safety Population	Up-Dosing Palforzia (N=98)	Up-Dosing Placebo (N=48)	Maintenance Palforzia (N=87)	Maintenance Placebo (N=45)	Overall Palforzia (N=98)	Overall Placebo (N=48)
Subjects with at least 1 episode[1]	6 (6.1%)	1 (2.1%)	5 (5.7%)	2 (4.4%)	11 (11.2%)	2 (4.2%)
1 episode	5 (5.1%)	0	4 (4.6%)	2 (4.4%)	9 (9.2%)	1 (2.1%)
2 episodes	1 (1.0%)	1 (2.1%)	1 (1.1%)	0	2 (2.0%)	0
3 episodes	0	0	0	0	0	1 (2.1%)
>3 episodes	0	0	0	0	0	0
Number of episodes	7	2	6	2	13	4
Epinephrine doses used per episode[2]	--	--	--	--	--	--
1 dose	7 (100.0%)	1 (50.0%)	5 (83.3%)	2 (100.0%)	12 (92.3%)	3 (75.0%)
2 doses	0	1 (50.0%)	1 (16.7%)	0	1 (7.7%)	1 (25.0%)
3 or more doses	0	0	0	0	0	0
Maximum severity of AE associated with the episode[2]	--	--	--	--	--	--
Grade 1	2 (28.6%)	0	2 (33.3%)	0	4 (30.8%)	0
Grade 2	3 (42.9%)	2 (100.0%)	4 (66.7%)	1 (50.0%)	7 (53.8%)	3 (75.0%)
Grade 3 or higher	2 (28.6%)	0	0	1 (50.0%)	2 (15.4%)	1 (25.0%)
SAE associated with an episode[2]	2 (28.6%)	0	0	1 (50.0%)	2 (15.4%)	1 (25.0%)
Treatment-related AE associated with an episode[2]	3 (42.9%)	0	0	0	3 (23.1%)	0
Location of episode[2]	--	--	--	--	--	--
Location other than study site	5 (71.4%)	2 (100.0%)	6 (100.0%)	1 (50.0%)	11 (84.6%)	3 (75.0%)
Study site	2 (28.6%)	0	0	1 (50.0%)	2 (15.4%)	1 (25.0%)

Source: ARC005 Applicant CSR, pg. 169, Table 59; Table 14.3.7.2.1
Abbreviations: DBPCFC=double-blind, placebo-controlled food challenge; na=not applicable; AE=adverse event; SAE=serious adverse event
Notes: All routes of epinephrine use were included, including inhalation and 1 administration of inhaled racemic epinephrine in the Palforzia group.
1. An episode was defined as an administration of 1 or more epinephrine doses within a 2-hour window.
2. The percentages were based on the number of episodes.

Clinical Reviewer comment: Palforzia recipients reported a higher rate of epinephrine use compared to placebo recipients (11.2% vs 4.2%). Three of these events in Palforzia recipients were related to the study treatment and occurred during up-dosing. Of the participants who used epinephrine in relation to study treatment: one subject used epinephrine at home to treat a

reaction (crying and holding throat) and was transported to the ED where the subject was found to be wheezing. The subject had received the product around 6pm that evening. The subject had been running around playing at home prior to the dose and this reaction was considered related. One subject experienced rhinorrhea, one hive, and coughing about 1.5 hours after a Palforzia dose. The patient also had URI symptoms that day. Epinephrine was administered at home. One subject had a reaction 20 minutes after a dose ("messing with ear," throat swelling, irritability). The subject received a dose of epinephrine.

The three reported SAEs associated with epinephrine use occurred as follows: One subject who received placebo was taken to a local urgent care due to stomach pains and was found pale and covered in vomit by medical staff. No urticaria or angioedema. Subject was found to be hypotensive. Initially this was thought to be due to anaphylaxis (and was treated with epinephrine) however the patient was found to have carbon monoxide poisoning from sitting in the waiting car (the car was apparently known to produce high carbon monoxide levels). One subject, treated with Palforzia, developed an asthma exacerbation after receiving a dose of Palforzia 4 hours earlier. Epinephrine was administered due to wheezing. The subject was taken to urgent care and tested positive for rhinovirus and enterovirus. A second dose of epinephrine was given due to continued wheezing and work of breathing. The patient was hospitalized and treated for asthma exacerbation in the setting of a viral URI. One subject received a dose of Palforzia the previous day. The previous day, the subject had developed mild URI symptoms and started inhaled budesonide treatment. The symptoms worsened and the subject developed a fever. Two days later, the patient was taken to a doctor's office for coughing, fever, and increased work of breathing. Testing was positive for RSV and coronavirus The patient was admitted and received numerous medications including salbutamol, inhaled budesonide and iv methylprednisolone as well as epinephrine nebulizer. The subject was diagnosed with status asthmaticus which resolved.

