NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sBLA
Application Number(s)	103976/S5245
Priority or Standard	Priority
Submit Date(s)	August 25, 2023
Received Date(s)	August 25, 2023
PDUFA Goal Date	February 25, 2024
Division/Office	Division of Pulmonology, Allergy, and Critical Care
Review Completion Date	February 15, 2024
Established/Proper Name	Omalizumab
(Proposed) Trade Name	XOLAIR
Pharmacologic Class	Anti-IgE
Applicant	Genentech/NIAID
Dosage form	Injection (single-dose prefilled syringe, single-dose prefilled autoinjector, lyophilized powder in a single dose vial for reconstitution).
Dosing Regimen	75 mg to 600 mg SC every 2 or 4 weeks. Determine dose (mg), and dosing frequency by serum total IgE level (IU/mL) measured before the start of treatment, and body weight (kg)
Applicant Proposed Indication(s)/Population(s)	For the reduction of allergic reactions, including anaphylaxis, that may occur with accidental exposure to one or more foods in adults and pediatric patients aged 1 year and older with food allergy. To be used in conjunction with food avoidance.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For IgE-mediated food allergy in adult and pediatric patients aged 1 year and older for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods. To be used in conjunction with food allergen avoidance.

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Abbreviations: OB, Office of Biostatistics

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Abbreviations: DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; OMP, Office of Medical Policy; OMPI, Office of Medical Policy Initiatives; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Glossary

ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CoFAR	Consortium for Food Allergy Research
COVID-19	coronavirus disease 2019
CRF	case report form
CRSwNP	chronic rhinosinusitis with nasal polyps
CSR	clinical study report
CSU	chronic spontaneous urticaria
CTCAE	Common Terminology Criteria for Adverse Event
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DBPCFC	double-blind, placebo-controlled food challenge
DNA	deoxyribonucleic acid
ELISA	enzyme-linked immunosorbent assay
FA-S1	full analysis set – Stage 1
FA-S1OLE	full analysis set – Stage 1 OLE
FAQLQ	Food Allergy Quality of Life Questionnaire
FcεRI	high-affinity immunoglobulin E receptor
FDA	Food and Drug Administration
GI	gastrointestinal
ICH	International Council for Harmonisation
IgE	immunoglobulin E
IND	investigational new drug
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MNAR	missing-not-at-random
MTD	maximum tolerated dose

NDA	new drug application
NIAID	National Institute of Allergy and Infectious Diseases
OCP	Office of Clinical Pharmacology
OCS	Office of Computational Science
OFC	oral food challenge
OIT	oral immunotherapy
OLE	open-label extension
PD	pharmacodynamics
PFA-S1	pediatric full analysis set – Stage 1
PFA-S1OLE	pediatric full analysis set – Stage 1 OLE
PI	prescribing information
PK	pharmacokinetics
PP	per protocol
PPP-S1	pediatric per-protocol set – Stage 1
PSS-S1	pediatric safety set – Stage 1
PSS-S1OLE	pediatric safety set – Stage 1 OLE
PT	preferred term
Q2W	every 2 weeks
Q4W	every 4 weeks
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental biologics license application
SD	standard deviation
SEE	substantial evidence of effectiveness
SOC	system organ class
SPT	skin prick testing
SS-S1	safety set – Stage 1
SS-S1OLE	safety set – Stage 1 OLE
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantitation

1 Executive Summary

1.1. Product Introduction

The Applicant, Genentech, Inc., in collaboration with their co-development partner, Novartis, submitted this supplement to biologics license application (BLA) 103976 seeking approval of XOLAIR (omalizumab) for the proposed novel indication of:

> "*Reduction of allergic reactions, including anaphylaxis, that may occur with accidental exposure to one or more foods in adult and pediatric patients aged 1 year and older with food allergy. To be used in conjunction with food avoidance.*"

Omalizumab is a recombinant, humanized, IgG1 kappa monoclonal antibody that selectively binds to the constant region (Fc) of human immunoglobulin E (IgE). Binding of omalizumab to IgE inhibits IgE binding to high-affinity IgE receptors (FcεRI) on the surface of mast cells, basophils, and dendritic cells, with subsequent down-regulation of the receptors. Downregulation of the IgE-FcεRI pathway attenuates degranulation of mast cells and basophils, and release of mediators of the allergic response. Following treatment with omalizumab, serum free IgE (not bound to omalizumab) is markedly diminished, while total serum IgE levels are increased due to slow clearance of omalizumab:IgE immune complexes (signs and symptoms of immune complex disease have been reported in some patients treated with omalizumab in post-marketing reports).

Omalizumab is currently approved for:

- Moderate to severe persistent asthma in adults and pediatric patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids (approved for ≥12 years of age on June 20, 2003; approved for ≥6 years of age on July 7, 2016)
- Chronic spontaneous urticaria (CSU) in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment (approved March 21, 2014)
- Chronic rhinosinusitis with nasal polyps (CRSwNP) in adult patients 18 years of age and older with inadequate response to nasal corticosteroids, (b) (4) (approved November 30, 2020)

Omalizumab is administered by subcutaneous injection. Approved dosage forms include:

- Lyophilized powder in a single-dose vial for reconstitution (150 mg)
- Single-dose prefilled syringe (75, 150, and 300 mg)
- Single-dose autoinjector (75, 150, and 300 mg)

Omalizumab is approved for administration by patients or caregivers, specifically in a subset of patients at lower risk of anaphylaxis, using a risk-based and shared decision-making approach.

The proposed omalizumab dosing for IgE-mediated food allergy is similar to that approved for (b) (4) CRSwNP, with dose (75 to 600 mg) and dosing frequency (Q2 weeks or Q4 weeks) determined using a dosing table that is dependent on the patient's weight (kg) and pre-dose total serum IgE level (IU/mL). A new dosing table is proposed for IgE-mediated food allergy that expands IgE categories to accommodate patients with pre-dose total IgE levels up to 1850 IU/mL (previous maximum was 1500 IU/mL for the CRSwNP indication) or a body weight down to 10 kg (previous minimum was 20 kg for the asthma indication). The algorithm used to generate the dosing table targets delivery of 0.016 mg/kg of omalizumab for every IU/mL of total IgE in a 4-week interval and does not exceed a 20 mg/kg dose for a single administration. The proposed dosing table was used in the pivotal trial, OUtMATCH, and enabled dosing in patients down to 1 year of age. Patients with pre-dose total serum IgE levels >1850 IU/mL are not candidates for omalizumab treatment for the IgE-mediated food allergy indication.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is **Approval** of omalizumab, at doses determined by the new food allergy-specific dosing table, for the new indication of:

> *"IgE-mediated food allergy in adult and pediatric patients aged 1 year and older for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods. To be used in conjunction with food allergen avoidance."*

Substantial evidence of effectiveness of omalizumab for the proposed indication is based on a single, highly persuasive, adequate and well-controlled trial, with confirmatory evidence provided by mechanistic evidence.

To support this application, the Applicant submitted data from a single adequate and well-controlled trial (OUtMATCH) conducted by the National Institute of Allergy and Infectious Diseases (NIAID) and the NIAID Consortium for Food Allergy Research (CoFAR), with omalizumab provided by the Applicant. The trial enrolled subjects with confirmed IgE-mediated allergy to peanut and two of the following foods: milk, egg, wheat, cashew, hazelnut, or walnut. IgE-mediated food allergy was verified at screening using double-blind, placebo-controlled food challenges (DBPCFC), which are considered the gold standard for the diagnosis of IgE-mediated food allergy. Prior to randomization, subjects had to demonstrate moderate-severe dose-limiting symptoms with DBPCFC to peanut, at a threshold of ≤100 mg peanut protein, and two additional foods, at a threshold of ≤300 mg food protein. Use of these defined thresholds in carefully conducted food challenges provides an objective measure of food allergy reactivity at baseline. The results submitted with this supplement are from a prespecified interim analysis. Following screening, 168 subjects (1 to 28 years of age) with confirmed multifood allergy were

randomized to receive either omalizumab or placebo at a 2:1 ratio. Following 16 to 20 weeks of treatment, DBPCFCs were repeated. The primary endpoint was the proportion of subjects able to consume ≥600 mg of peanut protein at the post-treatment DBPCFC, compared to placebo, without experiencing moderate-severe dose-limiting symptoms. Key secondary endpoints were the proportion of subjects able to consume ≥1000 mg of milk, egg, or cashew protein at the post-treatment DBPCFC, compared to placebo, without experiencing moderate-severe dose-limiting symptoms. Results of the post-treatment DBPCFCs demonstrated a higher proportion of responders who were able to consume a single dose of ≥600 mg of peanut protein without moderate-severe dose-limiting symptoms in the omalizumab arm compared to placebo:

- Peanut: 68.2% vs 5.5% (Difference: 62.7%, 95% CI: [50.4%, 72.1%], p<0.0001)

Results for the key secondary endpoints using the proportion of subjects able to consume ≥1000 mg to define responders similarly demonstrated a higher proportion of responders in the omalizumab arm compared to placebo:

- Cashew: 42.2% vs 3.3% (Difference: 38.9%, 95% CI: [22.6%, 52%], p<0.0001)
- Milk: 65.8% vs 10.5% (Difference: 55.3%, 95% CI: [29.8%, 71.9%], p<0.0001)
- Egg: 67.4% vs 0% (Difference: 67.4%, 95% CI: [48.5%, 79.2%], p<0.0001)

The trial design of OUtMATCH was robust, with objective primary and key secondary endpoints; the results were highly statistically significant and clinically meaningful, providing strong support for the efficacy of omalizumab in reducing allergic reactions, including anaphylaxis, that may occur with accidental exposure to one or more foods in adults and children ≥1 year of age with IgE-mediated food allergy. Of note, however, a moderate proportion of subjects treated with omalizumab were not able to tolerate food protein at levels above the pre-treatment thresholds required for randomization: 17% were not able to consume >100 mg of peanut protein without moderate-severe dose-limiting symptoms, and 18%, 22%, and 41% were not able to consume >300 mg of milk, egg, and cashew protein, respectively, without moderate-severe dose-limiting symptoms. As a result, treatment of IgE-mediated food allergy with omalizumab requires continued food allergen avoidance.

Confirmatory evidence to support substantial evidence of effectiveness is provided by mechanistic evidence. Mechanistic evidence to support the effectiveness of omalizumab in the treatment of IgE-mediated food allergy includes: 1) a well understood pathophysiology of IgE-mediated food allergy that is driven by allergen-specific IgE acting through FcεR1 receptors on mast cells and basophils, and 2) the well-defined mechanism of action of omalizumab in binding IgE and preventing binding of IgE to FcεR1 (reductions of free IgE levels [not bound to omalizumab] result in downregulation of FcεR1 on mast cells and basophils). Downregulation of FcεR1 on mast cells and basophils is the major downstream mechanism of action of omalizumab that reduces effector cell reactivity with food allergen exposure. Consistent with pharmacodynamic data from the development programs for the other omalizumab indications, about 97% of subjects treated with omalizumab in the OUtMATCH trial had Week 16 free IgE

values below 20 IU/mL (~50 ng/mL) across age groups and dosing regimens, including in children 1 to 5 years of age. Although only 3 adults were enrolled in the OUtMATCH trial, the mechanism of action of omalizumab in the treatment of IgE-mediated food allergy extends across the age spectrum; as a result, extrapolation of efficacy data from subjects 1 to 17 years of age (165/168 subjects in the OUtMATCH trial) to the >18 years of age population, with pharmacokinetic (PK) matching, is supported.

As noted above, omalizumab decreases the level of serum free IgE and decreases FcεRI density on effector cells; this mechanism of action is not allergen-specific (i.e., should affect IgE-mediated food allergy independent of IgE specificity). Based on this mechanism of action, it is expected that the efficacy findings from the OUtMATCH trial can be extended to IgE-mediated allergy to other foods not assessed in the trial.

There is an unmet need for treatments for patients with allergy to one or more foods to reduce the risk for serious outcomes, most notably fatal anaphylaxis. Given the strength of trial design and the persuasiveness of the results from the OUtMATCH trial, along with the strength of the mechanistic evidence, substantial evidence of effectiveness has been demonstrated and the recommended regulatory action is **Approval** of this supplement.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Omalizumab is a humanized anti-IgE monoclonal antibody that binds to the Fcε3 region of IgE and inhibits IgE binding to FcεRI on mast cells and basophils; inhibition of binding leads to downregulation of FcεRI on the surface of mast cells and basophils, which is thought to decrease IgE-mediated reactivity with allergen exposure. Allergen-specific IgE, acting through FcεRI on mast cells and basophils, is central to the pathophysiology of IgE-mediated food allergy. Omalizumab markedly decreases the level of serum free IgE (not bound to omalizumab) and subsequently decreases FcεRI density on effector cells; this effect is not allergen-specific (i.e., should affect IgE-mediated food allergy independent of IgE specificity).

The new indication for omalizumab is for:

> *"IgE-mediated food allergy in adult and pediatric patients aged 1 year and older for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods. To be used in conjunction with food allergen avoidance."*

This would be the first product approved for the treatment of IgE-mediated food allergy that is not allergen-specific and that is available for patients ≥1 year of age.

Efficacy for the proposed indication was evaluated in a single adequate and well-controlled trial that enrolled subjects ≥1 year of age with confirmed IgE-mediated food allergy to peanut plus 2 additional foods. IgE-mediated food allergy was confirmed by pre-treatment double-blind, placebo-controlled food challenges (DBPCFCs), with a threshold of development of moderate-severe dose-limiting symptoms at ≤100 mg of peanut protein, and at ≤300 mg of protein for milk, egg, and cashew; the higher thresholds for the latter foods were based on concerns with enrollment with the lower threshold (≤100 mg) used for all 3 foods. Following confirmation of food allergy, 168 subjects were randomized 2:1 to receive 16-20 weeks of treatment with omalizumab or placebo, followed by a second, post-treatment DBPCFC. The primary endpoint at the post-treatment DBPCFC was consumption of a single dose of ≥600 mg of peanut protein (~2.5 peanuts) without moderate-severe dose-limiting symptoms. The key secondary endpoints were consumption of single doses of ≥1000 mg of cashew (~3.5 cashews), milk (~2 tablespoons of cows' milk), and/or egg (~0.25 eggs) protein without moderate-severe dose-limiting symptoms. The thresholds used for the primary and key secondary endpoints were selected to be 2 doses higher on the food challenge protocol than the maximal doses used for confirmation of IgE-mediated food allergy, which accounts for variability in thresholds and sets thresholds that are clinically meaningful in reducing allergic

reactions from accidental food allergen exposures.

The trial results demonstrated statistically significant and clinically meaningful treatment effects for the primary and key secondary endpoints. Omalizumab was superior to placebo in the proportion of subjects meeting the primary and key secondary endpoints:

- Peanut: 68.2% vs 5.5% (Difference: 62.7%, 95% CI: [50.4%, 72.1%], p<0.0001)
- Cashew: 42.2% vs 3.3% (Difference: 38.9%, 95% CI: [22.6%, 52%], p<0.0001)
- Milk: 65.8% vs 10.5% (Difference: 55.3%, 95% CI: [29.8%, 71.9%], p<0.0001)
- Egg: 67.4% vs 0% (Difference: 67.4%, 95% CI: [48.5%, 79.2%], p<0.0001)

Notably, the treatment effects were consistent across all age groups (1-5 yo, 6-11 yo, 12-17 yo). Although only 3 adults (18-28 yo) were randomized, given the consistency in results across pediatric age groups, shared pathophysiology of IgE-mediated food allergy irrespective of age, and no age-related differences in the pharmacokinetics (PK), efficacy can be extrapolated to adults from benefits observed in the pediatric population.

Omalizumab was first approved for asthma in 2003 and safety has been extensively studied in randomized controlled trials for other indications, specifically in subjects ≥6 years of age, and in the post-marketing setting. No new safety signals were identified in the OUtMATCH trial; the most common (≥3%) adverse reactions noted were injection site reactions and pyrexia. There were no anaphylaxis events noted that were related to omalizumab administration. Since this will be the first approval of omalizumab for children 1-5 years of age, safety in this age cohort (n=61) was carefully reviewed and identified no new safety signals. There is a Boxed Warning on omalizumab labeling for anaphylaxis, based on results from pre-marketing clinical trials and post-marketing reports. In a case-control trial in subjects with asthma, a prior history of anaphylaxis to food was a risk factor for anaphylaxis associated with omalizumab. For patients prescribed omalizumab for the IgE-mediated food allergy indication, the benefits of reduction of allergic reactions from accidental exposures to food allergens need to be weighed against the risk of anaphylaxis to omalizumab when selecting candidates for omalizumab administration by the patient or caregiver, outside of a healthcare setting.

There is an unmet need for treatments for patients with allergy to one or more foods to reduce the risk for serious outcomes, most notably fatal anaphylaxis. Overall, there is a favorable benefit-risk assessment for omalizumab in the treatment of IgE-mediated food allergy in adult and pediatric patients aged 1 year and older for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods. As noted in Section 1.2, a moderate proportion of subjects treated with omalizumab were not able

to tolerate food protein at levels above the thresholds required for randomization without developing moderate-severe dose-limiting symptoms. As a result, there may be a population of patients with IgE-mediated food allergy who do not receive appreciable benefit from treatment that emphasizes the need for continued strict food allergen avoidance. Approval of omalizumab for this new indication provides a treatment option for patients ≥1 year of age with allergy to one or more foods, particularly for those patients at highest risk for severe anaphylaxis, such as those with a prior history of anaphylaxis from accidental food ingestions, those with low food allergen thresholds for reactivity, and those with comorbid conditions, such as poorly controlled asthma.		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition	• Approximately 33 million people in the United States (~8% of children and ~10% of adults) have at least one food allergy, with 30-86% having more than one food allergy. • Food allergy can negatively impact quality of life due to fear of reactions with accidental exposure to food allergens. • >40% of patients with IgE-mediated food allergy have experienced a severe allergic reaction from accidental exposure to a food allergen. • IgE-mediated food allergy can be life-threatening in patients who develop anaphylaxis following an accidental ingestion of a food allergen. • Approximately 150 deaths from food allergen-induced anaphylaxis are reported in the United States every year.	• IgE-mediated food allergy is common, both in children and adults, and can be fatal. • Strict food allergen avoidance is challenging and can have detrimental effects on quality of life and nutrition. • Accidental ingestion of food allergens is common and can cause significant morbidity, including fatalities.
Current Treatment Options	• There is no cure for food allergy. • Current standard of care for IgE-mediated food allergy requires strict food allergen avoidance and treatment with epinephrine injection in cases of anaphylaxis from accidental exposures. • Food allergen avoidance is challenging for all patients and families, and can be particularly difficult for patients and families of low income. • Palforzia, a peanut product for oral immunotherapy, is approved for the mitigation of allergic reactions, including anaphylaxis, that may occur with	• Strict food allergen avoidance is the current standard of care for IgE-mediated food allergy; however, accidental exposures may be unavoidable despite best efforts at avoidance. • There is an unmet need for treatments that reduce the risk of severe allergic reactions from accidental exposure to one or more

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	accidental exposure to peanut; benefits of Palforzia are limited to patients 4-17 years of age with IgE-mediated peanut allergy, and adverse events, including anaphylaxis, are common. • There is no approved drug for the reduction of allergic reactions for patients with IgE-mediated food allergy to multiple foods.	food allergens, particularly for those at highest risk of fatal anaphylaxis.
Benefit	• In a single adequate and well-controlled trial, subjects with challenge-confirmed multifood allergy were randomized to receive omalizumab or placebo for 16-20 weeks, followed by DBPCFCs; results demonstrated that omalizumab treatment, compared to placebo, resulted in increases in the proportion of subjects with higher thresholds for reaction to food allergens that were statistically persuasive and clinically meaningful. • Efficacy was consistent across the ages studied (1-5 yo; 6-11 yo; 12-17 yo) • Efficacy data for adults was very limited (n=3); based on a common mechanism of action across the age spectrum, efficacy can be extrapolated to adults. • The percentage of subjects who were able to consume at least two or all three foods during DBPCFCs demonstrated that: – 71% of omalizumab-treated subjects were able to consume a single dose of ≥600 mg of at least two foods versus 5% in the placebo group – 67% of omalizumab-treated subjects were able to consume a single dose of ≥1000 mg of at least two foods versus 4% in the placebo group – 48% of omalizumab-treated subjects were able to consume a single dose of ≥600 mg of all three foods versus 4% in the placebo group – 39% of omalizumab-treated subjects were able to consume a single dose of ≥1000 mg of all three foods versus 0% in the placebo group	• Omalizumab increased the threshold for reactivity to one or more food allergens to a level that should provide clinically meaningful reduction of risk for severe allergic reactions from accidental ingestions. • A moderate proportion of subjects had no or limited increase in threshold for reactivity, highlighting the need for continued allergen avoidance with omalizumab treatment. • There is currently no evidence that omalizumab treatment modifies the natural history of IgE-mediated food allergy; chronic therapy is indicated. • Treatment with omalizumab is limited to patients with pre-treatment total serum IgE levels ≤1850 IU/mL. • Given the high prevalence of IgE-mediated food allergy and variable risk factors for serious outcomes, selection of patients for

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• For 38 pediatric subjects who continued XOLAIR for an additional 24-28 weeks in an open-label extension, the percentage of subjects who were able to consume ≥600 mg of peanut protein and ≥1000 mg of egg, milk, and/or cashew protein without moderate-severe dose-limiting symptoms was maintained. • The impact of omalizumab on food allergy-related quality of life and reduction of allergic reactions with real-world exposures to allergens are unknown.	treatment with omalizumab post-approval will require careful consideration of individualized benefit-risk assessment.
Risk and Risk Management	• Omalizumab has been on the market for adults since 2003; as a result, omalizumab has a well characterized safety profile from randomized controlled clinical trials and from post-marketing experience. • Omalizumab carries a Boxed Warning for anaphylaxis based on pre-marketing trials and post-marketing reports; a case-control trial identified prior history of anaphylaxis to food as a risk factor for omalizumab anaphylaxis. • The most common adverse reactions reported in the OUtMATCH trial were injection site reactions and pyrexia. • This is the first approval of omalizumab for subjects 1 to 5 years of age; review of safety data from OUtMATCH in subjects 1-5 years of age (n=61) did not identify safety concerns. • Safety data for adults is very limited (n=3); safety for adults is extrapolated from the extensive safety data acquired for other indications. • A moderate population in OUtMATCH who received omalizumab did not achieve a threshold for reactivity above the threshold used for randomization and, as a result, may not receive benefit from treatment (risk of anaphylaxis)	• Safety review from OUtMATCH did not identify new safety signals when omalizumab is used for treatment of IgE-mediated food allergy, including in children 1-5 years of age. • Continued avoidance of food allergen is needed with omalizumab treatment; there are no measures to identify responders, other than performing controlled food challenges in a monitored setting, which would be prohibitive for the general population treated. • Selection of patients for administration outside of a healthcare setting should utilize risk assessment and shared decision-making.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		• Human factors studies identified risk for patients to treat acute allergic reactions, including anaphylaxis, with omalizumab; a limitation of use for acute allergic reactions, including anaphylaxis, and addition of a description in Warning and Precautions were added to labeling and adequately address this concern. • Post-marketing safety can be monitored though routine pharmacovigilance.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 8.1
		X	Observer reported outcome (ObsRO)	Section 8.1
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
X	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	X	Patient-focused drug development or other stakeholder meeting summary reports: Externally-Led PFDD Meeting (September 9, 2021)		Section 2.1
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Food allergy is defined as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food" (Boyce et al. 2010). Immune responses to food allergens can be caused by IgE-mediated mechanisms (e.g., anaphylaxis) or non-IgE-mediated immune mechanisms (e.g., food protein-induced enterocolitis syndrome). IgE-mediated food allergy results from the development of food allergen-specific IgE that binds to IgE receptors (FcεR1) on the surface of basophils and tissue mast cells. Recognition of food allergen by FcεR1-bound IgE leads to cross-linking of receptors and activation of basophils and mast cells, with release mediators of the allergic immune response, including histamine, leukotrienes, prostaglandins, and cytokines. Signs and symptoms of IgE-mediated immune responses include urticaria, angioedema, nausea, vomiting, diarrhea, abdominal pain, bronchospasm, hypotension, and loss of consciousness. IgE-mediated immune responses occur soon after allergen exposure (Type I or immediate hypersensitivity) and can progress rapidly to anaphylaxis and death.

Approximately 33 million people in the United States have at least one food allergy, including approximately 8% of children and 10% of adults (Gupta et al. 2011; Warren et al. 2023). Among these patients, 30 to 86% have IgE-mediated food allergy to more than one food (Gupta et al. 2011; Sindher et al. 2023). More than 40% of children with food allergy reported at least one lifetime food allergy-related emergency department visit, including 19% who reported a food allergy-related emergency department visit in the previous year (Gupta et al. 2018). IgE-mediated food allergy can be life-threatening in patients who develop anaphylaxis following accidental ingestion of a food allergen, with approximately 150 to 200 food allergy-related deaths reported each year.

Food allergy has a significant impact on quality of life for patients and caregivers/families. Daily management of IgE-mediated food allergy requires constant vigilance, with careful reading of food labels, to avoid accidental exposure to food allergens. Risk of accidental exposures increases when food is consumed outside of the home, including at restaurants and in the homes of family and friends. Living with food allergy can detrimentally affect quality of life and is associated with anxiety, depression, bullying, and strained interpersonal relationships (Bingemann et al. 2024).

An Externally-Led Patient-Focused Drug Development Meeting was organized by the Food Allergy Collaborative and was held virtually on September 9, 2021. The goal of the meeting was to share perspectives of patients with food allergy and their caregivers with health care providers, advocates, industry representatives, and government officials, including FDA. A summary report of the meeting was generated, *Voice of the Patient Report: Food Allergies, Externally-Led Patient-Focused Drug Development Meeting* (Food Allergy Collaborative 2022),

and released on September 30, 2022. Highlights of patient/caregiver perspectives summarized in the report include:

- Challenges of avoiding food allergens, including the need to educate others about the importance of strict food allergen avoidance
- Stigmatization experienced by some patients with food allergy
- Feelings of anxiety, anger, and being overwhelmed due to food allergy and the need to strictly avoid food allergens
- Impacts of food allergy and need for strict food allergen avoidance on socialization and safety when eating outside of one's home
- Challenges in managing food allergies among families of low income and among certain racial and ethnic groups, such as Black and Latino populations, who may be disproportionately affected
- Limitations of and frustrations with current diagnostic methods that can misdiagnose food allergy, including underdiagnosis and overdiagnosis
- Limitations of and frustrations with current treatments, notably food allergen avoidance, which is anxiety-provoking and sometimes unattainable
- Limitations of the only food allergy-specific treatment available, Palforzia, in that it is limited to patients with peanut allergy and to patients 4 to 17 years of age
- Need for improved food labeling for allergens
- Need for less-invasive diagnostic and treatment options
- Need for alternatives to epinephrine autoinjectors

Members of the CDER Division of Pulmonology, Allergy, and Critical Care, including the clinical review team and signatory for this application, were in attendance; patient perspectives gained from the meeting and summarized in the report were reviewed and considered during review of this supplement.

2.2. Analysis of Current Treatment Options

Current standard of care for the management of IgE-mediated food allergy is passive and consists of strict avoidance of known food allergens and provision of epinephrine injection products to treat severe allergic reactions/anaphylaxis should accidental exposures occur. Patients and caregivers require education on how to carefully read food labels and how to recognize early signs and symptoms of an allergic reaction and treat severe reactions with epinephrine injection products. Food allergen avoidance, especially to dietary staples, is difficult; accidental exposures are relatively common.

The only approved therapy for a food allergy is Palforzia (peanut allergen powder), which was approved in 2020 for use in oral immunotherapy (OIT) for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut, in patients 4 to 17 years of age. Palforzia is to be used in conjunction with continued avoidance of peanuts.

Oral immunotherapy with Palforzia requires Dose Escalation and Up-Dosing in a monitored setting over several months, then requires long-term daily Maintenance treatment (300 mg daily). Palforzia labeling includes Warnings and Precautions for anaphylaxis, eosinophilic esophagitis, and gastrointestinal reactions, and is contraindicated in patients with uncontrolled asthma. Due to the risk of anaphylaxis, Palforzia is only available through a risk evaluation and mitigation strategy to support safe use.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The key regulatory history is summarized in Table 1.

Table 1. Summary of Presubmission/Submission Regulatory Activity

Interaction	Date	Remarks
IND 5369 granted breakthrough drug designation	August 8, 2018	For food allergy indication
PIND (b) (4) type B face to face meeting	October 16, 2018	Relayed that only Stage 1 and Stage 1 OLE data would be used for regulatory purposes. Stage 2 and 3 of trial are exploratory.
Opening IND (b) (4)	February 12, 2019	
Initial agreed iPSP	August 16, 2019	Agreed to waiver <1 year of age
Type B meeting written response -interim analysis discussion	June 10, 2022	Agreed with details, including statistical criteria, of pre-specified interim analysis, allowing earlier assessment of efficacy.

Interaction	Date	Remarks
Teleconference with NIAID	December 7, 2022	With CBER OVRR, discussed concerns related to the discovery of visible mold in lots of their investigational food products used for OFC. Discussed mitigation procedures along with conducting analyses to assess if any compromise to allergenic quality would affect interpretation of the clinical trial.
IND 5369 pre-BLA meeting written response	June 2023	Discussed: the need to thoroughly frame how they propose to support SEE; the adequacy of supplemental analyses to assess allergenic potency in regard to the above visible mold issue; indication statement along with data needed to support the intended indication, such as efficacy for the intended ages; inclusion of data that would be informative for labeling, such as failure rate and efficacy and safety data for 1 to 5 year old population.

Abbreviations: BLA, biologics license application; IND, investigational new drug; iPSP, initial pediatric study plan; NIAID, National Institute of Allergy and Infectious Diseases; OFC, oral food challenge; OLE, open-label extension; PIND, pre-investigational new drug; SEE, substantial evidence of effectiveness

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

Two sites were selected to be inspected based on the high degree of enrollment: Dr. Robert Wood at Johns Hopkins (30 subjects) and Dr. Edwin Kim at University of North Carolina (23 subjects). Based on the inspection results, the Office of Scientific Investigations team concluded that “the study appears to have been conducted adequately, and the data generated by the

clinical investigator sites appear acceptable in support of this BLA." For further details, see the Clinical Inspection Summary submitted to the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) on December 14, 2023, by Suyoung Tina Chang, M.D., Good Clinical Practice Assessment Branch, Division of Clinical Compliance Evaluation, Office of Scientific Investigations.

4.2. Product Quality

Omalizumab

The proposed dosages for the new indication are within the currently approved dosage ranges for the previously approved indications. There are no chemistry, manufacturing, and controls (CMC) changes proposed in this supplement. The batch information for the clinical materials used in the clinical trial was provided and the tested quality attributes were within the respective historical ranges and comparable with the process validation batch data.

The CMC product quality assessment team in the Office of Biotechnology Products "has no objection to the approval of this supplement." For further details, see the Memorandum of Assessment completed by You Zhuo, Ph.D., Division of Biotechnology Review and Research II/Office of Biotechnology Products/Office of Pharmaceutical Quality/CDER.

Quality of Food Product Used for Oral Food Challenges

The primary and key secondary endpoints in the OUtMATCH trial are based on double-blind, placebo-controlled, oral food challenges (DBPCFCs). The CMC information for the food products used in the oral food challenges is regulated under investigational new drug (IND) 14831 through the Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccine Research and Review, Center for Biologics Evaluation and Research (CBER).

On November 30, 2022, NIAID, the holder of IND 140847 under which the OUtMATCH trial was performed, communicated with the Division that they discovered visual mold in several of their investigational food products used for oral food challenges and oral immunotherapy (Stage 2 of their trial which are marketing application). Mold was first noted in June 2022; at that time, visible mold was thought to be an isolated event. However, by November 2022, after several reports and upon inspection, visible mold was detected in additional food product kits. All kits identified with visible mold were over one year old.

The trial was paused until a proper mitigation strategy could be established. A remediation plan was put in place for quality control and to mitigate future mold growth:

(1) Expiration dates for all product kits were shortened to six months from the manufacturing date or parent material's expiration date, if sooner.

(2) Storage of the food allergen products was changed from souffle cups with lids to clear polystyrene jars with heat pressure seal and screw tops due to moisture concerns.

(3) Cold-chain transportation was instituted to transport the food allergen product kits. Previously the shipments were performed at room temperature, with storage at 2 to 8 degrees Celsius at study sites.

(4) Testing of bulk parent allergen material every 6 months was instituted at the Sean N. Parker Center at Stanford University

FDA had communicated via both videoconference and multiple IRs that the Agency expects updates and communications regarding the refinements to and results of mitigation strategies. Given the investigational food product is used to determine primary and key secondary endpoints, the Applicant performed multiple analyses to determine if the visible mold could have any impact on the allergenic potency of the food product and potentially the outcome of the trial. Results presented by the Applicant demonstrated that the mold did not impact efficacy.

The Division of Bacterial, Parasitic, and Allergenic Products in CBER was consulted and reviewed the quality summary of the investigational food product used in the OUtMATCH trial and a speciation report. Based on their review, they concluded: "The documentation provided indicate that the food challenge kits impacted by molds did not affect the outcome of the study. The potency of the foods was not affected by the mold. Additionally, the efficacy of XOLAIR in all subjects and in only subjects exposed to food challenge material younger than 6 months were identical. We conclude that the mold contamination does not affect interpretation of data provided by the sponsor to demonstrate efficacy of XOLAIR to prevent allergic reactions in food allergic subjects after accidental exposure to food as assessed by OFC [oral food challenge]." See the consult review from Alexander Zhovmer, PhD for more information.

4.3. Clinical Microbiology

Microbiology review was not conducted as there are no changes to the formulation and no new information was provided in this supplement.

4.4. Devices and Companion Diagnostic Issues

The CDRH review was not conducted as there are no changes to the injection devices (prefilled syringe, autoinjector) and no new information was provided in this supplement.

5 Nonclinical Pharmacology/Toxicology

Nonclinical review was not performed as there were no new nonclinical information for this supplement.

6 Clinical Pharmacology

6.1. Executive Summary

Omalizumab is a recombinant DNA-derived humanized IgG1 kappa monoclonal antibody that selectively binds to human IgE. Omalizumab inhibits binding of IgE to FcεRI located on the surface of mast cells, basophils, and dendritic cells. Currently, omalizumab is indicated for the treatment of moderate to severe persistent asthma in patients 6 years of age and older, CRSwNP in adults, and CSU in adults and adolescents 12 years of age and older. In this BLA supplement, the Applicant seeks approval for a new indication: reduction of allergic reactions, including anaphylaxis, that may occur with accidental exposure to one or more foods in adult and pediatric patients aged 1 year and older with food allergy. To be used in conjunction with food avoidance. The approved and proposed indications and dosage regimens are summarized in Table 2.

Table 2. Approved and Proposed Indications and Dosage Regimens

Indication	Population	Dosage Regimen
Approved		
Moderate to severe persistent asthma	Adult and pediatric patients 6 years of age and older	• 75 to 375 mg SC every 2 weeks (Q2W) or every 4 weeks (Q4W). • Dosage dependent on body weight (kg) and predose serum total IgE level (IU/mL)
CRSwNP	Adults 18 years of age and older	• 75 to 600 mg SC Q2W or Q4W • Dosage dependent on body weight (kg) and predose serum total IgE level (IU/mL)
CSU	Adults and adolescents 12 years of age and older	• 150 or 300 mg SC Q4W • Dosing not dependent on body weight or predose serum total IgE level
Proposed		
IgE-mediated food allergy	Adults and pediatric patients 1 year of age and older	• 75 to 600 mg SC Q2W or Q4W • Dosage dependent on body weight (kg) and predose serum total IgE level (IU/mL)

Source: Approved and proposed labeling for XOLAIR [omalizumab]
Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; SC, subcutaneous

The proposed dosing for IgE-mediated food allergy is similar to that approved for asthma and CRSwNP in that a dosing table is used to determine the dosage based on the patient's body weight (kg) and predose serum total IgE level (IU/mL). A new dosing table is proposed for IgE-mediated food allergy that expands IgE categories to accommodate patients with predose total IgE levels up to 1850 IU/mL or a body weight down to 10 kg. The algorithm used to generate

the dosing table targets delivery of 0.016 mg/kg of omalizumab for every IU/mL of total IgE in a 4-week interval and does not exceed a 20 mg/kg dose within a single administration. The proposed dosing table was used in pivotal trial, OUtMATCH, and enabled dosing in patients down to 1 year of age.

This supplement was supported by data from one multicenter, randomized, double-blind, placebo-controlled safety and efficacy trial in pediatric and adult subjects who are allergic to peanut and at least two other foods, including milk, egg, wheat, cashew, hazelnut, or walnut (OUtMATCH). OUtMATCH was designed to include three stages, but only data from an interim analysis of Stage 1 and an open-label extension (OLE) were provided in the present submission. Stage 1 enrolled 168 subjects, including 165 pediatric subjects with median (range) age of 7 (1, 17) years. A population PK report was also submitted to compare the PK of omalizumab in subjects with food allergy and in subjects with asthma.

A trend in Week 16 trough concentrations by age group was observed, such that younger subjects had greater trough concentrations, likely due to the impact of body weight on omalizumab PK. Although a trend was observed, the differences were overall ≤1.79-fold across age groups, irrespective of dosing frequency (i.e., every 2 weeks [Q2W] or every 4 weeks [Q4W]). Among subjects randomized to omalizumab treatment, total IgE increased approximately 3.1-fold from the time of Screening DBPCFC to Week 16. Free IgE level for most subjects could not be determined at Screening as most of the values were above the upper limit of quantitation (ULOQ) (62.5 IU/mL). At Week 16, the overall mean free IgE was about 10 IU/mL and about 97% of subjects had free IgE values below 20 IU/mL. Immunogenicity was not assessed due to drug interference.

Based on limited data, adult subjects (N=3, with 2 treated with omalizumab) had PK and pharmacodynamic (PD) data consistent with observations in pediatric subjects aged 12 to <18 years. Based on population PK analyses, the PK of omalizumab in patients with food allergy is generally consistent with that in patients with asthma, supporting PK similarity between pediatric and adult subjects. It was determined that aside from body weight and predose total IgE, no dose adjustments are necessary for (b) (4), race, ethnicity, or gender.

Recommendation

From a clinical pharmacology perspective, the data provided in this BLA supplement support approval of omalizumab for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods in adult and pediatric patients aged 1 year and older with IgE-mediated food allergy.

Postmarketing Requirement/Postmarketing Commitment

None

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

In general, the omalizumab dosage increased with increasing age group (<6, 6 to <12, or 12 to <18) due to increasing body weight. Across age groups, a similar proportion of subjects received omalizumab Q2W or Q4W.

Week 16 trough concentrations were greater in younger age groups. Among subjects that received omalizumab Q2W, Week 16 trough concentrations in subjects aged <6 years were 1.22- and 1.75-fold greater than that in subjects aged 6 to <12 years and 12 to <18 years, respectively. Among subjects that received omalizumab Q4W, Week 16 trough concentrations in subjects aged <6 years were 1.11- and 1.79-fold greater than that in subjects aged 6 to <12 years and 12 to <18 years, respectively. For subjects aged 6 to <12 years, Week 16 trough concentrations were 1.43- and 1.61-fold greater than that in subjects aged 12 to <18 years in the Q2W and Q4W groups, respectively. Overall, there was a <2-fold difference in omalizumab mean trough concentrations by age group at Week 16.

Serum total IgE (omalizumab-bound and non-omalizumab-bound IgE) and free IgE (non-omalizumab-bound IgE) were measured at Screening and at Week 16, at the time of the Stage 1 DBPCFC. Total IgE was measured at an initial Screening visit and at the time of Screening DBPCFC. Note that total IgE and free IgE were measured using different assays. In addition, free IgE level was measurable only from a few subjects (N=2) at Screening due to the limitation of bioanalytical assay (i.e., most subjects had values above the ULOQ of 62.5 IU/mL or ~150 ng/mL).

From the Screening DBPCFC to Week 16, mean serum total IgE concentration increased about 3.1-fold, with similar magnitudes of increase observed across all age groups. This behavior is expected due to the formation of omalizumab-IgE complexes, which have a longer half-life compared with free IgE. At Week 16, the mean (SD) free IgE among subjects receiving omalizumab was 10.0 (4.9) IU/mL (equivalent to 24.2 [11.8] ng/mL). Across age groups and dosing regimens, about 97% of subjects had Week 16 free IgE values below 20 IU/mL (~50 ng/mL).

In the OUtMATCH trial, PK and PD data were also collected in two adult subjects. Week 16 trough concentrations in these two adults were within the range of those observed in pediatric subjects aged 12 to <18 years of age. A similar trend was observed for total IgE at Screening and Week 16, and free IgE at Week 16 in these two adults.

Population PK analyses indicated that the PK of omalizumab in patients with food allergy is generally consistent with that in patients with asthma. This supports PK similarity between pediatric and adult subjects. Covariate analyses indicate that aside from body weight and predose total IgE, no dose adjustments are necessary for (b) (4)

Immunogenicity was not measured in OUtMATCH due to drug interference (i.e., omalizumab concentrations during the treatment period would exceed levels allowing for ADA detection).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed omalizumab dosing table for patients with food allergy is shown in Table 3. The dosage is determined based on the patient's body weight and predose serum total IgE. The algorithm used to generate the dosing table is the same to that used in asthma and CRSwNP programs, which targets delivery of 0.016 mg/kg of omalizumab for every IU/mL of total IgE in a 4-week interval and does not exceed a 20 mg/kg dose within a single administration. Therefore, the proposed dosing table for patients with food allergy is similar to that approved for patients with asthma and for patients with CRSwNP. Compared to the approved dosing tables, the dosing table proposed for food allergy expands the weight categories down to 10 to 12 kg, and the IgE categories up to >1500 to 1850 IU/mL. Across all body weight groups, the dosing does not exceed 20 mg/kg.

Table 3. Proposed Omalizumab Dosing Table for Patients With Food Allergy

Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight (kg)												
		≥10-12	>12-15	>15-20	>20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90 - 125	>125 - 150
		Dose (mg)												
≥30 - 100	Every 4 Weeks	75	75	75	75	75	75	150	150	150	150	150	300	300
>100 - 200		75	75	75	150	150	150	300	300	300	300	300	450	600
>200 - 300		75	75	150	150	150	225	300	300	450	450	450	600	375
>300 - 400		150	150	150	225	225	300	450	450	450	600	600	450	525
>400 - 500		150	150	225	225	300	450	450	600	600	375	375	525	600
>500 - 600		150	150	225	300	300	450	600	600	375	450	450	600	
>600 - 700		150	150	225	300	225	450	600	375	450	450	525		
>700 - 800	Every 2 Weeks	150	150	150	225	225	300	375	450	450	525	600		
>800 - 900		150	150	150	225	225	300	375	450	525	600			
>900 - 1000		150	150	225	225	300	375	450	525	600				
>1000 - 1100		150	150	225	225	300	375	450	600					
>1100 - 1200		150	150	225	300	300	450	525	600					
>1200 - 1300		150	225	225	300	375	450	525						
>1300 - 1500		150	225	300	300	375	525	600						
>1500 - 1850			225	300	375	450	600							

Insufficient data to Recommend a Dose

*Dosing frequency:

Subcutaneous doses to be administered every 4 weeks
Subcutaneous doses to be administered every 2 weeks

Source: Table 4, Proposed labeling for XOLAIR [omalizumab]
Abbreviations: IgE, immunoglobulin E

The dosing table shown in Table 3 is the same as that used to determine the omalizumab dosage for subjects enrolled in OUtMATCH. Expansion of weight categories down to 10 kg permitted dosing of subjects as young as 1 year of age.

Therapeutic Individualization

As described, the omalizumab dosage selected from the proposed dosing table considers the patient's body weight and predose serum total IgE. Covariate analyses demonstrate that no dose adjustments are necessary for age (1 year of age and older), race, ethnicity, or gender.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant submitted data from one clinical trial, OUtMATCH, to support the use of omalizumab for the mitigation of allergic reactions in patients aged 1 year and older with food allergy. OUtMATCH is an ongoing phase 3, multicenter, randomized, double-blind, placebo-controlled trial conducted in subjects aged 1 to <56 years who are allergic to peanut and at least two other foods, including milk, egg, wheat, cashew, hazelnut, or walnut. OUtMATCH is designed to include three stages. In the present submission, data are available from an interim analysis of Stage 1 and an OLE.