Parents/caregivers of study participants are counseled on how to recognize early signs of an allergic reaction and how to use epinephrine to treat a reaction prior to progression to a systemic allergic reaction/anaphylaxis. Therefore, it is expected that the rate of epinephrine use will be higher than the rate of systemic allergic reactions/anaphylaxis. The other 10 events were related to accidental food exposure. It is unclear why the rate of epinephrine use due to accidental food exposure is higher in Palforzia recipients, it is possible this imbalance is due to the relatively small sample size and 2:1 randomization scheme.

Gastrointestinal Adverse Events and Eosinophilic Esophagitis

GI disorders were the most common SOC of AEs overall (83.7% Palforzia vs 64.6% placebo). The most common GI AEs with at least 5% higher incidence in the Palforzia group compared to the placebo group were abdominal pain (15.3% vs 6.3%) and vomiting (15.3% vs 0%).

Chronic or recurrent GI AEs led to discontinuation of study product in 3 Palforzia recipients (3.1%; 1 during up-dosing and 2 during maintenance). These events were abdominal discomfort, eructation, and regurgitation. These events resolved after discontinuation of the study product. No placebo recipients discontinued due to a GI AE. None of the GI events were SAEs.

Subjects ingesting oral immunotherapy may be at higher risk for the development of EoE. No subject with chronic or recurrent GI event was diagnosed with EoE.

Clinical Reviewer comment: No ARC005 study participant developed EoE. However, EoE remains an important risk of Palforzia therapy. In total, 22 Palforzia recipients developed EoE

out of a total of 1337 Palforzia recipients in the Palforzia development program (data submitted to this sBLA in amendment 16), which highlights the necessity of ongoing vigilance for this disease by Palforzia prescribers. A clinical history of EoE is appropriately listed as a contraindication in the PI. The risk of EoE is discussed in the Warnings and Precautions section - prescribers are advised to consider a diagnosis of EoE in patients who experience severe or persistent GI symptoms, including dysphagia, vomiting, nausea, gastroesophageal reflux, chest pain, or abdominal pain.

6.1.12.6 Clinical Test Results

Not applicable.

6.1.12.7 Dropouts and/or Discontinuations

Of the 146 subjects enrolled in the study, 128 (87.7%) completed the study. In the Palforzia group, 83 of 98 (84.7%) completed the study, and in the placebo group 45 of 48 (93.8%) completed the study. Study discontinuation occurred in more Palforzia recipients (10.3%; 15/146) than placebo recipients (6.3%; 3/48). The AEs that led to discontinuation in the Palforzia group included wheezing, coughing, abdominal pain, intermittent regurgitation, and burping. In the placebo group the AE that led to discontinuation was gross motor regression. The table below summarizes the reasons for early discontinuation.

Table 23. Primary Reason for Early Discontinuation, All Subjects, Study ARC005

Reason	**Palforzia** (N=98)	**Placebo** (N=48)	**Total**
Total number of subjects who discontinued	15	3	18
Adverse event	5 (5.1%)	1 (2.1%)	6 (4.1%)
Use of prohibited medication	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subject withdrew consent	5 (5.1%)	1 (2.1%)	6 (4.1%)
Lost to follow-up	1 (1.0%)	0 (0.0%)	1 (0.7%)
Other[a]	4 (4.1%)	1 (2.1%)	5 (3.4%)
Follow-up due to chronic/ recurrent GI symptoms	--	--	--
Yes	3 (3.1%)	0 (0.0%)	3 (2.1%)
No	95 (96.9%)	48 (100%)	143 (97.9%)

Source: Applicant CSR ARC005, p. 211
Notes: Denominators for percentages were based on total subjects screened for screen failure and based on number of randomized subjects for all other percentages.
a. Reasons for Other, Palforzia: 1 investigator decision due to noncompliance, and 3 subjects' decision due to continued commitment to study treatment. Reasons for Other, Placebo: taste aversion to study product.