In Stage 1, subjects were randomized 2:1 to treatment with omalizumab or placebo. Dosages were determined based on body weight and predose serum total IgE, as listed in Table 3. Treatments were given for 16 to 20 weeks. After 16 weeks of treatment, subjects completed a set of DBPCFCs to placebo, peanut, and two other subject-specific foods. The first 60 subjects who completed Stage 1 moved on to the Stage 1 OLE, where subjects received treatment with open-label omalizumab for another 24 to 28 weeks.

A total of 168 subjects were enrolled in Stage 1, including 165 pediatric subjects with median (range) age of 7 (1, 17) years, and 3 adult subjects. Of the 165 pediatric subjects enrolled in Stage 1, 61 (37.0%) were <6 years of age, 62 (37.6%) were 6 to <12 years of age, and 42 (25.5%) were 12 to <18 years of age. Among pediatric subjects randomized to receive omalizumab (n=110), the median (range) body weight was 25.2 (10.1, 85.5) kg. A total of 60 subjects from Stage 1 (59 pediatric, 1 adult) continued on to the Stage 1 OLE, including 39 subjects who received omalizumab in Stage 1, and 21 subjects who received placebo in Stage 1.

Pharmacokinetics

In OUtMATCH, samples for PK assessment were collected in Stage 1 at Week 16 predose, and during the Stage 1 OLE at Week 24 predose. Omalizumab dosage by age group is shown in Table 4. In general, within each dosing frequency (i.e., Q2W or Q4W), the omalizumab dosage increased with increasing age group such that subjects aged 12 to <18 years received the highest dosages. Although dosing is dependent on both body weight and predose serum total IgE, this trend of the dosage is likely driven by increasing body weight in older age groups.

Table 4. Omalizumab Dosage by Age Group

Dosage	Age < 6 (N = 61) N (%)	Age 6 to < 12 (N = 62) N (%)	Age 12 to < 18 (N = 42) N (%)
150 mg Q2W	19 (31%)	1 (1.6%)	0 (0.0%)
225 mg Q2W	9 (15%)	10 (16%)	0 (0.0%)
300 mg Q2W	5 (8.2%)	11 (18%)	0 (0.0%)
375 mg Q2W	2 (3.3%)	5 (8.1%)	4 (9.5%)
450 mg Q2W	0 (0.0%)	3 (4.8%)	16 (38%)
525 mg Q2W	0 (0.0%)	1 (1.6%)	2 (4.8%)
600 mg Q2W	0 (0.0%)	3 (4.8%)	5 (12%)
75 mg Q4W	6 (9.8%)	0 (0.0%)	0 (0.0%)
150 mg Q4W	12 (20%)	1 (1.6%)	2 (4.8%)
225 mg Q4W	6 (9.8%)	8 (13%)	1 (2.4%)
300 mg Q4W	2 (3.3%)	13 (21%)	3 (7.1%)
450 mg Q4W	0 (0.0%)	5 (8.1%)	6 (14%)
600 mg Q4W	0 (0.0%)	1 (1.6%)	3 (7.1%)

Source: Reviewer-generated table using data from adsl dataset
The above table includes all pediatric subjects enrolled in OUtMATCH, including those subjects who were randomized to placebo. Numbers highlighted in red represent the largest proportion within each dosing frequency (i.e., Q2W or Q4W).
Abbreviations: Q2W, every 2 weeks; Q4W, every 4 weeks

Week 16 trough concentrations overall and by age group and dosing frequency are shown in Table 5. Boxplots of trough concentrations by age group are shown in Figure 1. Across age groups, similar proportions of subjects received omalizumab Q2W or Q4W.

- Age <6 years: 59% and 41%, respectively
- Age 6 to <12 years: 63% and 37%, respectively
- Age 12 to <18 years: 56% and 44%, respectively.

Data indicate that trough concentrations at Week 16 decreased in older age groups, both overall and within each dosing frequency group. Among subjects who received omalizumab Q2W, subjects aged <6 years had trough concentrations at Week 16 that were 1.22- and 1.75-fold greater than those in subjects aged 6 to <12 years and 12 to <18 years, respectively. Among subjects who received omalizumab Q4W, subjects aged <6 years had trough concentrations at Week 16 that were 1.11- and 1.79-fold greater than those in subjects aged 6 to <12 years and 12 to <18 years, respectively. Relative to subjects aged 12 to <18 years, trough concentrations in subjects aged 6 to <12 years were 1.43- and 1.61-fold greater in the Q2W and Q4W groups, respectively. For the two adult subjects who had PK samples collected at Week 16, omalizumab trough concentrations were within the range of concentrations observed among subjects aged 12 to <18 years.

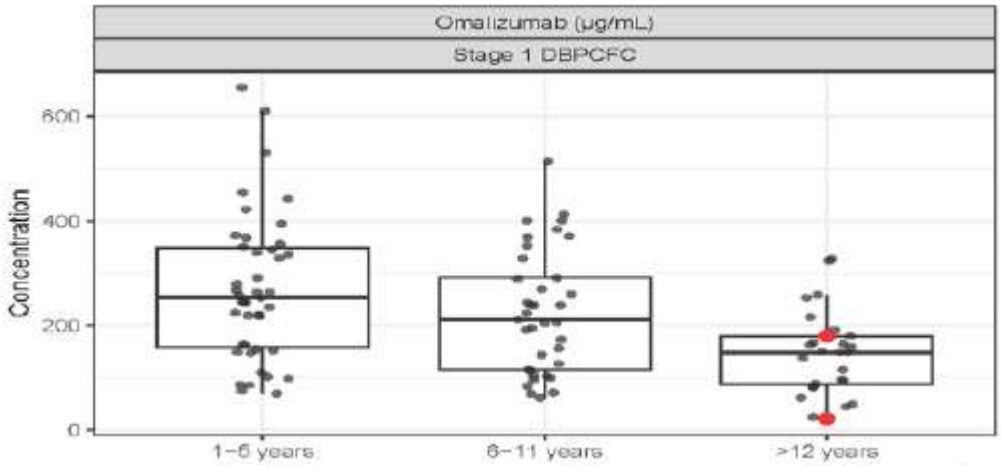
The trend in omalizumab trough concentrations by age group is likely due to the impact of body weight on omalizumab PK. Despite the observed trend, differences in exposure were ≤1.79-fold across all age groups.

Table 5. Omalizumab Trough Concentrations at Week 16 (Stage 1) by Age Group and Dosing Frequency

	Age Group			
Dosing Frequency Statistics	All (N=110)	<6 years (N=41)	6 to <12 years (N=43)	12 to <18 Years (N=26)
All Omalizumab dosing regimens				
n	105	39	41	25
Mean	225345.7	268238.5	231041.5	149092.0
SD	127403.99	144560.36	113899.84	80782.05
Median	216000.0	253000.0	224000.0	148000.0
Minimum	25200	69700	61600	25200
Maximum	655000	655000	514000	327000
Dosing every 2 weeks				
n	63	23	26	14
Mean	292317.5	352434.8	288000.0	201571.4
SD	114454.22	123623.26	94360.58	64731.06
Median	264000.0	339000.0	265000.0	173500.0
Minimum	126000	163000	126000	138000
Maximum	655000	655000	514000	327000
Dosing every 4 weeks				
n	42	16	15	11
Mean	124888.1	147206.3	132313.3	82300.0
SD	64296.91	63489.96	68540.48	38100.10
Median	102500.0	148000.0	104000.0	82500.0
Minimum	25200	69700	61600	25200
Maximum	291000	264000	291000	165000

Source: Table 2, Summary of Clinical Pharmacology
Data shown in units of ng/mL. This table includes all subjects in the pediatric safety set (N=165), which included all randomized subjects aged <18 years who received at least one dose of omalizumab or placebo in Stage 1.
Abbreviations: SD, standard deviation

Figure 1. Boxplots of Omalizumab Week 16 Trough Concentrations (mcg/mL) by Age Group



Source: Figure 1, Summary of Clinical Pharmacology
Black circles represent pediatric subjects, while red circles represent adult subjects.
Abbreviations: DBPCFC, double-blind, placebo-controlled food challenge

Similar trends in PK were observed at Week 24 of the Stage 1 OLE (Table 6). Among subjects who received omalizumab Q2W, subjects aged <6 years had trough concentrations at Week 24 that were 1.40- and 2.05-fold greater than those in subjects aged 6 to <12 years and 12 to <18 years, respectively. Among subjects who received omalizumab Q4W, subjects aged <6 years had trough concentrations at Week 24 that were 1.87- and 1.92-fold greater than those in subjects aged 6 to <12 years and 12 to <18 years, respectively. Relative to subjects aged 12 to <18 years, trough concentrations in subjects aged 6 to <12 years were 1.46- and 1.03-fold greater in the Q2W and Q4W groups, respectively.

Table 6. Omalizumab Trough Concentrations at Week 24 (Stage 1 OLE) by Age Group and Dosing Frequency

Dosing Frequency Statistics	Age Group All (N=38)	< 6 Years (N=12)	6 to < 12 years (N=15)	12 to < 18 years (N=11)
All Omalizumab dosing regimens				
n	37	12	14	11
Mean	210151.4	288750.0	192085.7	147400.0
SD	110320.33	120279.32	94962.23	63050.44
Median	193000.0	266000.0	203500.0	120000.0
Minimum	64000	140000	64000	68300
Maximum	493000	493000	368000	247000
Dosing every 2 weeks				
n	25	8	9	8
Mean	251356.0	342625.0	244888.9	167362.5
SD	107409.04	109524.87	72932.24	61993.27
Median	242000.0	323000.0	242000.0	153500.0
Minimum	95900	193000	105000	95900
Maximum	493000	493000	368000	247000
Dosing every 4 weeks				
n	12	4	5	3
Mean	124308.3	181000.0	97040.0	94166.7
SD	52558.22	42848.57	33229.63	24104.43
Median	119000.0	173000.0	79200.0	98200.0
Minimum	64000	140000	64000	68300
Maximum	238000	238000	142000	116000

Source: Table 14.2.5.1.2, CSR for OUtMATCH
Data shown in units of ng/mL.
Abbreviations: OLE, open-label extension; SD, standard deviation

Using population PK analysis, food allergy was identified as a significant covariate impacting omalizumab clearance. Patients with food allergy are estimated to have approximately 22% lower omalizumab clearance relative to nonfood allergy (i.e., asthma) patients. However, in general, omalizumab PK in patients with food allergy is consistent with the PK observed in nonfood allergy patients. Covariate analysis indicates that no dosage adjustments are needed based on (b) (4), gender, race, or ethnicity. For additional details on population PK analysis, refer to the Pharmacometrics Review in Section 15.3.3.

Omalizumab PK was previously evaluated in pediatric subjects with asthma aged 6 to <12 years. Steady-state trough concentrations by total serum IgE at baseline are shown in Table 7. Median omalizumab trough concentrations increase in subjects with higher total serum IgE at baseline due to increasing dose. Steady state trough omalizumab concentrations in pediatric subjects with asthma are numerically lower than those observed in pediatric subjects with food allergy (Table 5). Median trough concentrations in asthma subjects with baseline IgE of 30 to 500 IU/mL (who would likely receive doses Q4W) were 24 to 59% lower relative to food allergy subjects receiving omalizumab Q4W (median trough concentration =103 mcg/mL). Meanwhile, median trough concentrations in asthma subjects with baseline IgE greater than 700 IU/mL (who would likely receive doses Q2W) were about 30% lower relative to food allergy subjects receiving omalizumab Q2W (median trough concentration =264 mcg/mL).

The moderately higher C_{trough} value (~32% to 146%) in pediatric subjects 6 to <12 years of age with food allergy relative to pediatric subjects with asthma 6 to <12 years of age may be explained by a relatively higher omalizumab dose in subjects with food allergy compared to subjects with asthma due to higher baseline IgE level in subjects with food allergy (Table 7 and

Figure 2). However, since the dosing algorithm used in the dosing table studied in OUtMATCH is consistent with the approved dosing table in patients with asthma, the omalizumab exposure in pediatric patients with food allergy is expected to be close to pediatric patients with asthma with high baseline IgE level who are on the same high dose and dosing regimen. For further discussion of safety in pediatric subjects <6 years of age and pediatric subjects with food allergy who were dosed using the newly expanded sections of the dosing table, refer to Section 8. In addition, population PK analysis estimated slightly lower clearance (~22%) in pediatric subjects with food allergy compared to nonfood allergy subjects. Lower clearance also contributes to the higher exposure in pediatric subjects with food allergy when compared to nonfood allergy subjects. The root cause of the difference in clearance across different indications is unclear.

Table 7. Steady-State Omalizumab Trough Concentrations and IgE Concentrations in Pediatric (Age <12 Years) and Adult Subjects With Asthma

IgE at baseline	Statistic	Omalizumab (µg/mL)		Total IgE (ng/mL)		Free IgE (ng/mL)	
		Pediatric	Adult	Pediatric	Adult	Pediatric	Adult
30-200 IU/mL	№ patients	191	379	191	374	190	380
	5th	15.5	11.3	325	316	3.97	4
	Median	41.6	30.3	1111	963	12.3	12.8
	95th	85.5	76.1	2628	2166	35.0	34.4
	99th	122	96.2	3438	2872	50.3	54.2
200-500 IU/mL	№ patients	205	220	201	217	203	220
	5th	32.3	34.8	1095	1102	6.68	7.08
	Median	77.4	73.0	2521	2498	14.3	14.6
	95th	167	163	4810	4263	37	31.52
	99th	220	203	6587	5834	62.2	46.6
500-700 IU/mL	№ patients	65	40	65	38	65	41
	5th	57.0	47.7	1832	1115	7.40	8.24
	Median	135	117	3883	3446	16	15.4
	95th	218	186	6844	5496	39.8	32.8
	99th	307	205	8820	6000	51.4	57.6
More than 700 IU/mL	№ patients	118	8	119	8	119	8
	5th	96.1	84.7	2380	2886	7.61	10.3
	Median	185	163	4060	5965	14.0	21.5
	95th	318	305	7423	8087	26.8	30.9
	99th	374	305	9383	8087	33.5	30.9

Source: Table 3-1, Summary of Clinical Pharmacology, BLA 103976/S-5149 submitted December 5, 2008
Abbreviations: IgE, immunoglobulin E

Pharmacodynamics

Pharmacodynamics was assessed based on measurements of free serum IgE (non-omalizumab-bound IgE) and total serum IgE (omalizumab-bound and non-omalizumab-bound IgE). Samples for assessment of free IgE and total IgE were collected at the first Screening DBPCFC visit, Week 16 (Stage 1), and during the Stage 1 OLE at Week 24. Total IgE samples to determine the omalizumab dosage were also measured at an initial Screening visit separate from the Screening DBPCFC.

Separate assays were used to measure free IgE and total IgE. Free IgE was measured using a fluorometric enzyme-linked immunosorbent assay (ELISA). This assay has a narrow quantitation range ranging from 0.83 to 62.5 IU/mL. In addition, sample dilution used in this assay is limited to 1:2 to avoid disruption of omalizumab-IgE complexes. Total IgE was measured using a commercial system (ImmunoCAP, ThermoFisher/Phadia). The quantitation range for the assay is between 2.00 and 5000 IU/mL.

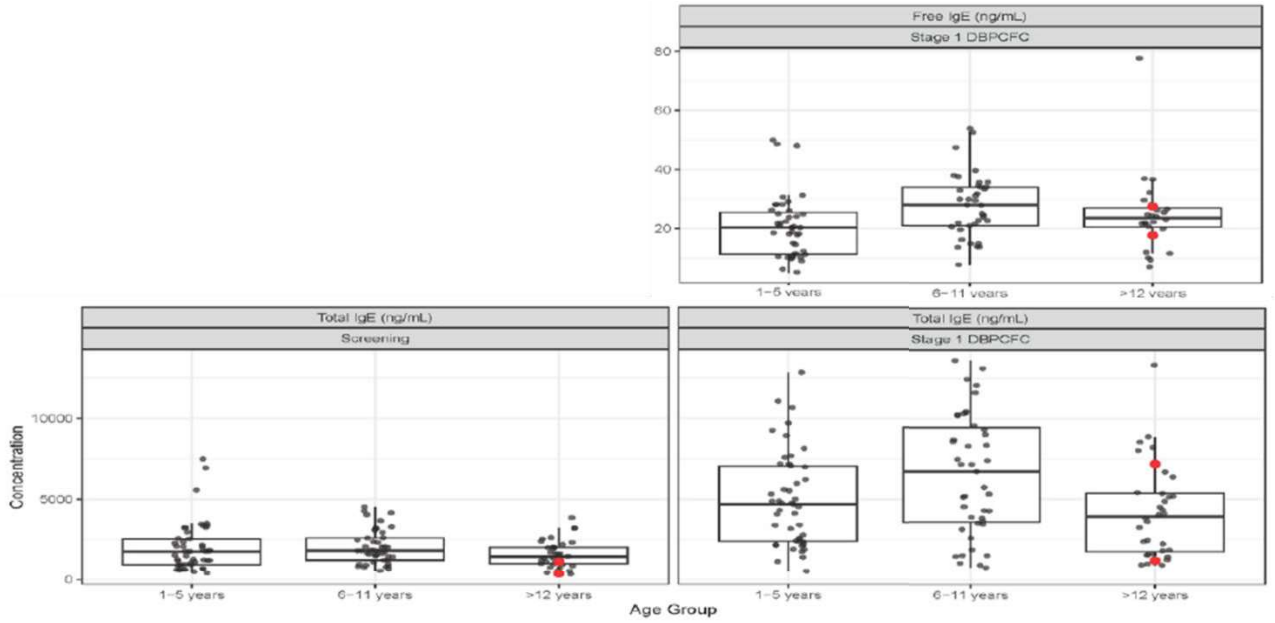
Boxplots of free IgE at Week 16, and total IgE at Screening and at Week 16 are shown in Figure 2. Although free IgE was also measured at Screening, values were not available as most subjects had measurements above the ULOQ (62.5 IU/mL or ~150 ng/mL). Although conceptually all the IgE molecules at baseline are not omalizumab-bound (free and total IgE are defined based on whether IgE is bound to omalizumab), because free IgE and total IgE are measured using separate assays, a direct comparison of total IgE at Screening with free IgE at Week 16 to obtain a nominal reduction of "free" IgE level is not appropriate.

At the time of the Screening DBPCFC, mean (SD) total IgE in the pediatric safety set among subjects randomized to omalizumab treatment was 810 (526) IU/mL. Note that total IgE values measured at the time of the screening DBPCFC were not used to determine omalizumab dosage. At Week 16, at the time of the Stage 1 DBPCFC, mean (SD) total IgE in subjects on omalizumab treatment increased approximately 3.1-fold to 2494 (1297) IU/mL. The increase in total IgE is expected due to the formation of omalizumab-IgE complexes, which have a longer half-life compared to free IgE. In contrast, no meaningful change in mean total IgE was observed among subjects in placebo group (Mean [SD] at Screening DBPCFC =831 [552] IU/mL; mean [SD] at Week 16=864 [529] IU/mL). No trend in total IgE by age group in placebo group was observed at Screening or at Week 16.

Free IgE values from most subjects on omalizumab treatment were measurable at Week 16. Free IgE values were below 20 IU/mL (50 ng/mL) in approximately 97% of subjects following omalizumab treatment. The overall (i.e., across all subjects and dosages) mean free IgE concentration at Week 16 was about 10 IU/mL (24.3 ng/mL). No trend was observed in free IgE in omalizumab group by age group.

For the two adult subjects who had PD samples collected at Screening and at Week 16, total IgE (Screening and Week 16) and free IgE (Week 16) were within the range of concentrations observed among subjects aged 12 to <18 years.

Figure 2. Boxplots of Free IgE (Week 16) (ng/mL) and Total IgE (Screening and Week 16) (ng/mL) by Age Group



Source: Figure 1, Summary of Clinical Pharmacology
Black circles represent pediatric subjects, while red circles represent adult subjects.
Abbreviations: IgE, immunoglobulin E

Based on an exploratory IgE-response analysis, steady-state trough free IgE concentrations were generally comparable between responder and nonresponder subjects in omalizumab group. No correlation was observed between Week 16 free IgE and experiencing a dose-limiting toxicity in response to peanut, cashew nut, milk and egg proteins, respectively. This is likely because free IgE was greatly suppressed following omalizumab treatment in most of the subjects. For additional details, refer to the Pharmacometrics Review in Section 15.3.3.

Serum total IgE concentrations at steady state are generally higher in pediatric patients with food allergy relative to pediatric asthma patients. In OUtMATCH, the median (range) serum total IgE at steady state among subjects aged 6 to 11 years was 7134 (1846, 13610) ng/mL (equivalent to 2958 IU/mL). According to the values in Table 7, the median (Q5, Q95) serum total IgE at steady state among pediatric asthma subjects with baseline IgE >700 IU/mL was 4060 (2380, 7423) ng/mL.

Immunogenicity

Immunogenicity was not measured in OUtMATCH. The Applicant's rationale is that omalizumab concentration levels during the treatment period exceeded levels that would allow for ADA detection due to drug interference. Per the current approved labeling for XOLAIR, ADA incidence is <0.2% across all indications.

It is recommended to update the proposed labeling to indicate that immunogenicity samples have not been collected along with the Applicant's justification.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The submission includes data from one clinical trial, OUtMATCH, to support the use of omalizumab for the mitigation of Type I allergic reactions in adult and pediatric subjects aged 1 year and older with food allergy. OUtMATCH was a multicenter, randomized, double-blind, placebo-controlled trial that primarily enrolled pediatric subjects aged 1 year and older (N=165). Thus, effectiveness in pediatric subjects was supported by evidence from an adequate and well-controlled trial. Refer to Section 7 for discussion of efficacy.

Pharmacodynamic data based on measurement of free IgE provides supportive evidence of effectiveness. Free IgE measurements were above the ULOQ (62.5 IU/mL) in all but two subjects at the time of the Screening DBPCFC. At Week 16, the mean free IgE among subjects receiving omalizumab was approximately 10 IU/mL. Thus, consistent with its mechanism of action, omalizumab treatment reduced free IgE levels. However, no correlation was observed between free IgE at Week 16 and achieving primary or secondary efficacy endpoints, likely as free IgE was suppressed with omalizumab treatment.

At the IND stage, FDA indicated that the adequacy of efficacy data in adults given the small population enrolled in OUtMATCH would be an area of focus for review and that extrapolation of efficacy from the studied population may be reasonable (refer to Meeting Preliminary Comments in DARRTS under IND 5369 dated June 16, 2023, reference ID: 5192862). In OUtMATCH, three adult subjects were enrolled. Omalizumab trough concentrations at Week 16 in two adult subjects were within the range of trough concentrations observed in pediatric subjects aged 12 to <18 years (Figure 1). In addition, population PK analyses indicate that the PK of omalizumab in subjects with food allergy is generally consistent with that in subjects with asthma. Lastly, covariate analyses indicate that no dose adjustments are necessary for (b) (4) after the body weight adjustment (refer to the Pharmacometrics Review in Section 15.3.3). Taken together, the data support PK similarity between pediatric and adult subjects with food allergy. Therefore, extrapolation of the food allergy indication from children to adults is reasonable from a clinical pharmacology perspective.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed omalizumab dosage is derived from the dosing table shown in Table 3. The algorithm used to generate the dosing table targets delivery of 0.016 mg/kg of omalizumab for every IU/mL of total IgE in a 4-week interval and does not exceed a 20 mg/kg dose within a single administration. The algorithm is an extension of that used to generate the dosing table used to determine the omalizumab dosage in patients with asthma. Compared to the dosing

table approved for the treatment of asthma, the dosing table proposed for mitigation of allergic reactions due to food allergy expands the body weight and total IgE categories to accommodate patients with lower body weight (down to 10 kg), and patients with higher predose total IgE (up to 1850 IU/mL). Accommodating lower body weights permits dosing of patients as young as 1 year of age, as defined in the proposed indication. Meanwhile, in population PK analyses, baseline total IgE values were greater in patients with food allergy relative to nonfood allergy (i.e., asthma) patients. Thus, increasing the total IgE categories for the food allergy population is appropriate.

The proposed dosing table was used to determine the omalizumab dosage for subjects enrolled in OUtMATCH based on body weight and predose serum total IgE determined at an initial screening visit (i.e., not at the time of the screening DBPCFC). With dosing according to Table 3, Week 16 trough concentrations were greater in younger age groups relative to older subjects, with the greatest concentrations observed in subjects aged <6 years. Despite this, differences were ≤1.79-fold across all age groups. In addition, analysis of covariates using population PK indicates that no dosage adjustments are necessary based on age after the body weight adjustment (1 year and older). Thus, the proposed dosing table is appropriate for the general food allergy population.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The omalizumab dosage is derived from a dosing table that accounts for the patient's body weight and predose serum total IgE. The dosing table proposed for mitigation of IgE-mediated food allergy is similar to dosing tables approved for other indications, including asthma and CRSwNP. Per the current approved labeling for XOLAIR, no dose adjustments are necessary in patients with asthma based on age (6 to 76 years), race, ethnicity, or gender. In patients with CRSwNP, no dose adjustments are necessary for age (18 to 75 years) or gender. Race and ethnicity data are too limited in CRSwNP studies to inform dose adjustment.

Analysis of covariates using population PK in patients with food allergy indicates that no dose adjustments are necessary for age (1 year and older), race, ethnicity, or gender. Thus, an alternative dosing regimen or management strategy based on intrinsic patient factors is not required beyond those factors accommodated by the proposed dosing table (i.e., body weight and predose total IgE).

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Omalizumab is administered via subcutaneous injection. Therefore, there are no clinically relevant food-drug interactions.

Per the approved labeling for XOLAIR, no formal drug interaction studies have been performed. In patients with asthma and CRSwNP, the concomitant use of XOLAIR and allergen

immunotherapy has not been evaluated. In patients with CSU, the use of XOLAIR in combination with immunosuppressive therapies has not been studied. No new data was submitted in this sBLA regarding drug-drug interactions with omalizumab.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

A single adequate and well-controlled trial was conducted to support this supplement-Omalizumab as Monotherapy and as Adjunct Therapy to Multi-allergen OIT in Food Allergic Children and Adults (OUtMATCH). A summary of the OUtMATCH trial is provided in Table 8.

Table 8. Clinical Trial Submitted in Support of Efficacy and Safety Determination

Trial Identifier	Trial Population	Trial Design	Number Treated, Regimen	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Enrolled	Number of Centers and Countries
OUtMATCH	Pediatric and Adult subjects aged 1 to 56 years old with peanut Allergic to at least two of the six other foods (milk, egg, wheat, cashew, hazelnut, walnut).	Stage 1: 16-20 week R, DB, PC Stage 1 OLE: 24-28 weeks of open label	Number Treated: 165 -pediatric 3 adults Pediatric: 110 to omalizumab (q2w or q4w based on weight and baseline IgE level) 55 to placebo Adults: 2 to omalizumab 1 to placebo	Primary: Consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 Key Secondary: 1. Consumption of a single dose of ≥1000 mg of cashew protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1. 2. Consumption of a single dose of ≥1000 mg of milk protein without	210 pediatric subjects and up to 225 total subjects were planned. Interim analysis was conducted at 165 pediatric subjects with prespecified statistical criteria for primary and key secondary endpoints.	10 centers 1 country- USA

Trial Identifier	Trial Population	Trial Design	Number Treated, Regimen	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Enrolled	Number of Centers and Countries
				dose-limiting symptoms during the DBPCFC at the end of Stage 1. 3. Consumption of a single dose of ≥1000 mg of egg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1.		

Source: Clinical Review.
Abbreviations: DB, double-blind; DBPCFC, double-blind, placebo-controlled food challenge; IgE, immunoglobulin E; OLE, open-label extension; PC, placebo-controlled; q2w, every 2 weeks; q4w, every 4 weeks; R, randomized; USA, United States of America

7.2. Review Strategy

The review team for the safety and efficacy review consisted of one primary clinical reviewer and one primary statistical reviewer. The submitted sBLA included data from one randomized, double-blind, placebo-controlled trial (OUtMATCH), and included data from an open-label extension portion of the trial that is also reviewed to assess durability of omalizumab efficacy. Data were analyzed using JMP Clinical (version 8.0), OCS Analysis Studio (version 1.8.0), and R (version 4.3.1) programs. Section 8 includes the protocol description and review of efficacy and safety.

Data Sources

Data sources in this electronic submission and used for this review include clinical trial protocols, clinical study reports, subject narratives, and statistical analysis systems transport datasets in ADaM format.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. OUtMATCH: Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Children and Adults

The OUtMATCH trial is a single adequate and well controlled trial and is the primary basis of support for this supplement. The trial consisted of a double-blind, placebo-controlled portion (Stage 1) in which the primary efficacy endpoint was assessed at the end of 16 to 20 weeks. The first 60 subjects who completed this portion went on to an OLE portion (Stage 1 OLE) for 24 to 28 weeks. This review only analyzes data from OUtMATCH Stage 1 and Stage 1 OLE that studied omalizumab as monotherapy; subsequent stages included omalizumab treatment with oral immunotherapy and are not discussed.

8.1.2. Administrative Information

Trial Title

Omalizumab as Monotherapy and as Adjunct Therapy to Multi-allergen OIT in Food Allergic Children and Adults (OUtMATCH)

Trial Dates

July 26, 2019; December 17, 2022

Trial Sites

- Arkansas Children's Hospital
- Children's Hospital of Philadelphia
- Emory University School of Medicine
- Icahn School of Medicine at Mount Sinai
- Johns Hopkins Children's Center
- Massachusetts General Hospital
- National Jewish Health
- North Carolina Children's Hospital
- Stanford School of Medicine
- University of Texas Southwestern

Trial Report Date

June 30, 2023

8.1.3. Objective

The Applicant specified the following primary objective for the OUtMATCH trial in the interim clinical study report (CSR; dated June 30, 2023):

> *To compare the ability to consume foods without dose-limiting symptoms during a double-blind placebo-controlled food challenge (DBPCFC) after treatment with either omalizumab or placebo for omalizumab.*

8.1.4. Trial Design and Conduct

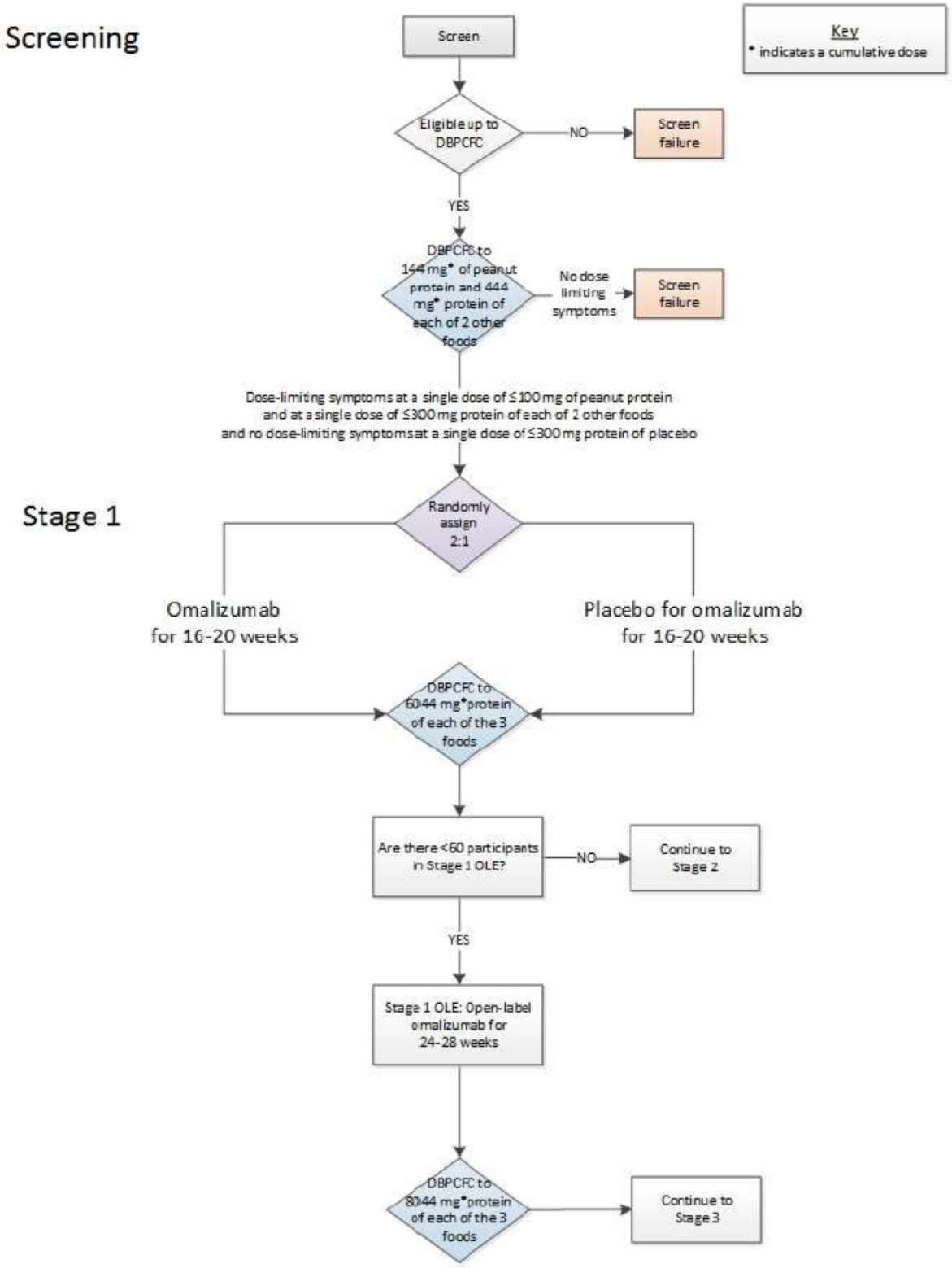
The OUtMATCH trial (Figure 3) is a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial in subjects 1 to less than 56 years of age who were allergic to peanut *and* at least two of six other foods (milk, egg, wheat, cashew, hazelnut, or walnut). While each subject may be allergic to more than two of the six foods listed above, the trial assessed treatment effect on only peanut and two of the other foods for each subject (a total of three subject-specific foods). The OUtMATCH trial has three stages, but interim data (see Interim Analysis below) from Stage 1 and Stage 1 OLE were submitted with this application and reviewed.

Stage 1 of OUtMATCH included subjects aged 1 to less than 56 years of age who experienced moderate-severe dose-limiting symptoms to a single dose of ≤100 mg of peanut protein, ≤300 mg of protein for each of the other two subject-specific foods, and no dose-limiting symptoms (no more than mild symptoms; see Efficacy Parameters below) to placebo (oat flour) at any single dose up to 300 mg during the screening DBPCFC. Subjects were randomized 2:1 for 16 to 20 weeks of treatment with omalizumab or placebo. After 16 to 20 weeks of treatment, each subject completed a DBPCFC consisting of placebo and each of their three subject-specific foods to a maximum cumulative dose of 6044 mg of each food protein. While Stage 1 enrolled a

total of 168 subjects (165 pediatric subjects and 3 adults), the Applicant's primary and key secondary analyses, in addition to several other analyses, focused on the pediatric population only (N=165). Of the 3 adults, 2 were randomized to omalizumab (1 did not complete food challenges) and 1 was randomized to placebo.

The first 60 subjects (59 pediatric subjects and 1 adult) who completed Stage 1 continued to Stage 1 OLE, while the rest went on to Stage 2 of OUtMATCH (an oral immunotherapy trial that is not discussed in this review). The goal of Stage 1 OLE was to assess the durability of omalizumab efficacy for the Applicant's proposed indication. In Stage 1 OLE, each subject, previously treated with either omalizumab or placebo, received 24 to 28 weeks of open-label omalizumab. After 24 to 28 weeks of treatment, each subject completed a DBPCFC consisting of placebo and each of their three subject-specific foods to a maximum cumulative dose of 8044 mg of each food protein. One adult subject completed Stage 1 OLE, but for consistency with Stage 1, the Applicant's Stage 1 OLE analyses focused on the pediatric population only (N=59).

Figure 3. OUtMATCH Trial Schematic



Source: Interim CSR (dated June 30, 2023), Figure 1, p. 20
Abbreviations: DBPCFC, double-blind, placebo-controlled food challenge; OLE, open-label extension

The food challenges performed at screening and at the end of the treatment and OLE periods consisted of each subject ingesting incremental amounts of food protein or placebo (Figure 4). When subjects exhibited moderate-severe dose-limiting symptoms (see Efficacy Parameters below), the food challenge was discontinued and the dose at the previous step was used to define the tolerated dose. The food product used for the food challenges was obtained from Stanford University under IND 14831.

Figure 4. Dosing Schedule for Food Challenges

Dose #	Food Protein/Placebo (mg protein)	Cumulative Dose (mg protein)
1	1	1
2	3	4
3	10	14
4	30	44
5	100	144
6	300	444
7	600	1044
8	1000	2044
9	2000	4044
10	2000	6044
11 [a]	2000	8044

DBPCFC = double-blind placebo-controlled food challenge; OLE = open-label extension
[a] Dose #11 will only be performed for the DBPCFC at the end of Stage 1 OLE.

Source: OUtMATCH protocol (dated December 23, 2023), Table 3.1.2, p. 41

Schedules of assessments for Screening/Stage 1 and Stage 1 OLE are displayed in Table 9 and Table 10, respectively.

Table 9. Schedule of Events for Screening and Stage 1

	Screen	Screening DBPCFC	Omalizumab Injection[1]		DBPCFC		UV[2]	Early Discontinuation[3]
Week During Stage 1	-15 weeks[4]		0	2-14	16	17-20		
Study Assessments								
ICF	X							
Demographics	X							
Vitals & Growth Parameters	X	X	X	X	X	X	X	X
Medical History	X	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
Physical Exam	X	X	X[6]	X[6]	X	X	X[7]	X[6]
Spirometry and PEF	X[8]	X[9]			X[9]	X[9]	X[10]	
SCORAD[11]		X[12]			X			
Diet & Allergy Questionnaire	X	X	X	X	X	X	X	X
GI Symptoms Questionnaire		X	X	X	X	X	X	X
Family History Questionnaire			X					
FAQLQ			X		X			
Review Diaries							X[13]	X[13]
Monthly Long-Term Follow-Up Questionnaires							X[22]	X[22]
Epinephrine Autoinjector Training Form and Food Allergy Action Plan	X							
Concomitant Medications	X	X	X	X	X	X	X	X
SPT	X[14]				X[15]			X[15, 16]
Blinded OFC		X			X	X		
AEs	X	X	X	X	X	X	X	X
Randomization			X					
Omalizumab or placebo for omalizumab administration			X	X	X	X	X	
Sample Collections								
Blood[17]								
Total IgE	X	X[16]			X			X[16]
Total Free IgE		X[16]			X			X[16]
Allergen-Specific IgE	X	X[16]			X			X[16]
Allergen-Specific IgG4 and IgA		X[16]			X			X[16]
Basophil Activation		X[16]			X			X[16]
PK Sampling		X[16]			X			
Samples for Mechanistic Studies		X[16]			X			
Provide Stool Collection Kit and Specimen Information Questionnaire		X[19]						
Collect Stool Collection Kit and Specimen Information Questionnaire		X[20]	X[20]					
Urine			X		X			
Saliva			X		X			
Safety Sample Collections								
Blood								
CBC With Differential	X	Every 3 months					X	X[16]
CMP	X	Every 3 months					X	X[16]
Urine								
Urinalysis	X	Every 3 months					X	X[16]
Urine Pregnancy Test[21]	X	Monthly					X	X

1. Omalizumab injection visits may occur every two or four weeks, determined by the body weight in kilograms and total serum IgE level at the Screening Visit.
2. Unscheduled Visits (UV) may occur at any time during the study.
3. Early Discontinuation Visits may occur at any time during the study.
4. Screening may take up to 15 weeks.
5. An interim medical history will be collected.
6. A limited physical exam will be performed.
7. A comprehensive or limited physical exam will be performed, as needed.
8. Spirometry will be performed for participants who are age seven years or older and are able to perform spirometry; peak flow will be performed for participants who are unable to perform spirometry.
9. Peak flow only.
10. Peak flow, as needed.
11. SCORAD will be performed for participants with AD. AD is determined by the PI or licensed clinician based on the current medical history and/or the physical exam.
12. SCORAD will only be assessed prior to initiating the blinded OFC at the first Screening DBPCFC Visit.
13. Only performed if participant is in Stage 2, Stage 3 Rescue OIT, or if participant has less than or equal to six months of Long-term follow-up with dietary consumption in Stage 3.
14. SPT to food and environmental allergens.
15. SPT to peanut and two other foods.
16. Only applicable if has not been completed within the eight weeks preceding the Early Discontinuation Visit.
17. If safety labs coincide with the bioassay/mechanistic blood collection, the priority, in terms of blood volume, is the safety labs.

18. Samples will be collected prior to initiating the blinded OFC at the first Screening DBPCFC Visit.
19. Provide stool collection kit and specimen information questionnaire at the first Screening DBPCFC Visit.
20. Collect stool collection kit and specimen information questionnaire at any time prior to the first injection visit in Stage 1 (or Stage 2 for replacement participants).
21. Only needed for female participants of child-bearing potential
22. Monthly questionnaires only completed if participant has more than six months of follow-up in Stage 3 with dietary consumption or avoidance .

Source: Interim CSR (dated June 30, 2023), Table 4, p. 37-38
Abbreviations: AE, adverse event; CBC, complete blood count; CMP, complete metabolic panel; DBPCFC, double-blind, placebo-controlled food challenge; FAQLQ, Food Allergy Quality of Life Questionnaire; ICF, informed consent form; IgA, immunoglobulin A; IgE, immunoglobulin E; IgG4, immunoglobulin G4; OFC, oral food challenge; OLE, open-label extension; PEF, peak expiratory flow; PK, pharmacokinetic; SCORAD, SCORing Atopic Dermatitis; SPT, skin prick test

Table 10. Schedule of Events for Stage 1 OLE

	Omalizumab Injection[1]		DBPCFC	
Week During Stage 1 OLE	0	2-22	24	25-28
Study Assessments				
Vitals & Growth Parameters	X	X	X	X
Interim Medical History	X	X	X	X
Physical Exam	X[2]	X[2]	X	X
PEF			X	X
SCORAD[3]			X	
Diet & Allergy Questionnaire	X	X	X	X
GI Symptoms Questionnaire	X	X	X	X
Family History Questionnaire	X[4]			
FAQLQ	X		X[5]	X[5]
Concomitant Medications	X	X	X	X
SPT			X[6]	
Blinded OFC			X	X
AEs	X	X	X	X
Open label omalizumab administration	X	X	X	X
Unblinding to DBPCFC Results				X[7]
Sample Collections				
Blood				
Total IgE			X	
Total Free IgE			X	
Allergen-Specific IgE, IgG4, IgA			X	
Basophil Activation			X	
PK Sampling			X	
Safety Sample Collections				
Blood				
CBC With Differential	Every 3 months			
CMP	Every 3 months			
Urine				
Urinalysis	Every 3 months			
Urine Pregnancy Test[8]	Monthly			

1. Omalizumab injection visits may occur every two or four weeks, determined by the body weight in kilograms and total serum IgE level at the Screening Visit.
2. A limited physical exam will be performed.
3. SCORAD will be performed for participants with AD. AD is determined by the PI or licensed clinician based on the current medical history and/or the physical exam.
4. An interim family history questionnaire will be collected.
5. FAQLQ will be collected prior to initiating the first blinded OFC and after completing the last blinded OFC in the OLE.
6. SPT to peanut and two other foods.
7. Unblind each participant to OFC results after completing the last blinded OFC in the OLE.
8. Only needed for female participants of child-bearing potential.