Clinical Reviewer comment: The study discontinuation rate was almost 2-fold greater in the Palforzia group compared to placebo. The most common reasons for discontinuation were AEs and withdrawal of consent. It is likely that treatment in patients who had AEs that did not meet criteria for dose-limiting symptoms (see Table 2) was discontinued by parents/caregivers based on individual judgment of tolerability.

6.1.13 Study Summary and Conclusions

Study ARC005 was a Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of Palforzia oral immunotherapy in peanut-allergic children 1 through 3 years of age. The majority of enrolled subjects were White males from the United States. Other atopic conditions such as food allergies other than peanut, allergic rhinitis, or atopic dermatitis/eczema were generally balanced evenly between treatment arms.

The study met the pre-specified criterion for success on the primary endpoint of the proportion of subjects tolerating a single highest dose of at least 600 mg of peanut protein with no more than mild symptoms at the exit DBPCFC with a lower bound of the corresponding 95% CI greater than 15% with a result of 67.2% (95% CI 50.0%, 84.5%).

Palforzia recipients reported more AEs overall. While the number of systemic allergic reactions was similar between the treatment groups (8.2% Palforzia vs. 8.3% placebo, overall), three events were considered related to the study treatment in the Palforzia group. The frequency of epinephrine use was greater in the Palforzia group (11.2%) than in the placebo group (4.2%). Three of these events in 3 Palforzia recipients were related to the study treatment. All events were mild to moderate. No deaths occurred in the study. No cases of EoE were reported. No SAEs were considered related to the study product.

The efficacy and safety data from ARC005, along with proper risk mitigation strategies to diminish the risk of systemic allergic reactions including anaphylaxis outlined in the existing REMS, support the approval of Palforzia in pediatric subjects 1 through 3 years of age.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No human data are available to establish the presence or absence of the risks due to Palforzia in pregnant women. ARC005 enrolled children 1 through 3 years of age. No pregnancies occurred in Palforzia recipients prior to licensure. Palforzia can cause anaphylaxis, which can cause a dangerous decrease in blood pressure, which could result in compromised placental perfusion and significant risk to a fetus. A postmarketing pregnancy registry study is underway. There have been no reported exposures to Palforzia during pregnancy as of Jan 30, 2024.

9.1.2 Use During Lactation

The safety of Palforzia in women who are lactating has not been established.

Clinical Reviewer comment: As noted above, no exposures to Palforzia have occurred during pregnancy and no patients initiated Palforzia therapy while breastfeeding.

9.1.3 Pediatric Use and PREA Considerations

This submission has fulfilled the PMR to conduct a study in children 1 through 3 years of age evaluating the efficacy and safety of Palforzia. A partial waiver from PREA requirements is granted for subjects <1 year of age because necessary studies are impossible or highly impracticable on the basis that peanut allergy is not typically diagnosed before the age of 1 year.

9.1.4 Immunocompromised Patients

Clinical studies that evaluated Palforzia excluded individuals on immunomodulatory medications. Therefore, no data are available on the safety or effectiveness of Palforzia in this population.

9.1.5 Geriatric Use

No studies in the clinical development program included individuals ≥65 years of age. The Applicant does not seek an indication for use in this age group.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not applicable.

10. CONCLUSIONS

Efficacy and safety data contained in this supplemental BLA from Study ARC005 support the effectiveness and safety of Palforzia in children 1 through 3 years of age in the setting of a requirement for a REMS with ETASU to mitigate the risk of systemic allergic reactions, put in place with the original BLA approval, to ensure a favorable benefit-risk balance.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 24 below summarizes the risk-benefit considerations to extend the use of Palforzia to individuals 1 through 3 years of age.