Source: Interim CSR (dated June 30, 2023), Table 5, p. 39
Abbreviations: AE, adverse event; CBC, complete blood count; CMP, complete metabolic panel; DBPCFC, double-blind, placebo-controlled food challenge; FAQLQ, Food Allergy Quality of Life Questionnaire; IgA, immunoglobulin A; IgE, immunoglobulin E; IgG4, immunoglobulin G4; OFC, oral food challenge; OLE, open-label extension; PEF, peak expiratory flow; PK, pharmacokinetic; SCORAD, SCORing Atopic Dermatitis; SPT, skin prick test

8.1.5. Subject Population

Key Inclusion Criteria

(1) Male or female, 1 year to less than 56 years of age at Screening

(2) Peanut allergic: Positive skin prick testing (SPT) ≥4 mm wheal greater than saline control to peanut; positive peanut IgE ≥6 kUA/L; positive blinded OFC to peanut at Screening DBPCFC defined as experiencing dose-limiting symptoms at a single dose of ≤100 mg of peanut protein

(3) Allergic to at least two of the six other foods (milk, egg, wheat, cashew, hazelnut, walnut)

   a. Allergy to milk and egg is defined as unable to tolerate both cooked and uncooked forms

   b. Milk, egg, or wheat: Positive SPT ≥4 mm wheal greater than the saline control to food; positive food specific IgE ≥6 kUA/L; positive blinded OFC to peanut at Screening DBPCFC defined as experiencing dose-limiting symptoms at a single dose of ≤300 mg of food protein

   c. Cashew, hazelnut, or walnut: Positive SPT ≥4 mm wheal greater than the saline control to food; positive food specific IgE ≥6 kUA/L; positive blinded OFC to peanut at Screening DBPCFC defined as experiencing dose-limiting symptoms at a single dose of ≤300 mg of food protein

Key Exclusion Criteria

(1) Dose-limiting symptoms to the blinded OFC to placebo during the Screening DBPCFC

(2) Poorly controlled atopic dermatitis at Screening

(3) Poorly controlled or severe asthma/wheezing at Screening

(4) History of severe anaphylaxis to subject-specific foods that will be used in this trial, defined as neurological compromise or requiring intubation

(5) Treatment with a burst of oral, intramuscular, or intravenous steroids of more than two days for an indication other than asthma/wheezing within 30 days of screening

(6) Currently receive corticosteroids, tricyclic antidepressants, or beta-blockers

(7) Past or current history of eosinophilic gastrointestinal disease within three years of Screening

(8) Past or current history of any immunotherapy to any of the foods being treated

(9) Previous adverse reaction to omalizumab

(10) Treatment with monoclonal antibody therapy or other immunomodulatory therapy within 6 months of Screening

(11) Currently on build up phase of inhalant allergen immunotherapy

(12) Inability to discontinue antihistamines for the minimum wash-out periods required for SPTs or OFCs

8.1.6. Treatment

The treatments administered to trial subjects, and the formulations, are provided in Table 11 and Table 12. In this trial, the presentations for omalizumab and placebo were marketed prefilled syringes. Dosing for each subject was determined based on weight and screening total serum IgE levels, according to the dosing table previously described (Table 3).

Table 11. Omalizumab Prefilled Syringe Formulation

Ingredient	Target Amount per PFS (75 mg/0.5 mL)	Target Amount per PFS (150 mg/1 mL)	Function	Reference to Standards
Omalizumab (mg)	75.00	150.00	Active substance	Novartis
(b) (4) Arginine Hydrochloride (mg)	21.05	42.10	(b) (4)	USP-NF, Ph. Eur.
L-Histidine Hydrochloride Monohydrate (mg)	1.17	2.34		Ph. Eur.
L-Histidine (mg)	0.68	1.37		USP-NF, Ph. Eur.
Polysorbate 20 (mg)	0.20	0.40		USP-NF, Ph. Eur.
Water for Injection	q.s. 0.50 mL	q.s. 1.00 mL		USP-NF, Ph. Eur.
Total Volume (mL)	0.50	1.00		

Abbreviations: PFS = prefilled syringe; q.s. = quantity sufficient.

Source: Applicant Information Request Response October 27, 2023

Table 12. Placebo for Omalizumab Prefilled Syringe Formulation

(b) (4)

[redacted]

8.1.7. Trial Endpoints

Primary Endpoint

Consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1

Key Secondary Endpoints

(1) Consumption of a single dose of ≥1000 mg of cashew protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1

(2) Consumption of a single dose of ≥1000 mg of milk protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1

(3) Consumption of a single dose of ≥1000 mg of egg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1

Other Secondary Endpoints

(1) Consumption of a single dose of ≥1000 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1

(2) Consumption of a single dose of ≥600 mg or ≥1000 mg of at least two foods or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1

(3) Number of foods consumed at a single dose of ≥600 mg or ≥1000 mg of each food protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1

Exploratory Endpoints

(4) Consumption of a single dose of ≥600 mg or ≥1000 mg of each food protein, at least two foods, or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1 OLE

8.1.8. Efficacy Parameters

Dose-Limiting Symptoms

Categorization of 'dose-limiting symptoms' is described below (Chinthrajah et al. 2022). All moderate and severe symptoms were considered dose-limiting. Mild symptoms were not usually considered dose-limiting, although a combination of mild symptoms during a single dose may have led to the cessation of an OFC at the discretion of the PI and were categorized as dose-limiting.

Mild Symptoms

- Skin – limited (few) or localized hives, swelling (e.g., mild lip edema), skin flushing (e.g., few areas of faint erythema) or mild pruritus (e.g., occasional scratching)
- Respiratory – rhinorrhea (e.g., occasional sniffling or sneezing), nasal congestion, occasional cough, throat discomfort
- Gastrointestinal (GI) – mild abdominal discomfort (including mild nausea with or without decreased activity), isolated emesis thought to be secondary to gag

Moderate Symptoms:

- Skin – 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
- Respiratory – throat tightness without hoarseness, persistent cough, wheezing without dyspnea
- GI – persistent moderate abdominal pain/cramping/nausea with decreased activity, vomiting

Severe Symptoms:

- Skin – severe generalized urticaria/angioedema/erythema
- Respiratory – laryngeal edema, throat tightness with hoarseness, wheezing with dyspnea, stridor
- GI – severe abdominal pain/cramping/repetitive vomiting

- Neurological – change in mental status
- Circulatory – clinically significant hypotension

Food Allergy Quality of Life Questionnaire:

The Food Allergy Quality of Life Questionnaire (FAQLQ) was administered to subjects or their guardians. The FAQLQ is a tool for assessing the emotional impact, food anxiety, and social and dietary limitations in people with food allergy. The version of the FAQLQ used was based on the age of the subject:

- FAQLQ-PF administered to parents/legal guardians of participants under 12 years of age
- FAQLQ-CF administered to children/adolescents aged 8 to 12 years
- FAQLQ-TF administered to adolescents aged 13 to 17 years
- FAQLQ-AF administered to adults aged ≥18 years

8.1.9. Safety Parameters

Safety parameters assessed included clinical laboratory values (hematology, serum chemistry, urine analysis, and pregnancy testing), vital signs (blood pressure, heart rate, respiratory rate, temperature, and weight), and physical examination findings.

8.1.10. Statistical Analysis Plan

Analysis Populations

The Applicant defined the following analysis populations for Stage 1:

- Pediatric Full Analysis Set – Stage 1 (PFA-S1): All subjects aged less than 18 years at randomization who were randomized to receive either omalizumab or placebo for omalizumab in Stage 1. Subjects were analyzed according to the treatment arm to which they were randomized at Stage 1, regardless of the treatment they actually received in Stage 1.
- Full Analysis Set – Stage 1 (FA-S1): All subjects who were randomized to receive either omalizumab or placebo for omalizumab in Stage 1. Subjects were analyzed according to the treatment arm to which they were randomized at Stage 1, regardless of the treatment they actually received in Stage 1.
- Pediatric Safety Set – Stage 1 (PSS-S1): All randomized subjects aged less than 18 years at randomization who received at least one dose of omalizumab or placebo for omalizumab in Stage 1. Subjects were analyzed according to the treatment they actually received in Stage 1, defined as “omalizumab” if a subject received any dose (including a

partial single dose) of omalizumab during Stage 1 and "placebo for omalizumab" otherwise, regardless of the treatment arm to which they were randomized in Stage 1.

- Safety Set – Stage 1 (SS-S1): All subjects who received at least one dose of omalizumab or placebo for omalizumab in Stage 1. Subjects were analyzed according to the treatment they actually received in Stage 1, defined as "omalizumab" if a subject received any dose (including a partial single dose) of omalizumab during Stage 1 and "placebo for omalizumab" otherwise, regardless of the treatment arm to which they were randomized in Stage 1.

The main analysis populations used for evaluating efficacy and safety in Stage 1 were PFA-S1 and PSS-S1, respectively. All other analysis populations were intended for supplementary or supportive safety and efficacy analyses.

The Applicant defined the following analysis populations for Stage 1 OLE:

- Pediatric Full Analysis Set – Stage 1 OLE (PFA-S1OLE): All subjects aged less than 18 years at randomization in Stage 1 who moved to Stage 1 OLE, grouped according to treatment arm to which they were randomized in Stage 1.
- Full Analysis Set – Stage 1 OLE (FA-S1OLE): All subjects who moved to Stage 1 OLE, grouped according to treatment arm to which they were randomized in Stage 1.
- Pediatric Safety Set – Stage 1 OLE (PSS-S1OLE): All subjects in the PFA-S1OLE population who received any dose (including a partial single dose) of open label omalizumab during Stage 1 OLE, grouped according to the treatment received in Stage 1 defined as "omalizumab" if a subject received any dose (including a partial single dose) of omalizumab during Stage 1 and "placebo for omalizumab" otherwise.
- Safety Set – Stage 1 OLE (SS-S1OLE): All subjects who moved to Stage 1 OLE and received any dose (including a partial single dose) of open label omalizumab during Stage 1 OLE, grouped according to the treatment received in Stage 1 defined as "omalizumab" if a subject received any dose (including a partial single dose) of omalizumab during Stage 1 and "placebo for omalizumab" otherwise.

The main analysis populations used for evaluating longer-term efficacy (descriptively) and safety in Stage 1 OLE were PFA-S1OLE and PSS-S1OLE, respectively. All other analysis populations were intended for additional exploration of safety and efficacy.

Sample Size Calculation

The Stage 1 sample size was chosen by the Applicant based on the power to detect an odds ratio (via two-sided Fisher's exact test with alpha=5%) of consuming a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC (the primary endpoint) between the omalizumab and placebo arms. Assuming 10% of subjects on placebo respond to treatment and 70% of subjects on omalizumab respond to treatment, a total sample size of 210 subjects would provide >99% power to detect an odds ratio of 21. When keeping the

percentage of responders on placebo at 10% but decreasing the percentage of responders on omalizumab to 27 to 30%, a sample size of 210 would detect an odds ratio of 3.3 to 3.8 with 80 to 90% power.

The Applicant's proposed indication involves allergy to multiple foods (not just peanut), which is captured by the three key secondary endpoints. Assuming a prevalence of 59% (124/210), 30% (63/210), and 20% (42/210) for cashew, milk, and egg allergy, respectively, according to data from two prior phase 2 studies involving omalizumab (Andorf et al. 2018; Andorf et al. 2019), and a 10% response rate among subjects on placebo (as done above for the primary endpoint), this trial would provide 90%, 58%, and 30% power to detect an odds ratio of 5.3 for cashew, milk, and egg, respectively (without multiplicity adjustment).

Overall, the Applicant planned to enroll 225 subjects in Stage 1 (150 on omalizumab and 75 on placebo), of which at least 210/225 (93%) would be 1 to less than 18 years of age (at least 50 aged 1 to less than 6 years and about 160 aged 6 to less than 18 years) and about 15/225 (7%) would be 18 to less than 56 years of age. Although the initial sample size planned for Stage 1 was 225 subjects, the Applicant submitted their sBLA based on a prespecified interim analysis of 165 pediatric subjects (see Interim Analysis below).

The Applicant did not select the Stage 1 OLE sample size (the first 60 subjects who completed Stage 1) based on hypothesis testing or power calculation; the Applicant did not provide justification for this choice.

Estimands

The Applicant specified the following five attributes of the Stage 1 primary estimand:

- Treatment: The estimand was intended to provide an estimate of the treatment effect of omalizumab in comparison to placebo for omalizumab.
- Population: All subjects who were randomized to receive either omalizumab or placebo for omalizumab in Stage 1 (PFA-S1). Subjects were analyzed according to the treatment arm to which they were randomized in Stage 1, regardless of the treatment they actually received in Stage 1.
- Variable: A binary response based on the primary endpoint of the consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1. A subject who met this endpoint was considered a success, while a subject who did not meet this endpoint was considered a failure.
- Intercurrent events: All intercurrent events (e.g., death, stopping the blinded OFC to peanut prior to the 600 mg dose, having dose-limiting symptoms at any dose of the blinded OFC to placebo, or stopping the blinded OFC to placebo at any dose) were handled following the composite strategy (the subject was considered a failure for the primary endpoint). Subjects who discontinued treatment were withdrawn and therefore were also considered a failure for any missing endpoints.

- Population-level summary: The odds ratio comparing consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 between the omalizumab and placebo for omalizumab arms.

The estimands for the three key secondary endpoints in Stage 1 were structured similarly to the primary estimand above.

The population in the estimands for the primary and key secondary endpoints in Stage 1 was pediatric patients only, while the study objective was targeting both adult and pediatric patients aged 1 year and older. As discussed in Section 1.2 and Section 6.1, the mechanism of action of omalizumab in the treatment of IgE-mediated food allergy extends across the age spectrum; as a result, extrapolation of efficacy data from subjects 1 to 17 years of age to the >18 years of age population, with PK matching, is supported.

No additional secondary or exploratory estimands were specified for Stage 1, and no estimands were specified for Stage 1 OLE.

Type I Error Control

Interim Analysis

While the initial sample size planned for Stage 1 was 225 subjects, a prespecified interim analysis of the Stage 1 data was conducted following a database lock on February 2, 2023, for the population of subjects who were randomized by July 8, 2022 (the date on which the trial reached randomization of 165 pediatric subjects; that is, when 79% [=165/210] of pediatric information was available).

At interim, the Applicant specified that efficacy would be declared only if the two-sided p-value for the primary endpoint (peanut) was significant at $p<0.0001$ and the two-sided p-values for all three key secondary endpoints (cashew, milk, and egg) were significant at $p<0.005$, with all p-values being significant in the right direction (i.e., favoring omalizumab).

The data and safety monitoring board reviewed the interim results, determined that the prespecified thresholds for significance were met, and recommended that Stage 1 of the trial be stopped early for efficacy with no further enrollment. The Applicant accepted this recommendation and terminated Stage 1 prior to reaching the target enrollment of 225.

(b) (4)

(b) (4)

The Applicant's statistical analysis plan (SAP; version 2.0 [dated October 26, 2022]) specified the following testing hierarchy for Stage 1, which follows an "overall hierarchical" structure (Glimm et al. 2010) that was recommended by the Agency during the IND stage (see IND 005369):

- Peanut: successful if peanut is significant at the interim analysis ($p<0.0001$) (b) (4)
- Cashew: successful if peanut is successful AND cashew is significant at the interim analysis ($p<0.005$) (b) (4)
- Egg: successful if peanut and cashew are successful AND egg is significant at the interim analysis ($p<0.005$) (b) (4)
- Milk: successful if peanut, cashew, and egg are successful AND milk is significant at the interim analysis ($p<0.005$) (b) (4)

Due to the exploratory nature of Stage 1 OLE, a plan for type I error control was not specified.

Statistical Analyses

The Applicant's statistical analyses in Stage 1 focused on the interim data from the pediatric population aged 1 to less than 18 years (N=165; PFA-S1).

Primary Analysis

For the Stage 1 primary endpoint, the following hypotheses were tested in PFA-S1 using a two-sided Fisher's exact test:

- Null hypothesis: The odds a subject consumes a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 in the omalizumab and placebo arms are equal.
- Alternative hypothesis: The odds a subject consumes a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1 in the omalizumab and placebo arms are not equal.

Both the odds ratio and the difference in proportions (and associated 95% exact Clopper-Pearson confidence intervals for each) comparing consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms between the omalizumab and placebo arms were reported. Subjects with missing data for any reason (e.g., due to withdrawals or missed visits) were considered nonresponders in the analysis.

A completer analysis of the primary endpoint was also performed in PFA-S1, including only subjects who completed the blinded OFC to peanut at the end of Stage 1. As a supportive analysis for the primary endpoint in PFA-S1, exact logistic regression was used with the following fixed effects: treatment arm, age at randomization (<6 years or ≥6 years), milk as a subject-specific food (yes/no), and the order of the blinded OFC to peanut relative to the other three foods during the DBPCFC at the end of Stage 1 (first, second, third, or fourth). The adjusted proportion (and associated standard error and 95% confidence interval) in each arm was reported, in addition to the odds ratio (and associated 95% exact confidence interval) comparing the omalizumab and placebo arms.

Subgroup analyses of the primary endpoint were also conducted for PFA-S1 (the difference in proportions and associated 95% exact confidence intervals were reported using forest plots) for each of the categorical variables below:

- Age at Stage 1 randomization (<6 years, 6 to <12 years, 12 to <18 years)
- Sex (female, male)
- Order of the blinded OFC to peanut relative to the other three foods during the DBPCFC at the end of Stage 1 (first, second, third, fourth)
- Site/clinical research unit (10 total; see Section 8.1.2)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, more than one race, unknown, not reported)
- Peanut dose eliciting dose-limiting symptoms during the screening DBPCFC (≤30 mg peanut protein, 100 mg peanut protein)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Dosing frequency (every two weeks, every four weeks)

Secondary Analyses

For the three Stage 1 key secondary analyses, the hypotheses to be tested in PFA-S1 were identical to those for the primary analysis above, except the binary outcomes here signify a tolerated dose of ≥1000 mg of the food proteins (cashew, egg, and milk) rather than ≥600 mg. Two-sided Fisher's exact tests were used for each key secondary analysis and the same quantities were reported as the primary analysis described above.

As was done for the primary endpoint, completer analyses for the key secondary endpoints were performed including only PFA-S1 subjects who completed the blinded OFC to the subject-specific food at the end of Stage 1. As supportive analyses, exact logistic regression models were built for the key secondary endpoints for PFA-S1 (each was structured the same as the model for the primary endpoint described above, with the "milk as a participant-specific food" effect being excluded from the model for the milk key secondary endpoint), where the adjusted proportion (and associated standard error and 95% confidence interval) in each arm and the

odds ratio (and associated 95% confidence interval) comparing the omalizumab and placebo arms were reported.

Additional Stage 1 secondary endpoints considered in PFA-S1 included (1) consumption of a single dose of ≥1000 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1, (2) consumption of a single dose of ≥600 mg or ≥1000 mg of at least two foods (not necessarily including peanut) without dose-limiting symptoms during the DBPCFC at the end of Stage 1, (3) consumption of a single dose of ≥600 mg or ≥1000 mg of all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1, and (4) the number of foods consumed at a single dose of ≥600 mg or ≥1000 mg without dose-limiting symptoms during the DBPCFC at the end of Stage 1. Endpoints (1), (2), and (3) were analyzed using two-sided Fisher's exact tests (not multiplicity adjusted), with the same quantities reported as the primary analysis. Endpoint (4) was analyzed using two-sided Wald chi-square (type III) tests (not multiplicity adjusted) and an ordinal logistic regression model with the same fixed effects as the exact logistic regression model described above for the primary endpoint, where the odds ratios and associated 95% Wald confidence intervals comparing consumption of a higher number of foods without dose-limiting symptoms between the omalizumab and placebo arms were reported.

All Stage 1 OLE analyses were exploratory and summarized descriptively; no formal statistical testing was conducted.

8.1.11. Protocol Amendments

There were six protocol amendments. These amendments were made to clarify various trial procedures and did not significantly impact the design of the trial.

8.1.12. Trial Results

Compliance With Good Clinical Practices

This trial was conducted in accordance with the ethical principles of Good Clinical Practice according to the ICH Harmonized Tripartite Guideline.

Financial Disclosure

The financial disclosure information from this trial does not impact the interpretation of the safety or efficacy results. There was one investigator who had a financial disclosure: (b) (6) disclosed payments >$15,000/year for participation (b) (6). In review of the Sunshine Act data, the Applicant observed that (b) (6) has been a (b) (6) and a total of $103,942 was paid to (b) (6) for speaking and consulting fees. The site at which (b) (6) serves as a subinvestigator enrolled (b) (6) of the (b) (6) subjects enrolled. (b) (6) serves as one of (b) (6) subinvestigators at the site. The Applicant believes

there is limited risk of bias given his role as subinvestigator and the number of subjects at the site. Review of the individual trial sites did not show deviation of efficacy results.

Subject Disposition

Disposition of subjects is presented in Table 13. A total of 428 individuals were screened for the trial, of whom 260 failed screening. Of the 168 subjects who were randomized, 112 were assigned to omalizumab and 56 were assigned to placebo for omalizumab (2:1 allocation ratio). Of the 168 subjects, 165 (98%) were less than 18 years of age and were included in the Stage 1 interim analyses (PFA-S1 and PSS-S1). Three adults aged 18, 20, and 28 years were randomized.

Table 13. Subject Screening and Disposition (Stage 1 and Stage 1 OLE, OUtMATCH)

Disposition	Omalizumab (N=112)	Placebo (N=56)	Overall (N=168)
Screened	–	–	428
Screen failed	–	–	260
Randomized	112 (100%)	56 (100%)	168 (100%)
Age <18 years	110 (98.2%)	55 (98.2%)	165 (98.2%)
Continued to Stage 1 OLE participation	39 (34.8%)	21 (37.5%)	60 (35.7%)
Analysis Populations			
Full analysis set – Stage 1 (FA-S1)	112 (100%)	56 (100%)	168 (100%)
Safety set – Stage 1 (SS-S1)	112 (100%)	56 (100%)	168 (100%)
Pediatric full analysis set – Stage 1 (PFA-S1)	110 (98.2%)	55 (98.2%)	165 (98.2%)
Pediatric safety set – Stage 1 (PSS-S1)	110 (98.2%)	55 (98.2%)	165 (98.2%)
Pediatric full analysis set – Stage 1 OLE (PFA-S1OLE)	38 (33.9%)	21 (37.5%)	59 (35.1%)
Pediatric safety set – Stage 1 OLE (PSS-S1OLE)	38 (33.9%)	21 (37.5%)	59 (35.1%)

Source: Statistical reviewer; Interim CSR (dated June 30, 2023), Table 7, p. 77
Abbreviations: OLE, open-label extension

A total of 160/165 pediatric subjects (97%) completed Stage 1 treatment. Five subjects (3%) withdrew from Stage 1, all of whom were assigned to omalizumab. Of them, two withdrew due to adverse events (AEs), one withdrew for the reasons of withdrawal by subject, one was withdrawn by a parent/guardian, and one withdrew due to failure to meet continuation criteria. Of the three adult subjects, one elected to withdraw during Stage 1.

Sixty subjects continued to, and completed, Stage 1 OLE. Of them, 59 were less than 18 years of age and were included in the Stage 1 OLE analyses (PFA-S1OLE and PSS-S1OLE).

Protocol Violations/Deviations

Protocol deviations for PFA-S1 are summarized in Table 14 and were reported for 95/165 subjects (58%). A major protocol deviation was reported for 54/165 subjects (33%). The most common categories of major protocol deviations were visit window (15 subjects; 9% of PFA-S1) and informed consent (12 subjects; 7% of PFA-S1). Informed consent deviations included minor deviations (signing incorrectly formatted consent or incorrect versions, failure to reconsent to new version of consent, or missing parental/staff signatures to addendums). Nine subjects (6%) had protocol deviations related to coronavirus disease 2019 (COVID-19).

Table 14. Protocol Deviations (PFA-S1, OUtMATCH)

	Omalizumab (N=110)	Placebo for omalizumab (N=55)	All Patients (N=165)
Participants with Any Protocol Deviation	61 (55.5%)	34 (61.8%)	95 (57.6%)
Category of Protocol Deviation			
COVID-19 RELATED	4 (3.6%)	5 (9.1%)	9 (5.5%)
INFORMED CONSENT	9 (8.2%)	5 (9.1%)	14 (8.5%)
IRB/REGULATORY	1 (0.9%)	0	1 (0.6%)
MISSED VISIT	6 (5.5%)	1 (1.8%)	7 (4.2%)
NON-COMPLIANCE WITH GCP	2 (1.8%)	0	2 (1.2%)
PROTOCOL/MOP	6 (5.5%)	4 (7.3%)	10 (6.1%)
RANDOMIZATION RELATED	1 (0.9%)	0	1 (0.6%)
SAFETY, EFFICACY, OR ENDPOINT ASSESSMENTS	9 (8.2%)	10 (18.2%)	19 (11.5%)
SIGNIFICANT MECHANISTIC/LAB RESULT	13 (11.8%)	6 (10.9%)	19 (11.5%)
SIGNIFICANT SITE FINDING	3 (2.7%)	0	3 (1.8%)
STUDY PROCEDURE	30 (27.3%)	13 (23.6%)	43 (26.1%)
STUDY TREATMENT RELATED	0	1 (1.8%)	1 (0.6%)
VISIT WINDOW	13 (11.8%)	9 (16.4%)	22 (13.3%)
Participants with Any Major Protocol Deviation	33 (30.0%)	21 (38.2%)	54 (32.7%)
Category of Protocol Deviation			
COVID-19 RELATED	4 (3.6%)	4 (7.3%)	8 (4.8%)
INFORMED CONSENT	8 (7.3%)	4 (7.3%)	12 (7.3%)
IRB/REGULATORY	1 (0.9%)	0	1 (0.6%)
MISSED VISIT	6 (5.5%)	1 (1.8%)	7 (4.2%)
NON-COMPLIANCE WITH GCP	1 (0.9%)	0	1 (0.6%)
PROTOCOL/MOP	3 (2.7%)	2 (3.6%)	5 (3.0%)
RANDOMIZATION RELATED	1 (0.9%)	0	1 (0.6%)
SAFETY, EFFICACY, OR ENDPOINT ASSESSMENTS	3 (2.7%)	3 (5.5%)	6 (3.6%)
SIGNIFICANT MECHANISTIC/LAB RESULT	1 (0.9%)	1 (1.8%)	2 (1.2%)
SIGNIFICANT SITE FINDING	3 (2.7%)	0	3 (1.8%)
STUDY PROCEDURE	6 (5.5%)	3 (5.5%)	9 (5.5%)
VISIT WINDOW	9 (8.2%)	6 (10.9%)	15 (9.1%)

NOTE: Participants who had multiple protocol deviations are counted once in each applicable category.
NOTE: Denominators for percentages are based on N, the number of participants in thepopulation being analyzed.

Source: Applicant response to information request (submitted December 8, 2023)
Abbreviations: COVID-19, coronavirus disease 2019; PFA-S1, pediatric full analysis set – Stage 1

Protocol deviations for PFA-S1OLE are summarized in Table 15 and were reported for 27/59 subjects (46%). A major protocol deviation was reported for 16/59 subjects (27%). The most common categories of major protocol deviations were informed consent (4 subjects; 7% of PFA-S1OLE), trial procedure (4 subjects; 7% of PFA-S1OLE) and missed visit (4 subjects; 7% of PFA-S1OLE).

Table 15. Protocol Deviations (PFA-S1OLE, OUtMATCH)

	Omalizumab (N=38)	Placebo for omalizumab (N=21)	All Patients (N=59)
Participants with Any Protocol Deviation	17 (44.7%)	10 (47.6%)	27 (45.8%)
Category of Protocol Deviation			
COVID-19 RELATED	0	1 (4.8%)	1 (1.7%)
INFORMED CONSENT	3 (7.9%)	1 (4.8%)	4 (6.8%)
MISSED VISIT	4 (10.5%)	2 (9.5%)	6 (10.2%)
PROTOCOL/MOP	2 (5.3%)	1 (4.8%)	3 (5.1%)
SAFETY, EFFICACY, OR ENDPOINT ASSESSMENTS	2 (5.3%)	2 (9.5%)	4 (6.8%)
SIGNIFICANT MECHANISTIC/LAB RESULT	1 (2.6%)	1 (4.8%)	2 (3.4%)
SIGNIFICANT SITE FINDING	0	1 (4.8%)	1 (1.7%)
STUDY PROCEDURE	5 (13.2%)	3 (14.3%)	8 (13.6%)
VISIT WINDOW	4 (10.5%)	4 (19.0%)	8 (13.6%)
Participants with Any Major Protocol Deviation	9 (23.7%)	7 (33.3%)	16 (27.1%)
Category of Protocol Deviation			
COVID-19 RELATED	0	1 (4.8%)	1 (1.7%)
INFORMED CONSENT	3 (7.9%)	1 (4.8%)	4 (6.8%)
MISSED VISIT	2 (5.3%)	2 (9.5%)	4 (6.8%)
PROTOCOL/MOP	1 (2.6%)	1 (4.8%)	2 (3.4%)
SAFETY, EFFICACY, OR ENDPOINT ASSESSMENTS	1 (2.6%)	2 (9.5%)	3 (5.1%)
SIGNIFICANT SITE FINDING	0	1 (4.8%)	1 (1.7%)
STUDY PROCEDURE	2 (5.3%)	2 (9.5%)	4 (6.8%)
VISIT WINDOW	1 (2.6%)	2 (9.5%)	3 (5.1%)

NOTE: Participants who had multiple protocol deviations are counted once in each applicable category.
NOTE: Denominators for percentages are based on N, the number of participants in the population being analyzed.
Source: Applicant response to information request (submitted December 21, 2023)
Abbreviations: COVID-19, coronavirus disease 2019; PFA-S1OLE, pediatric full analysis set – Stage 1 open-label extension

All protocol deviations were unlikely to have impacted the quality of the trial or the overall interpretation of results.

Demographic Characteristics

Subject demographics are summarized in Table 16, which includes all 168 subjects who were randomized in Stage 1 (FA-S1). However, safety and efficacy analyses were conducted in the 165 pediatric subjects under 18 years of age (PFA-S1). The trial enrolled a higher proportion of males (57% versus 43%) and white subjects (63%). Enrollment in the two youngest age groups (<6 years and 6 to <12 years) was closely equal.

Table 16. Subject Demographics (FA-S1, OUtMATCH)

Demographics	Omalizumab (N=112)	Placebo (N=56)	Total (N=168)
Age			
<6 years	41 (37%)	20 (36%)	61 (36%)
6 to <12 years	43 (38%)	19 (34%)	62 (37%)
12 to <18 years	26 (23%)	16 (29%)	42 (25%)
≥18 years	2 (2%)	1 (2%)	3 (2%)
Sex			
Female	47 (42%)	26 (46%)	73 (43%)
Male	65 (58%)	30 (54%)	95 (57%)
Race			
Asian	11 (10%)	11 (20%)	22 (13%)
Black or African American	8 (7%)	4 (7%)	12 (7%)
Multiple	20 (18%)	7 (13%)	27 (16%)
White	72 (64%)	34 (61%)	106 (63%)
Ethnicity			
Hispanic or Latino	10 (9%)	4 (7%)	14 (8%)
Not Hispanic or Latino	102 (91%)	52 (93%)	154 (92%)

Source: adsl.xpt; Software: JMP Clinical
Abbreviations: FA-S1, full analysis set – Stage 1

All Stage 1 OLE subjects were carried over from Stage 1. The demographics of FA-S1OLE (Table 17) were similar to those shown in Table 16 for FA-S1.

Table 17. Subject Demographics (FA-S1OLE, OUtMATCH)

Demographics	Omalizumab (N=60)
Age	
<6 years	24 (40%)
6 to <12 years	16 (27%)
12 to <18 years	19 (32%)
≥18 years	1 (2%)
Sex	
Female	21 (35%)
Male	39 (65%)
Race	
Asian	6 (11%)
Black or African American	8 (14%)
Multiple	5 (9%)
White	38 (67%)

Demographics	Omalizumab (N=60)
Age	
<6 years	24 (40%)
Ethnicity	
Hispanic or Latino	2(3%)
Not Hispanic or Latino	52 (88%)
Not reported	4 (7%)
Unknown	1 (2%)

Source: JMP Clinical
Abbreviations: FA-S1OLE, full analysis set – Stage 1 open-label extension

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Subject-specific foods were comprised of milk (57 subjects; 35% of PFA-S1), egg (65 subjects; 39% of PFA-S1), wheat (18 subjects; 11% of PFA-S1), cashew (94 subjects; 57% of PFA-S1), hazelnut (23 subjects; 14% of PFA-S1), and walnut (73 subjects; 44% of PFA-S1). The proportion of subject-specific foods approximately followed a 2:1 ratio between the omalizumab and placebo arms. All other baseline characteristics provided by the Applicant for the 165 subjects in PFA-S1, and the 59 subjects in PFA-S1OLE, were generally balanced between the omalizumab and placebo arms.

A summary of the screening doses where moderate-severe dose-limiting symptoms were experienced for subjects in PFA-S1 is provided in Table 18.

Table 18. Screening Dose Where Moderate-Severe Dose-Limiting Symptoms Were Experienced (PFA-S1, OUtMATCH)

Food Allergen, Dose	Omalizumab n/N (%)	Placebo n/N (%)
Peanut		
100 mg	64/110 (58)	29/55 (53)
30 mg	23/110 (21)	17/55 (31)
10 mg	19/110 (17)	9/55 (16)
3 mg	3/110 (3)	0/55 (0)
1 mg	1/110 (1)	0/55 (0)
Cashew		
300 mg	6/64 (9)	2/30 (7)
100 mg	9/64 (14)	6/30 (20)
30 mg	19/64 (30)	6/30 (20)
10 mg	16/64 (25)	8/30 (27)
3 mg	12/64 (19)	7/30 (23)
1 mg	2/64 (3)	1/30 (3)

Food Allergen, Dose	Omalizumab n/N (%)	Placebo n/N (%)
Milk		
300 mg	10/38 (26)	5/19 (26)
100 mg	15/38 (39)	5/19 (26)
30 mg	8/38 (21)	4/19 (21)
10 mg	4/38 (11)	2/19 (11)
3 mg	1/38 (3)	2/19 (11)
1 mg	0/38 (0)	1/19 (5)
Egg		
300 mg	5/46 (11)	4/19 (21)
100 mg	13/46 (28)	5/19 (26)
30 mg	16/46 (35)	1/19 (5)
10 mg	10/46 (22)	7/19 (37)
3 mg	2/46 (4)	2/19 (11)
1 mg	0/46 (0)	0/19 (0)

Source: Statistical reviewer
Notes: All results were obtained using R (version 4.3.1)
Abbreviations: n, number of subjects with the respective dose; N, number of randomized subjects in PFA-S1; PFA-S1, pediatric full analysis set – Stage 1

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

A total of 160/165 pediatric subjects (97%) in PFA-S1 completed Stage 1 treatment and the Stage 1 DBPCFC to peanut. A total of 163/165 pediatric subjects (99%) in PFA-S1 received at least 75% of their expected doses in the trial (the 2 subjects who did not receive at least 75% of their expected doses were on placebo).

Subjects continued their usual medications, including those taken for asthma, allergic rhinitis, and atopic dermatitis, during the trial. However, each subject had to be able to discontinue antihistamines prior to the skin prick tests and all OFCs. Regular topical steroid use was permitted at the time of a skin prick test.

Subjects were required to have epinephrine autoinjectors to use in the event of a severe reaction to one of the investigational agents, as omalizumab (although rare) may induce severe allergic reactions/anaphylaxis. Epinephrine was used to treat life-threatening and nonlife-threatening allergic reactions to food allergens during the OFCs. Treatment of individual allergic reactions during a skin prick test and/or to local skin anesthetic (as applicable) used during the blood draw was with an antihistamine and/or epinephrine, along with IV fluids, albuterol, and corticosteroids (including topicals), as indicated.

Efficacy Results – Primary Endpoint

The primary endpoint in Stage 1 was binary: the consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1. The

Applicant's prespecified primary analysis was a two-sided Fisher's exact test, conducted in PFA-S1 (N=165). For the primary endpoint, all 4 subjects (2%) in PFA-S1 with missing data were on omalizumab and were considered nonresponders in the analysis. Omalizumab met statistical significance for the primary endpoint at the prespecified interim alpha level of 0.0001, demonstrating a meaningful improvement over placebo. Results are shown in Table 19. Additionally, 19/110 subjects (17%) on omalizumab were not able to consume >100 mg of peanut protein without moderate-severe dose-limiting symptoms.

Table 19. Primary Efficacy Analysis: Proportion of Responders (PFA-S1, OUtMATCH)

Analysis Statistic	Omalizumab (N=110)	Placebo (N=55)
n (%)	75 (68.2)	3 (5.5)
Odds ratio[a] (95% CI)	37.1 (10.6, 193.9)	
Difference[b] (95% CI)	62.7% (50.4%, 72.1%)	
P-value[c]	<0.0001	

Source: Statistical reviewer
[a] Calculated as omalizumab / placebo
[b] Calculated as omalizumab – placebo
[c] P-value from two-sided Fisher's exact test
Notes: All results were obtained using R (version 4.3.1)
Abbreviations: CI, confidence interval; n, number of responders; N, number of randomized subjects in PFA-S1; PFA-S1, pediatric full analysis set – Stage 1

A completer analysis was conducted to determine if the primary analysis was impacted by subjects in PFA-S1 who were missing the blinded OFC to peanut and thus were considered nonresponders in the primary analysis. This occurred for 4/165 subjects (2%) in PFA-S1, and all four were on omalizumab. The results of this completer analysis are shown in Table 20 and do not notably differ from the primary analysis results displayed in Table 19.

Table 20. Completer Analysis for the Primary Endpoint (PFA-S1, OUtMATCH)

Analysis Statistic	Omalizumab (N=106)	Placebo (N=55)
n (%)	75 (70.8)	3 (5.5)
Odds ratio[a] (95% CI)	41.9 (11.9, 219.4)	
Difference[b] (95% CI)	65.3% (52.9%, 74.5%)	
P-value[c]	<0.0001	

Source: Statistical reviewer
[a] Calculated as omalizumab / placebo
[b] Calculated as omalizumab – placebo
[c] P-value from two-sided Fisher's exact test (not multiplicity adjusted)
Notes: All results were obtained using R (version 4.3.1)
Abbreviations: CI, confidence interval; n, number of responders; N, number of randomized subjects in PFA-S1 who completed Stage 1; PFA-S1, pediatric full analysis set – Stage 1

The Applicant performed a supportive analysis of the primary endpoint in PFA-S1 using exact logistic regression with the following fixed effects: treatment arm, age at randomization (<6 years or ≥6 years), milk as a subject-specific food (yes/no), and the order of the blinded OFC to peanut relative to the other three foods during the DBPCFC at the end of Stage 1 (first, second, third, or fourth). The results of this supportive analysis are shown in Table 21 and also closely align with the primary analysis results in Table 19.

Table 21. Exact Logistic Regression Analysis for the Primary Endpoint (PFA-S1, OUtMATCH)

Analysis Statistic	Omalizumab (N=110)	Placebo (N=55)
n (%)	75 (68.2)	3 (5.5)
Adjusted odds ratio[a] (95% CI)	37.2 (10.7, 202.4)	
Adjusted difference[b] (95% CI)	62.7% (61.6%, 63.9%)	
P-value[c]	<0.0001	

Source: Interim CSR (dated June 30, 2023), Table 11 (p. 86) and Table 14.2.1.5 (p. 223)
[a] Calculated as omalizumab / placebo
[b] Calculated as omalizumab – placebo
[c] P-value from two-sided Fisher's exact test (not multiplicity adjusted)
Abbreviations: CI, confidence interval; n, number of responders; N, number of randomized subjects in PFA-S1; PFA-S1, pediatric full analysis set – Stage 1

Subgroup analyses of the primary endpoint in PFA-S1 were also performed by the Applicant. The estimated odds ratios and the estimated differences in the proportion of responders within the age, sex, race, and ethnicity subgroups did not raise any notable concerns and all favored omalizumab, though sample sizes within some of the subgroups are too small to draw definitive conclusions. Results are shown in Table 22 (see Figure 3 in the interim CSR [dated June 30, 2023] for the results of additional subgroups considered by the Applicant as described in Section 8.1.10).

Table 22. Subgroup Analyses for the Primary Endpoint (PFA-S1, OUtMATCH)

Subgroup	Omalizumab (N=110)	Placebo (N=55)	Proportion of Responders[a] (%)	Estimated Difference[b] (%) (95% CI)	Odds Ratio[c] (95% CI)
Age (years)					
<6	41 (37.3)	20 (36.4)	63.4 v 10.0	53.4 (28.9, 69.8)	15.6 (2.9, 149.9)
6 to <12	43 (39.1)	19 (34.5)	74.4 v 0.0	74.4 (55.5, 85.1)	X (10.6, X)
12 to <18	26 (23.6)	16 (29.1)	65.4 v 6.3	59.1 (31.2, 76.8)	28.3 (3.1, 1251.2)
Sex					
Female	47 (42.7)	26 (47.3)	72.3 v 0.0	72.3 (57.5, 83.1)	X (13.8, X)
Male	63 (57.3)	29 (52.7)	65.1 v 10.3	54.7 (35.2, 68.4)	16.2 (4.1, 89.6)
Race					
Asian	11 (10.0)	11 (20.0)	63.6 v 18.2	45.5 (3.5, 74.0)	7.9 (0.8, 100.6)
Black or African American	8 (7.3)	3 (5.5)	75.0 v 0.0	75.0 (5.6, 93.2)	X (0.6, X)
More than 1 race	20 (18.2)	7 (12.7)	70.0 v 14.3	55.7 (12.1, 78.4)	14.0 (1.2, 685.3)
White	70 (63.6)	34 (61.8)	67.1 v 0.0	67.1 (55.4, 77.0)	X (15.5, X)
Ethnicity					
Hispanic or Latino	10 (9.1)	4 (7.3)	60.0 v 0.0	60.0 (0.5, 83.7)	X (0.6, X)
Not Hispanic or Latino	100 (90.9)	51 (92.7)	69.0 v 5.9	63.1 (50.0, 72.8)	35.6 (10.0, 187.3)

Source: Statistical reviewer

[a] Displayed as omalizumab versus (v) placebo

[b] Calculated as omalizumab – placebo

[c] Calculated as omalizumab / placebo

Notes: All other race categories (American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, unknown, and not reported) had N ≤1 and are excluded; Undefined values are displayed as X; All results were obtained using R (version 4.3.1)

Abbreviations: CI, confidence interval; N, number of randomized subjects in PFA-S1; PFA-S1, pediatric full analysis set – Stage 1

Efficacy Results – Secondary and Other Relevant Endpoints

The three key secondary endpoints in Stage 1 were also binary: consumption of a single dose of ≥1000 mg of cashew/milk/egg protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1. The Applicant's prespecified key secondary analyses (two-sided Fisher's exact tests) were based on PFA-S1. Omalizumab met statistical significance for each key secondary endpoint at the prespecified interim alpha level of 0.005, demonstrating a meaningful improvement over placebo for all three foods. Results are shown in Table 23. Additionally, 7/38 (18%), 10/46 (22%), and 26/64 (41%) subjects on omalizumab were not able to consume >300 mg of milk, egg, and cashew protein, respectively, without moderate-severe dose-limiting symptoms.