Table 24. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• IgE-mediated peanut allergy is a common disease affecting 5.1% of children and adolescents in the US. Only about 20% children grow out of a peanut allergy (Skolnick, 2001), highlighting the need for an effective long-term therapy. • Exposure to peanut allergens in allergic individuals can result in systemic allergic reactions that can be life-threatening. • Peanut allergy results in significant impairment of Quality of Life (QoL) due to the fear of accidental ingestion as well as the burden of avoiding allergenic foods.	• IgE-mediated peanut allergy is a life-threatening disease that results in significant disruption of QoL for individuals and their families.
Unmet Medical Need	• All peanut-allergic individuals must maintain a strict avoidance diet. • Palforzia is the only licensed oral allergen immunotherapy for peanut allergy. It is intended for use in conjunction with strict peanut avoidance. • Oral peanut immunotherapy is provided in a fixed daily dosing regimen. It can be disease modifying; it can lead to sustained unresponsiveness in some individuals (Jones, 2022). • Omalizumab, a subcutaneously administered monoclonal antibody, inhibits the binding of IgE to the high-affinity IgE receptor on the surface of mast cells, basophils, and dendritic cells, resulting in receptor down-regulation on these cells.. Dosing is based on body weight and serum IgE and is administered every 2 to 4 weeks. It is indicated in patients 1 year and older for the reduction of allergic reactions including anaphylaxis with accidental exposure to one or more foods. • When symptoms to accidental peanut exposures occur, treatment is limited to mitigating the symptoms of allergic reactions either with immediate injection of epinephrine or with antihistamines for milder symptoms.	• Palforzia offers one option to mitigate allergic reactions in peanut allergic children 1 through 3 years of age, for whom treatment with an omalizumab antibody may not be appropriate.
Clinical Benefit	• Phase 3 Study ARC005 was a double-blind, randomized, placebo-controlled efficacy and safety study that demonstrated the effectiveness of Palforzia in individuals 1 through 3 years of age with the treatment difference (efficacy) estimate of 67.2% (95% CI (50.0, 84.5)) in the ability to tolerate 600 mg of peanut at the exit DBPCFC. • Study ARC005 met pre-specified key secondary endpoints at the exit DBPCFC with the ability to tolerate 300 mg (56.7% (95%CI: 39.8, 73.5)) and 1000 mg (64.2% (95% CI: 47.0, 81.4)). • The overall severity of symptoms occurring during the exit DBPCFC decreased in Palforzia recipients compared to placebo recipients, meeting the 3rd pre-specified key secondary endpoint.	• Treatment with Palforzia reduces the severity of allergic symptoms upon exposure to a quantifiable amount of peanut protein during an OFC in individuals 1 through 3 years of age.
Risk	• Palforzia recipients reported more systemic allergic reactions triggered by the study product (in ARC005, 3.1% of Palforzia recipients vs. 0% of placebo recipients), epinephrine use (in ARC005, 11.2% of Palforzia recipients vs. 4.2% of placebo recipients), and allergic symptoms, particularly GI-related allergic symptoms. • Palforzia recipients discontinued at a higher rate than placebo recipients.	• Palforzia is associated with an increased risk of systemic allergic reactions, allergic reactions requiring epinephrine, and EoE.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	• No cases of EoE were reported in Study ARC005; however, 22 cases of EoE in Palforzia recipients were reported in overall clinical development program (N =1337 Palforzia recipients in 8 clinical studies) while no placebo recipient developed EoE. • No deaths were associated with Palforzia.	
Risk Management	• A REMS program is in place to ensure patients have access to epinephrine, continue to avoid peanut in the diet, and are observed in a clinical setting with certified providers and healthcare settings capable of treating systemic allergic reactions during initial dose escalation and on the first day of each new dose during up-dosing to ensure patients objectively tolerate the higher dose of Palforzia prior to daily home administration. • Product labeling conveys information to patients about the risks of systemic allergic reactions, GI-related allergic reactions, and EoE and to directly to contact a health care professional if any of these signs or symptoms occur.	• Review of 48-month REMS report (by the PVP reviewer) reveals that the current REMS with ETASU appears to satisfactorily mitigate the risk of systemic allergic reactions, therefore this strategy should be extended to individuals from 1 through 3 years of age. • The package insert is adequate to communicate the risks of EoE and GI-related symptoms.

11.2 Risk-Benefit Summary and Assessment

Peanut allergy is a life-threatening disorder that, unlike other IgE-mediated food allergies, persists into adulthood for most patients (Skolnick, 2001). This condition greatly affects the QoL of patients, patients' parents, and caregivers who, due to the fear of a fatal system allergic reaction, must maintain constant vigilance to avoid accidental exposure to peanut proteins. This includes dietary restrictions and social monitoring, particularly when the patient is consuming meals outside of the home environment such as at day care, parties, picnics, and other social activities.