Table 23. Key Secondary Efficacy Analyses: Proportion of Responders (PFA-S1, OUtMATCH)

Food Allergen	Omalizumab (n/N)	Placebo (n/N)	Proportion of Responders[a] (%)	Estimated Difference[b] (%) (95% CI)	Odds Ratio[c] (95% CI)	P-Value[d]
Cashew	27/64	1/30	42.2 v 3.3	38.9 (22.6, 52.0)	21.2 (3.0, 891.8)	<0.0001
Milk	25/38	2/19	65.8 v 10.5	55.3 (29.8, 71.9)	16.3 (3.0, 158.7)	<0.0001
Egg	31/46	0/19	67.4 v 0.0	67.4 (48.5, 79.2)	X (7.9, X)	<0.0001

Source: Statistical reviewer
[a] Displayed as omalizumab versus (v) placebo
[b] Calculated as omalizumab – placebo
[c] Calculated as omalizumab / placebo
[d] P-value from two-sided Fisher's exact test
Note: Undefined values are displayed as X; All results were obtained using R (version 4.3.1)
Abbreviations: CI, confidence interval; n, number of responders; N, number of randomized subjects in PFA-S1; PFA-S1, pediatric full analysis set – Stage 1

For the milk and egg key secondary endpoints, all subjects (milk: 4%; egg: 2%) with missing data were on omalizumab and were considered nonresponders in the analyses. For the cashew key secondary endpoint, there were 4 subjects (4%) with missing data (3 on omalizumab and 1 on placebo). Per the Applicant's interim CSR (dated June 30, 2023), all 4 subjects were considered treatment failures, producing a treatment difference (omalizumab – placebo) of 38.9% (see Table 23). When continuing to treat the 3 subjects on omalizumab as failures but the 1 subject on placebo as a success, the treatment difference decreases to 35.5%, which still represents a meaningful improvement over placebo. Overall, the amount of missingness in this trial was very small and did not substantially impact trial results; no issues arose regarding missing data.

Like for the primary analysis, completer analyses were conducted to determine if the key secondary analyses were impacted by subjects in PFA-S1 who were missing the blinded OFC to the subject-specific food at the end of Stage 1 and thus were considered nonresponders in the key secondary analyses. In PFA-S1, this occurred for 4/94 subjects (4%) in the cashew group (3 on omalizumab and 1 on placebo), 2/57 subjects (4%) in the milk group (both on omalizumab), and 1/65 subjects (2%) in the egg group (on omalizumab). The results of the completer analyses for cashew, milk, and egg are shown in Table 24, where the estimated treatment differences

and odds ratios were not notably different from the respective key secondary analysis results in Table 23.

Table 24. Completer Analyses for the Key Secondary Endpoints (PFA-S1, OUtMATCH)

Food Allergen	Omalizumab (n/N)	Placebo (n/N)	Proportion of Responders[a] (%)	Estimated Difference[b] (%) (95% CI)	Odds Ratio[c] (95% CI)	p-Value[d]
Cashew	27/61	1/29	44.3 v 3.4	40.8 (24.0, 54.2)	22.2 (3.2, 937.8)	<0.0001
Milk	25/36	2/19	69.4 v 10.5	58.9 (33.3, 75.3)	19.3 (3.4, 188.5)	<0.0001
Egg	31/45	0/19	68.9 v 0.0	68.9 (49.9, 80.5)	X (8.4, X)	<0.0001

Source: Statistical reviewer
[a] Displayed as omalizumab versus (v) placebo
[b] Calculated as omalizumab – placebo
[c] Calculated as omalizumab / placebo
[d] P-value from two-sided Fisher's exact test (not multiplicity adjusted)
Note: Undefined values are displayed as X; All results were obtained using R (version 4.3.1)
Abbreviations: CI, confidence interval; n, number of responders; N, number of randomized subjects in PFA-S1 who completed Stage 1; PFA-S1, pediatric full analysis set – Stage 1

For each key secondary endpoint, the Applicant used exact logistic regression as a supportive analysis with the same set of fixed effects that were used for the supportive analysis of the primary endpoint (see Statistical Analyses). The results of the supportive analyses for cashew and milk are provided in Table 25 and were also very similar to the respective key secondary results in Table 23. This sensitivity analysis could not be completed for the egg key secondary endpoint, as there were no responders in the placebo group.

Table 25. Exact Logistic Regression Analyses for the Key Secondary Endpoints (PFA-S1, OUtMATCH)

Food Allergen	Omalizumab (n/N)	Placebo (n/N)	Adjusted Proportion of Responders[a] (%)	Adjusted Difference[b] (%) (95% CI)	Adjusted Odds Ratio[c] (95% CI)	p-Value[d]
Cashew	27/64	1/30	42.8 v 3.0	39.7 (36.8, 42.7)	26.4 (3.5, 1240)	<0.0001
Milk	25/38	2/19	65.8 v 10.5	55.3 (54.8, 55.8)	13.0 (2.6, 127.8)	0.0002

Source: Interim CSR (dated June 30, 2023), Table 14.2.2.2, p. 255
[a] Displayed as omalizumab versus (v) placebo
[b] Calculated as omalizumab – placebo
[c] Calculated as omalizumab / placebo
[d] P-value from two-sided Fisher's exact test (not multiplicity adjusted)
Abbreviations: CI, confidence interval; n, number of responders; N, number of randomized subjects in PFA-S1; PFA-S1, pediatric full analysis set – Stage 1

Several additional secondary endpoints were explored in PFA-S1 (at an unadjusted alpha level of 5%), including the consumption of a single dose of ≥1000 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of Stage 1. This endpoint, like the primary and

key secondary endpoints, was analyzed using a two-sided Fisher's exact test, which favored omalizumab (Table 26). Interestingly, the estimated treatment difference for a single dose of ≥1000 mg of peanut protein was higher than the value obtained in the primary analysis (Table 19) for a single dose of ≥600 mg of peanut protein (treatment difference: 65.5% versus 62.7%) due to the different response rates in the placebo group.

Table 26. Supplementary Secondary Efficacy Analysis: DBPCFC Response Rates for a Single Dose of ≥1000 mg of Peanut Protein (PFA-S1, OUtMATCH)

Analysis Statistic	Omalizumab (N=110)	Placebo (N=55)
n (%)	72 (65.5)	0 (0.0)
Odds ratio[a] (95% CI)	X (24.9, X)	
Difference[b] (95% CI)	65.5 (56.2, 73.7)	
p-value[c]	<0.0001	

Source: Statistical reviewer
[a] Calculated as omalizumab / placebo
[b] Calculated as omalizumab – placebo
[c] p-value from two-sided Fisher's exact test (not multiplicity adjusted)
Note: Undefined values are displayed as X; All results were obtained using R (version 4.3.1)
Abbreviations: CI, confidence interval; n, number of responders; N, number of randomized subjects in PFA-S1; PFA-S1, pediatric full analysis set – Stage 1

Other secondary endpoints that were considered in PFA-S1 (without multiplicity adjustment) were the consumption of a single dose of ≥600 mg or ≥1000 mg of at least two foods (not necessarily including peanut) or all three foods without dose-limiting symptoms during the DBPCFC at the end of Stage 1. Each was analyzed using a two-sided Fisher's exact test at an unadjusted alpha level of 5%. As shown in Table 27, omalizumab treatment led to a notably higher proportion of responders compared to placebo in all four categories.

Table 27. Supplementary Secondary Efficacy Analyses: DBPCFC Response Rates for a Single Dose of ≥600 mg or ≥1000 mg of at Least Two Foods or All Three Foods (PFA-S1, OUtMATCH)

Challenge Dose (Number of Foods)	Omalizumab (N=110)	Placebo (N=55)	Proportion of Responders[a] (%)	Estimated Difference[b] (%) (95% CI)	Odds Ratio[c] (95% CI)	p-Value[d]
≥600 mg (at least 2)	78 (71%)	3 (5%)	70.9 v 5.5	65.5 (53.2, 74.5)	42.3 (12.0, 220.7)	<0.0001
≥1000 mg (at least 2)	74 (67%)	2 (4%)	67.3 v 3.6	63.6 (51.9, 72.6)	54.5 (12.8, 474.7)	<0.0001
≥600 mg (all 3)	53 (48%)	2 (4%)	48.2 v 3.6	44.5 (32.8, 54.6)	24.6 (5.9, 214.8)	<0.0001
≥1000 mg (all 3)	43 (39%)	0 (0%)	39.1 v 0.0	39.1 (30.5, 48.5)	X (8.5, X)	<0.0001

Source: Statistical reviewer
[a] Displayed as omalizumab versus (v) placebo
[b] Calculated as omalizumab – placebo
[c] Calculated as omalizumab / placebo
[d] P-value from two-sided Fisher's exact test (not multiplicity adjusted)
Note: Undefined values are displayed as X; All results were obtained using R (version 4.3.1)
Abbreviations: CI, confidence interval; N, number of randomized subjects in PFA-S1; PFA-S1, pediatric full analysis set – Stage 1

The Applicant also used ordinal logistic regression to analyze the proportion of subjects on omalizumab and placebo in PFA-S1 who were able to tolerate a single dose of ≥600 mg or ≥1000 mg of 0, 1, 2, or all 3 food proteins without dose-limiting symptoms during the DBPCFC at the end of Stage 1. Odds ratios were reported comparing consumption of a higher number of foods without dose-limiting symptoms between the omalizumab and placebo arms. Results are shown in Table 28 and further demonstrate greater efficacy in the omalizumab arm versus placebo**.**

Table 28. Supplementary Secondary Efficacy Analyses: Number of Foods Consumed at a Single Dose of ≥600 mg or ≥1000 mg (PFA-S1, OUtMATCH)

Challenge Dose, Number of Foods	Omalizumab (N=110)	Placebo (N=55)	Odds Ratio[a] (95% CI)	p-Value[b]
≥600 mg			37.8 (14.3, 100.2)	<0.0001
0	21 (19.1%)	49 (89.1%)		
1	11 (10.0%)	3 (5.5%)		
2	25 (22.7%)	1 (1.8%)		
3	53 (48.2%)	2 (3.6%)		

Challenge Dose, Number of Foods	Omalizumab (N=110)	Placebo (N=55)	Odds Ratio[a] (95% CI)	p-Value[b]
≥1000 mg			39.8 (14.7, 107.3)	<0.0001
0	23 (20.9%)	49 (89.1%)		
1	13 (11.8%)	4 (7.3%)		
2	31 (28.2%)	2 (3.6%)		
3	43 (39.1%)	0 (0.0%)		

Source: Interim CSR (dated June 30, 2023), Table 14.2.3.10, p. 299
[a] Calculated as omalizumab / placebo
[b] p-value from two-sided Wald chi-square (type III) test (not multiplicity adjusted)
Abbreviations: N, number of randomized subjects in PFA-S1; PFA-S1, pediatric full analysis set – Stage 1

Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment (Patient-Reported Outcome) Endpoints

The Food Allergy Quality of Life Questionnaire (FAQLQ) is not a validated patient-reported outcome and was used by the Applicant solely for exploratory purposes. Therefore, the FAQLQ data will not be used in determining whether the product meets substantial evidence of effectiveness (SEE).

Additional Analyses Conducted on the Individual Trial

Since there were only 3 adults enrolled in Stage 1 (2 completed Stage 1 and 1 withdrew) and 1 adult who continued to, and completed, Stage 1 OLE, it is difficult to draw conclusions from the adult population in this trial. In general, the Applicant's supplementary/exploratory analyses of the FA-S1 and FA-S1OLE populations (which included all pediatric and adult subjects in Stage 1 and Stage 1 OLE, respectively) yielded very similar results to those obtained for the PFA-S1 and PFA-S1OLE populations (which included only the pediatric subjects in Stage 1 and Stage 1 OLE, respectively). Of the two adults who completed Stage 1, 1 on omalizumab met the primary endpoint (peanut) and two of the key secondary endpoints (cashew and egg), while the other was on placebo and did not meet the primary or any key secondary endpoints. The 1 adult in Stage 1 OLE completed omalizumab treatment during Stage 1, but the Applicant did not submit any data or analyses related to efficacy for this subject.

Regarding the mold discovered in some of the Applicant's investigational food products used for OFCs (see Section 3.1), there were no notable changes in the results of the primary and key secondary analyses after removing subjects in PFA-S1 who were treated with mold-affected lots, or any lots, that were >6 or >12 months old (see Tables 14.2.1.7.1 to 14.2.1.7.4 and Tables 14.2.2.7.1 to 14.2.2.7.4 in the Applicant's interim CSR [dated June 30, 2023] for more details).

The Agency was also interested in looking at how many subjects in PFA-S1 experienced zero symptoms for the primary and key secondary endpoints, since a subject could have had symptoms, but still been considered a success as long as they did not have symptoms that were deemed dose-limiting (see dose-limiting criteria in Section 8.1.8). From Table 29, the proportion of responders among subjects on omalizumab who had zero symptoms were almost 50% for

those with peanut, milk, and egg as subject-specific foods, while the response rate was 27% for those with cashew as a subject-specific food. Additionally, all placebo responders had zero symptoms.

Table 29. DBPCFC Response Rates for Subjects With Zero Symptoms (PFA-S1, OUtMATCH)

	Omalizumab	Placebo
Peanut, N	110	55
Met Criteria*, n (%)	53 (48.2%)	3 (5.5%)
Cashew, N	64	30
Met Criteria**, n (%)	17 (26.6%)	1 (3.3%)
Milk, N	38	19
Met Criteria**, n (%)	17 (44.7%)	2 (10.5%)
Egg, N	46	19
Met Criteria**, n (%)	21 (45.7%)	0

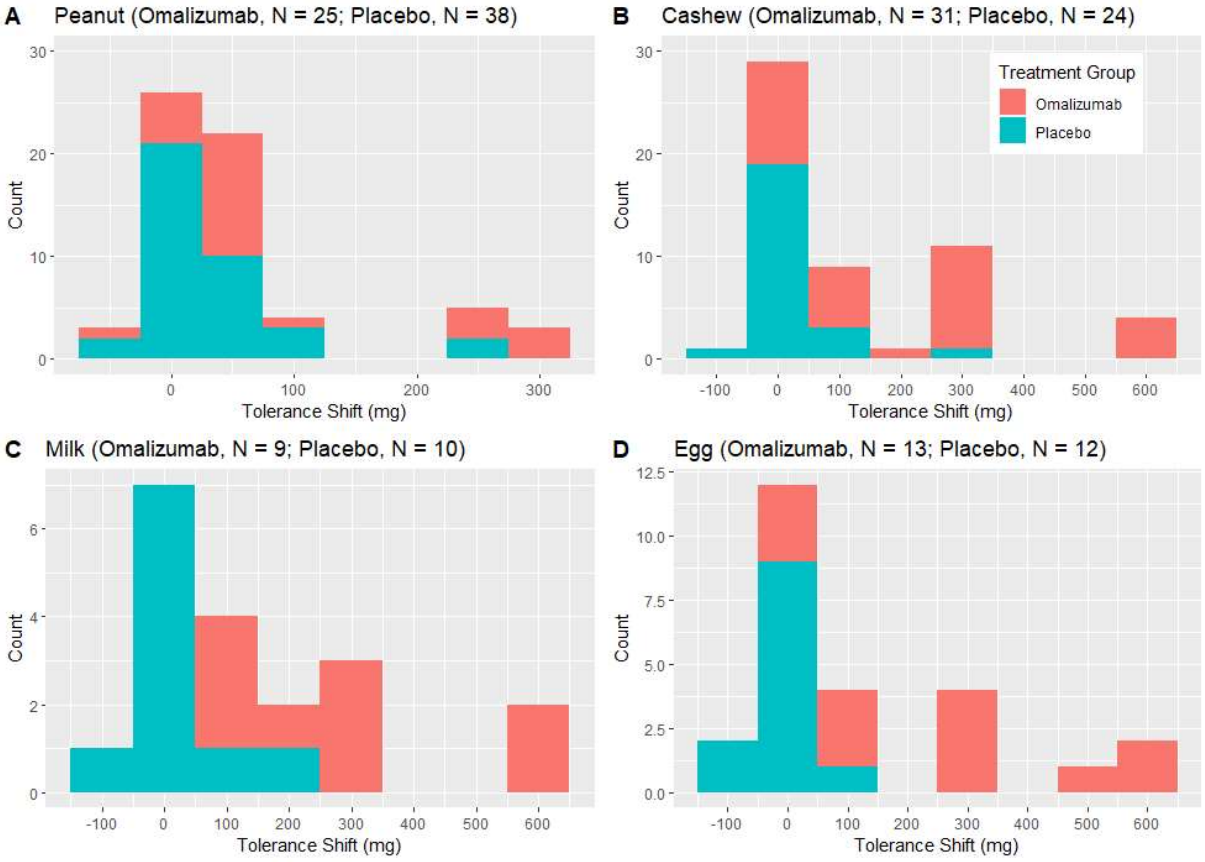
Source: Applicant's response to information request sent on October 19, 2023
* Met the primary endpoint and had no symptoms at doses up to and including 600 mg of peanut protein
** Met the respective key secondary endpoint and had no symptoms at doses up to and including 1000 mg of cashew/milk/egg protein
Abbreviations: DBPCFC, double-blind, placebo-controlled food challenge; n, number of responders; N, total number of subjects randomized in PFA-S1; PFA-S1, pediatric full analysis set – Stage 1

The Applicant further investigated the nonresponders from the primary and key secondary analyses in PFA-S1 who were on omalizumab to see if these subjects had positive shifts (increases) in maximum tolerated dose (MTD) from Screening to Stage 1, even though they did not meet the 600 mg (primary) or 1000 mg (key secondary) thresholds to be considered a success. For the primary endpoint (peanut), 1 had a decrease in MTD (30 mg during Screening to 3 mg in Stage 1), 2 had the same MTD during Screening and Stage 1 (30 mg), and 22 had increases in MTD (ranging from 9 mg to 300 mg). Similar trends were seen for cashew, milk, and egg. For cashew, 1 had a decrease in MTD (3 mg during Screening to 1 mg in Stage 1), 3 had the same MTD during Screening and Stage 1 (1 at 30 mg and 2 at 100 mg), and 33 had increases in MTD (ranging from 3 mg to 599 mg). For milk, 0 had a decrease in MTD, 0 had the same MTD during Screening and Stage 1, and 9 had increases in MTD (ranging from 70 mg to 570 mg). For egg, 0 had a decrease in MTD, 0 had the same MTD during Screening and Stage 1, and 13 had increases in MTD (ranging from 2 mg to 597 mg). Overall, a large majority of the nonresponders receiving omalizumab still achieved higher tolerances to peanut, cashew, milk, and egg protein (see Tables 5, 7, 9, and 11 in the Applicant's Clinical Overview for more details).

Histograms were used to more thoroughly explore shifts in MTD from Screening to Stage 1 for both responders and nonresponders in the omalizumab and placebo arms in PFA-S1. These tolerance shifts were calculated as the maximum tolerated dose in Stage 1 that was valid minus the maximum tolerated dose during Screening that was valid (validity was based on whether the subject successfully completed and passed the blinded OFC to placebo/oat). Figure 5 displays the distribution of tolerance shifts for the nonresponders in the omalizumab and placebo groups for all four foods. For cashew, milk, and egg (panels B, C, and D, respectively),

many of the nonresponders on omalizumab fall to the right of the nonresponders on placebo, signifying that most of the nonresponders on omalizumab did better than the nonresponders on placebo. However, this is not the case for peanut, as the right side of panel A is not as red-heavy as the other three panels.

Figure 5. Tolerance Shifts (Screening to Stage 1) for Nonresponders by Treatment Arm (PFA-S1, OUtMATCH)



Source: Statistical reviewer
Notes: Histogram bars are stacked; The following number of subjects were excluded from each panel due to invalid maximum tolerated doses: (A) 24, (B) 11, (C) 11, (D) 9; All results were obtained using R (version 4.3.1)
Abbreviations: N, number of nonresponders in the respective treatment arm with a valid shift in maximum tolerated dose; PFA-S1, pediatric full analysis set – Stage 1

Table 30 provides a breakdown of the tolerance shift distributions shown in Figure 5. For all four foods, the nonresponders on omalizumab generally had larger tolerance shifts compared to the nonresponders on placebo.

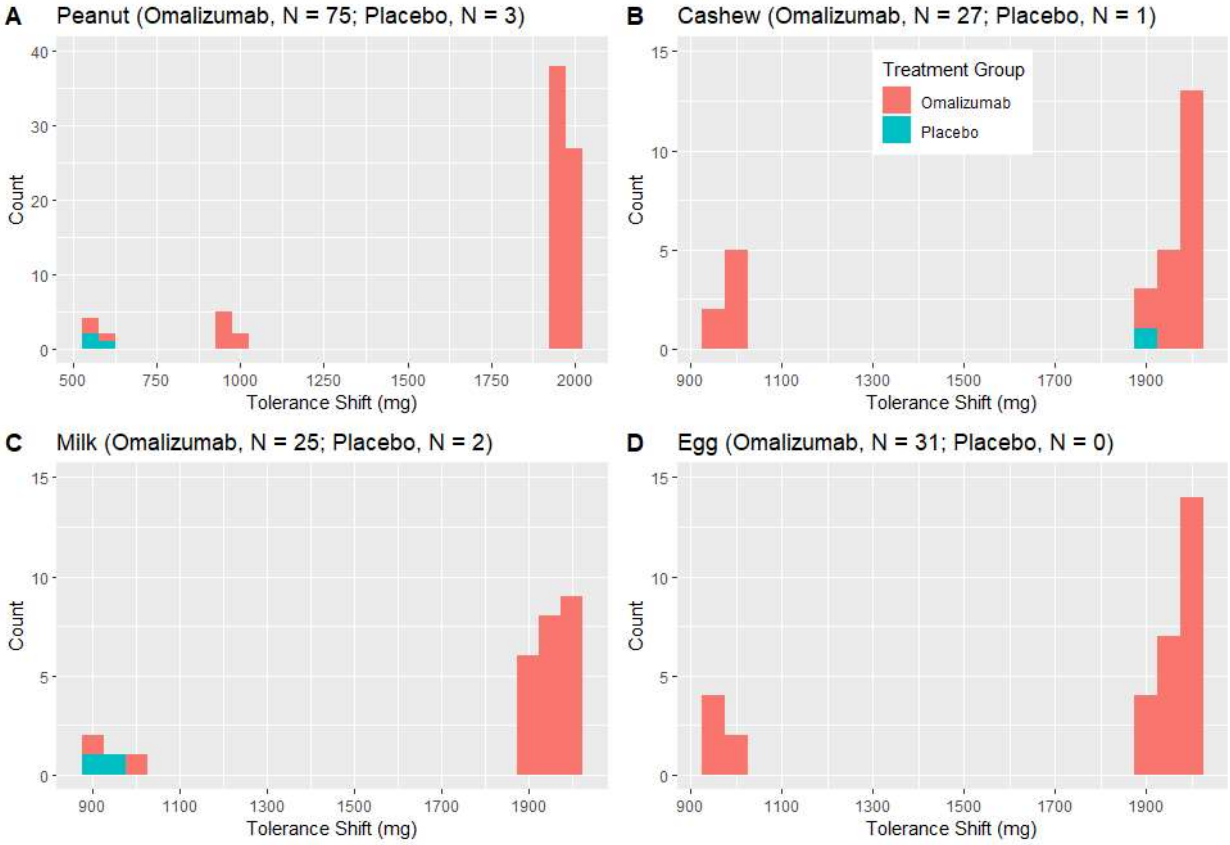
Table 30. Tabulation of Tolerance Shifts (Screening to Stage 1) for Nonresponders by Treatment Arm (PFA-S1, OUtMATCH)

Food Allergen, Tolerance Shift	Omalizumab n/N (%)	Placebo n/N (%)
Peanut		
≤0 mg	3/25 (12)	20/38 (53)
≤100 mg	19/25 (76)	36/38 (95)
≤300 mg	25/25 (100)	38/38 (100)
Cashew		
≤0 mg	5/31 (16)	16/24 (67)
≤100 mg	16/31 (52)	23/24 (96)
≤300 mg	27/31 (87)	24/24 (100)
Milk		
≤0 mg	0/9 (0)	4/10 (40)
≤100 mg	3/9 (33)	9/10 (90)
≤300 mg	7/9 (78)	10/10 (100)
Egg		
≤0 mg	0/13 (0)	9/12 (75)
≤100 mg	6/13 (46)	12/12 (100)
≤300 mg	10/13 (77)	12/12 (100)

Source: Statistical reviewer
Abbreviations: n, number of nonresponders with the respective tolerance shift; N, total number of nonresponders with a valid shift in maximum tolerated dose; PFA-S1, pediatric full analysis set – Stage 1

Tolerance shift was also assessed for the responders in the omalizumab and placebo arms in PFA-S1. Figure 6 shows that an overwhelming majority of subjects on omalizumab had tolerance shifts ≥1900 mg for all four foods (peanut: 65/75 [87%]; cashew: 20/27 [74%]; milk: 23/25 [92%]; egg: 25/31 [81%]). Since there were only a total of 6 responders on placebo, we cannot draw definitive conclusions about the placebo group. Unexpectedly, as shown in Panel B of Figure 6, 1 responder on placebo in the cashew group had a large shift in tolerance (~1900 mg). For reference, the smallest possible tolerance shift from Screening to Stage 1 for a responder in the peanut group was 300 mg, while it was 700 mg for the cashew, milk, and egg groups (this is due to the Screening and Stage 1 dosing schedules, the 600 mg threshold for the primary food [peanut], and the 1000 mg threshold for the key secondary foods [cashew, milk, and egg]).