Data from Study ARC005 demonstrate a therapeutic benefit of Palforzia as an oral immunotherapy treatment to mitigate allergic reactions, including anaphylaxis, after accidental exposure to peanut in patients 1 through 3 years of age with a confirmed diagnosis of peanut allergy. The risks associated with the use of Palforzia compared to placebo include local allergic reactions, systemic allergic reactions including anaphylaxis, and EoE, all of which had been previously established during review of the original BLA. Due to the seriousness of the risk of anaphylaxis, a REMS with ETASU in was put in place through negotiations with the Applicant during review of the original BLA. These risks are expected as allergen immunotherapy (and in this case the oral route of exposure influences the risk of EoE) exposes individuals to the peanut protein epitopes to which they are allergic. However, the younger children in ARC005 reported less systemic allergic reactions and epinephrine use overall than children 4 years of age and older enrolled in Study ARC003 (reviewed in the original BLA). The reasons for this trend are unclear as the mechanisms by which peanut oral immunotherapies function to decrease allergic responsiveness to peanut protein have not yet been completely elucidated. This result may be a combination of immune plasticity and/or that children between 1 and 3 years of age cannot verbally express that they are experiencing the early symptoms of an allergic reaction (e.g., itching), though it would be expected that symptoms would become physically observable if a reaction were to progress and require medical attention. However, given the nature of the therapy and the known risk of anaphylaxis, it is important that these risks continue to be assessed in the postmarketing setting through the current REMS where patients and caregivers are administering Palforzia outside of the controlled conditions of a clinical protocol.

11.3 Discussion of Regulatory Options

The decision to extend the indication of Palforzia to children 1 through 3 years of age was based on efficacy and safety data from one major study, ARC005. These data are sufficient to support approval of Palforzia; therefore, consideration of other regulatory options was not necessary. This reviewer continues to agree with the Applicant's rationale for a partial waiver in children <1 year of age.

11.4 Recommendations on Regulatory Actions

Palforzia is recommended for approval (21 CFR 601.4) based on the data from the primary efficacy and safety analyses of Study ARC003 in children 1 through 3 years of age as oral immunotherapy treatment to mitigate allergic reactions, including anaphylaxis, after accidental exposure to peanut.

11.5 Labeling Review and Recommendations

Concurrence on a revised package insert and medication guide was reached with the Applicant. Minor changes in structure, grammar, and punctuation were made throughout both documents to enhance readability. The following sections were revised as described below:

- Section 1 Indications and Usage was revised to indicate that the product is approved for use in patients 1 through 17 years of age.
- Section 2 Dosage was revised to update dosing configuration tables and instructions for initial dose escalation and up-dosing for patients 1 through 3 years of age.
- Section 5 Warnings and Precautions was revised to include data on the incidence of anaphylaxis, epinephrine use, and EoE in Study ARC005 (for subjects 1 through 3 years of age). The paragraph discussing study data from ARC003 (reviewed in the original BLA submission) was updated to include an assessment of relatedness for systemic reactions.
- Section 6 was revised to include safety data from Study ARC005
- Section 14 was revised to include efficacy data (primary and key secondary efficacy endpoints) from Study ARC005
- Medication guide was updated to include a list of symptoms that may indicate an allergic reaction in young children

11.6 Recommendations on Postmarketing Actions

Palforzia was originally approved with a REMS with ETASU to support safe use of the product and ensure that the benefits of the drug outweigh the risks. Review of postmarking data and the REMS program are ongoing. No additional changes were made to the PVP, and no new safety concerns were identified through review of the submitted clinical safety data or review of available postmarketing safety data in FAERS by the PVP reviewer. Additionally, findings from REMS assessment reports have not resulted in any major REMS modifications. The PVP reviewer determined that according to the most recently reviewed REMS assessment report (36-month), the Palforzia REMS Program was meeting its goal of mitigating the risk of anaphylaxis . Accordingly, the REMS program has been effective in sustaining the safe use of this product in the approved population, children 4 through 17 years of age. In order to maintain a favorable risk-benefit ratio for use of Palforzia in children 1 through 3 years of age, this reviewer recommends that the REMS program remain in place to support safe use and gather postmarketing data in this pediatric subpopulation. Therefore, additional postmarketing safety studies are not recommended because the current plan is adequate to surveil and mitigate the risks of Palforzia therapy. A pregnancy registry to collect, analyze, and report data on pregnancy outcomes and infant outcomes after exposure of Palforzia during pregnancy is ongoing as a PMC.