Figure 6. Tolerance Shifts (Screening to Stage 1) for Responders by Treatment Arm (PFA-S1, OUtMATCH)



Source: Statistical reviewer
Notes: Histogram bars are stacked; All results were obtained using R (version 4.3.1)
Abbreviations: N, number of responders in the respective treatment arm with a valid shift in maximum tolerated dose; PFA-S1, pediatric full analysis set – Stage 1

Additionally, there was a total of 22 subjects in PFA-S1 (14 on omalizumab and 8 on placebo) who reported an accidental ingestion of a study food or any other food allergen during Stage 1. Tolerance shift, as defined above, was also investigated within this subgroup to gain insights into whether inadvertent exposure to a food allergen impacted efficacy. Among the 14 subjects who were on omalizumab, 12/14 (86%) met the primary endpoint (peanut), 4/8 (50%) met the cashew key secondary endpoint, 2/4 (50%) met the milk key secondary endpoint, and 4/8 (50%) met the egg key secondary endpoint. Most of these 14 subjects had high tolerance shifts (≥1900 mg), while there were no placebo responders across the four foods.

Since there were only 3 adult subjects enrolled in the trial, the Agency was also interested in looking at efficacy in the oldest group of subjects aged 16 to 17 years (N=14). Among these subjects, while no formal conclusions could be made due to the small sample sizes, there was higher response in the omalizumab arm compared to placebo for all four foods (Table 31).

Table 31. Efficacy in the Subgroup of Subjects Aged 16-17 Years (PFA-S1, OUtMATCH)

Food Allergen (Challenge Dose)	Omalizumab (n/N)	Placebo (n/N)	Proportion of Responders[a] (%)	Estimated Difference[b] (%)
Peanut (≥600 mg)	8/11	1/3	73 v 33	40
Peanut (≥1000 mg)	8/11	0/3	73 v 0	73
Cashew (≥1000 mg)	3/6	0/1	50 v 0	50
Milk (≥1000 mg)	3/3	0/0	100 v X	X
Egg (≥1000 mg)	3/5	0/1	60 v 0	60

Source: Statistical reviewer
[a] Displayed as omalizumab versus (v) placebo
[b] Calculated as omalizumab – placebo
Note: Undefined values are displayed as X; All results were obtained using R (version 4.3.1)
Abbreviations: n, number of responders; N, number of randomized subjects; PFA-S1, pediatric full analysis set – Stage 1

Furthermore, Table 32 provides a post-hoc comparison of efficacy across three age groups of interest (<6 years, 6 to 12 years, and 13 to 17 years). Overall, no notable trends in efficacy by age were identified.

Table 32. Efficacy Trends by Age Group (PFA-S1, OUtMATCH)

Food Allergen (Challenge Dose)	Age Group (years)	Omalizumab (n/N)	Placebo (n/N)	Proportion of Responders[a] (%)	Estimated Difference[b] (%)
Peanut (≥600 mg)	<6	29/45	2/21	64 v 10	54
	6-12	32/47	0/24	68 v 0	68
	13-17	14/18	1/10	78 v 10	68
Peanut (≥1000 mg)	<6	28/45	0/21	62 v 0	62
	6-12	32/47	0/24	68 v 0	68
	13-17	12/18	0/10	67 v 0	67
Cashew (≥1000 mg)	<6	11/22	1/9	50 v 11	39
	6-12	11/31	0/15	35 v 0	35
	13-17	5/11	0/6	45 v 0	45
Milk (≥1000 mg)	<6	14/21	1/10	67 v 10	57
	6-12	8/13	1/7	62 v 14	48
	13-17	3/4	0/2	75 v 0	75
Egg (≥1000 mg)	<6	19/28	0/11	68 v 0	68
	6-12	8/11	0/5	73 v 0	73
	13-17	4/7	0/3	57 v 0	57

Source: Statistical reviewer
[a] Displayed as omalizumab versus (v) placebo
[b] Calculated as omalizumab – placebo
Note: All results were obtained using R (version 4.3.1)
Abbreviations: n, number of responders; N, number of randomized subjects; PFA-S1, pediatric full analysis set – Stage 1

Furthermore, Table 33 shows the proportion of subjects in PFA-S1 who were able to achieve a cumulative dose >1000 mg, and the maximum cumulative dose of 6044 mg, for peanut, cashew, milk, and egg. Across the four foods, 54 to 79% of subjects on XOLAIR were able to achieve a cumulative dose >1000 mg compared to only 0 to 17% on placebo. Furthermore, 28 to 65% of subjects on XOLAIR were able to achieve the maximum cumulative dose of 6044 mg compared to 0% on placebo.

Table 33. Response Rates for Cumulative Doses of Peanut, Cashew, Milk, and Egg Protein (PFA-S1, OUtMATCH)

Food Allergen, Cumulative Dose	Omalizumab (n/N)	Placebo (n/N)	Proportion of Responders[a] (%)	Estimated Difference[b] (%)
Peanut				
>1000 mg	75/100	3/41	75 v 7	68
6044 mg	50/100	0/41	50 v 0	50
Cashew				
>1000 mg	31/57	1/24	54 v 4	50
6044 mg	16/57	0/24	28 v 0	28
Milk				
>1000 mg	27/34	2/12	79 v 17	62
6044 mg	22/34	0/12	65 v 0	65
Egg				
>1000 mg	34/44	0/12	77 v 0	77
6044 mg	23/44	0/12	52 v 0	52

Source: Statistical reviewer
[a] Displayed as omalizumab versus (v) placebo
[b] Calculated as omalizumab – placebo
Note: All results were obtained using R (version 4.3.1)
Abbreviations: n, number of responders; N, number of randomized subjects with a valid cumulative dose; PFA-S1, pediatric full analysis set – Stage 1

For Stage 1 OLE, all efficacy endpoints were exploratory, summarized descriptively (no formal statistical testing was completed), and were similar or identical to those defined in Stage 1. In Stage 1 OLE, longer-term efficacy was evaluated among the 59 pediatric subjects who completed Stage 1. While longer-term efficacy cannot be established from uncontrolled, open-label studies, such as Stage 1 OLE, the proportion of responders who received omalizumab in Stage 1 (N=38) were numerically improved for all four foods by the end of Stage 1 OLE (peanut: 71% to 74%; cashew: 33% to 61%; milk: 69% to 81%; egg: 72% to 89%). Subjects who received placebo in Stage 1 (N=21) also responded favorably to omalizumab by the end of Stage 1 OLE. Results are shown in Table 34.

Table 34. DBPCFC Response Rates for a Single Dose of ≥600 mg of Peanut Protein and ≥1000 mg of Cashew, Milk, and Egg Protein (PFA-S1OLE, OUtMATCH)

	Stage 1		Stage 1 OLE	
Food Allergen, Challenge Dose	**Omalizumab (N=38)**	**Placebo (N=21)**	**Omalizumab (N=38)**	**Placebo (N=21)**
Peanut, ≥600 mg	27 (71.1%)	0 (0%)	28 (73.7%)	14 (66.7%)
Cashew, ≥1000 mg	6 (33.3%)	0 (0%)	11 (61.1%)	4 (44.4%)
Milk, ≥1000 mg	11 (68.8%)	0 (0%)	13 (81.3%)	6 (66.7%)
Egg, ≥1000 mg	13 (72.2%)	0 (0%)	16 (88.9%)	5 (55.6%)

Source: Interim CSR (dated June 30, 2023), Tables 14.2.4.1 – 14.2.4.4, p. 303-306
Abbreviations: DBPCFC, double-blind, placebo-controlled food challenge; N, number of subjects randomized in PFA-S1OLE; PFA-S1OLE, pediatric full analysis set – Stage 1 open-label extension

An overview of the Stage 1 and Stage 1 OLE efficacy analyses conducted is provided in Table 6 of the Applicant's interim CSR (dated June 30, 2023).

Data Quality and Integrity

Data for each subject were recorded on a case report form (CRF). Data collection was completed for each subject for whom an informed consent form was signed. In accordance with good clinical practice and ICH guidelines, the trial monitor conducted source document verification and requested clarification at regular intervals to ensure that the data collected in the CRF were accurate, complete, and reliable. The trial monitor had the responsibility of assessing the progress of the trial, checking that the informed consent forms had been signed by the subject, and ensuring adherence to and compliance with the trial protocol and other trial-related documents. The PI was required to provide the following authorities with direct access to all trial-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs: the trial monitor, the institutional review board, the Applicant's internal auditors, and regulatory representatives.

(b) (4) was responsible for activities associated with the data management for this trial. This included setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical trial was handled according to the relevant standard operating procedures of the data management and biostatistics departments of the Applicant/contract research organization. Trial centers entered data directly into the CRF. All data was to be verifiable against source documents at the trial center. Any changes to the data entered in the CRF were to be recorded in the audit trail and were to be compliant with FDA Code of Federal Regulations (CFR) Title 21 Part 11. Medical coding used Medical Dictionary for Regulatory Activities (MedDRA; Version 22.0) for concomitant diseases and AEs and World Health Organization Drug (V2019-MAR) for medications. Missing or inconsistent data were queried for clarification. Subsequent modifications to the CRFs were documented.

8.1.13. Assessment of Efficacy Across Trials

The Applicant conducted a single adequate and well-controlled trial (Stage 1) of 16 to 20 weeks duration in 168 subjects (165 pediatric, 3 adults) with multifood allergies. The Applicant also conducted an open-label trial (Stage 1 OLE) of 24 to 28 weeks duration in 60 subjects who completed Stage 1 (59 pediatric, 1 adult).

Primary Endpoints

The primary endpoint in Stage 1 was met and demonstrated a highly significant improvement for subjects on omalizumab compared to placebo. The treatment difference estimate (omalizumab – placebo) was 62.7% [95% CI: 50.4%, 72.1%; p<0.0001]. The primary treatment effect was generally preserved across the subgroup and supplementary/supportive analyses described in Section 8.1.10.

Secondary and Other Endpoints

All three key secondary endpoints in Stage 1 were also met and demonstrated highly significant improvements for subjects on omalizumab compared to placebo. The treatment difference (omalizumab – placebo) estimates for cashew, milk, and egg were 38.9% (95% CI: 22.6%, 52.0%), 55.3% (95% CI: 29.8%, 71.9%), and 67.4% (95% CI: 48.5%, 79.2%), respectively. The key secondary treatment effects were also generally preserved across the supplementary and supportive analyses described in Section 8.1.10.

Additional Efficacy Consideration: Confirmatory Evidence

Confirmatory evidence to support SEE is provided by mechanistic evidence. Mechanistic evidence to support the effectiveness of omalizumab in the treatment of IgE-mediated food allergy includes: 1) a well understood pathophysiology of IgE-mediated food allergy that is driven by allergen-specific IgE acting through FcεR1 receptors on mast cells and basophils, and 2) the well-defined mechanism of action of omalizumab in binding IgE and preventing binding of IgE to FcεR1 (reductions of free IgE levels [not bound to omalizumab] result in downregulation of FcεR1 on mast cells and basophils). Downregulation of FcεR1 on mast cells and basophils is the major downstream mechanism of action of omalizumab that reduces effector cell reactivity with food allergen exposure. Consistent with pharmacodynamic data from the development programs for the other omalizumab indications, about 97% of subjects treated with omalizumab in the OUtMATCH trial had Week 16 free IgE values below 20 IU/mL (~50 ng/mL), across age groups and dosing regimens, including in children 1 to 5 years of age. Although only 3 adults were enrolled in the OUtMATCH trial, the mechanism of action of omalizumab in the treatment of IgE-mediated food allergy extends across the age spectrum; as a result, extrapolation of efficacy data from subjects 1 to 17 years of age (165/168 subjects) in the OUtMATCH trial to the >18 years of age population, with PK matching, is supported.

As noted above, omalizumab decreases the level of serum free IgE and decreases FcεRI density on effector cells; this mechanism of action is not allergen-specific (i.e., should affect IgE-mediated food allergy independent of IgE specificity). Based on this mechanism of action, it is expected that the efficacy findings from the OUtMATCH trial can be extended to IgE-mediated allergy to other foods not assessed in the trial.

8.1.14. Integrated Assessment of Effectiveness

To support this application, the Applicant, working with NIAID and the NIAID CoFAR, conducted a single adequate and well-controlled trial (OUtMATCH). The trial enrolled subjects with IgE-mediated allergy to peanut and two of the following foods: milk, egg, wheat, cashew, hazelnut, or walnut. Prior to randomization, subjects had to demonstrate moderate-severe dose-limiting symptoms to peanut protein via DBPCFC, at a threshold of ≤100 mg, and two additional foods, at a threshold of ≤300 mg food protein, providing an objective measure of food allergy reactivity at baseline. Following screening, 168 subjects (1 to 28 years of age) with confirmed multifood allergy were randomized to receive either omalizumab or placebo at a 2:1 ratio. Following 16 to 20 weeks of treatment, DBPCFCs were repeated.

The primary endpoint, the proportion of subjects who were able to consume a single dose of ≥600 mg of peanut protein without moderate-severe dose limiting symptoms (responders) in the omalizumab arm compared to placebo, was met:

- Peanut: 68.2% vs 5.5% (Difference: 62.7%, 95% CI: [50.4%, 72.1%], p<0.0001)

The key secondary endpoints, the proportion of subjects who were able to consume a single dose of ≥1000 mg of non-peanut food protein without moderate-severe dose limiting symptoms (responders) in the omalizumab arm compared to placebo, were also met:

- Cashew: 42.2% vs 3.3% (Difference: 38.9%, 95% CI: [22.6%, 52%], p<0.0001)
- Milk: 65.8% vs 10.5% (Difference: 55.3%, 95% CI: [29.8%, 71.9%], p<0.0001)
- Egg: 67.4% vs 0% (Difference: 67.4%, 95% CI: [48.5%, 79.2%], p<0.0001)

The trial design of OUtMATCH was robust, with objective primary and key secondary endpoints; the trial results were highly statistically significant and clinically meaningful, providing strong support for the efficacy of omalizumab for the new indication. There is an unmet need for treatments for patients with allergy to one or more foods to reduce the risk for serious outcomes, most notably fatal anaphylaxis. Given the strength of the OUtMATCH trial design and the persuasiveness of the trial results, along with the strength of the mechanistic evidence, SEE has been demonstrated.

8.2. Review of Safety

Safety review of omalizumab for the IgE-mediated food allergy indication included review and verification of safety results from the OUtMATCH trial (Stage 1 and Stage 1 OLE) submitted with

this application, and review of the Summary of Clinical Safety and relevant sections of the clinical study report.

8.2.1. Safety Review Approach

Omalizumab has been marketed since 2003, with postmarketing exposure estimated at 1,992,779 patient treatment years (Periodic Safety Update Report, up to December 31, 2022). As a result, safety has been extensively assessed in patients ≥6 years of age, including in the postmarketing setting. The safety review of this program is based on safety findings from the OUtMATCH trial, specifically on the 165 pediatric subjects 1 to 17 years of age. Although adults were eligible for this trial, only 3 were enrolled (males 18, 20, and 28 years of age); therefore, safety data for adults in the OUtMATCH trial are very limited. Since prior approvals for omalizumab were limited to patients ≥6 years of age, a particular focus of this safety review will be on the cohort of children 1 to 5 years of age.

The primary safety review focuses on the safety data set from Stage 1 (PSS-S1). Safety review of data from the Stage 1 OLE trial is reviewed separately given that is an open-label extension trial with no comparator (PSS-S1OLE).

8.2.2. Review of the Safety Database

The safety database was adequate to support this review of safety.

8.2.3. Overall Exposure

Subjects in OUtMATCH were randomized to receive placebo or omalizumab, either every 2 weeks or every 4 weeks, with dose and dosing interval based on weight and pretreatment total serum IgE level (Table 3). Planned duration of treatment in Stage 1 was 16 to 20 weeks.

In Stage 1, the distribution of subjects randomized to Q2 weeks and Q4 weeks dosing schedules was identical between placebo and treatment arms, with 58% in each arm on a Q2 week schedule and 42% on a Q4 week schedule. Most subjects received the study treatment for the entire planned duration of Stage 1. In the omalizumab arm, 74 subjects (67%) had a treatment duration between 16 and 20 weeks and 28 subjects (26%) had a duration >20 weeks. In the placebo arm, 32 subjects (58%) had a treatment duration between 16 and up to 20 weeks and 20 subjects (36%) had a treatment duration >20 weeks. Treatment duration was similar between treatment arms, with mean treatment duration for the omalizumab arm of 142 days and a mean treatment for the placebo arm of 149 days. Treatment duration was similar regardless of dosage frequency. In addition, assigned doses (75 to 600 mg) were similar between omalizumab and placebo arms, both for Q2 weeks dosing and Q4 weeks dosing (Table 35).

Table 35. Exposure for Pediatric Safety Set Stage 1 (PSS-S1, OUtMATCH)

Exposure	Omalizumab (N=110)	Placebo (N=55)	Total (N=165)
Received at least one injection of study drug	110 (100)	55 (100)	165 (100)
Dosing schedule			
Every 2 weeks	64 (58)	32 (58)	96 (58)
Every 4 weeks	46 (42)	23 (42)	69 (42)
Total duration of exposure (days)			
Mean (SD)	142 (56)	149 (54)	145 (55)
Median (Min, Max)	127 (30, 332)	131 (96, 311)	128 (30, 332)
Total duration of exposure (weeks)			
[4,8) weeks	1 (1)	0	1 (1)
[8,12) weeks	2 (2)	0	2 (1)
[12,16) weeks	5 (5)	3 (6)	8 (5)
[16, 20] weeks	74 (67)	32 (58)	106 (64)
>20 weeks	28 (26)	20 (36)	48 (29)
Duration of exposure (days) after restart from study hold if applicable			
Mean (SD)	125 (18)	128 (13)	126 (16)
Median (Min, Max)	126 (30, 168)	127(96, 153)	126(30, 168)
Duration of exposure (weeks) after restart from study hold if applicable			
[4, 8) weeks	1 (1)	0	1 (1)
[8, 12) weeks	2 (2)	0	2 (1)
[12, 16) weeks	6 (6)	3 (6)	9 (6)
[16, 20] weeks	82 (75)	40 (73)	122 (74)
>20 weeks	19 (17)	12 (22)	31 (19)
Dosing every 2 weeks: Assigned dose (mg)			
150	13 (12)	7 (13)	20 (12)
225	15 (14)	4 (7)	19 (12)
300	11 (10)	5 (9)	16 (10)
375	8 (7)	3 (6)	11 (7)
450	11 (10)	8 (15)	19 (12)
525	2 (2)	1 (2)	3 (2)
600	4 (4)	4 (7)	8 (5)
Dosing every 2 weeks: Total duration of exposure (days)			
Mean (SD)	149 (60)	147.5 (42.69)	148.7 (54.63)
Median (Min, Max)	130 (30, 332)	132.0 (114, 279)	131.0 (30, 332)

Exposure	Omalizumab (N=110)	Placebo (N=55)	Total (N=165)
Dosing every 2 weeks: Total duration of exposure (weeks)			
[4, 8) weeks	1 (1)	0	1 (1)
[16, 20] weeks	46 (42)	19 (35)	65 (39)
>20 weeks	17 (16)	13 (24)	30 (18)
Dosing every 2 weeks: Duration of exposure after restart from study hold if applicable (days)			
Mean (SD)	128 (17)	131 (10)	129 (15)
Median (Min, Max)	128 (30, 160)	130 (114, 148)	129 (30, 160)
Dosing every 2 weeks: Duration of exposure after restart from study hold if applicable (weeks)			
[4, 8) weeks	1 (1)	0	1 (1)
[12, 16) weeks	1 (1)	0	1 (1)
[16, 20] weeks	52 (47)	23 (42)	75 (46)
>20 weeks	10 (9)	9 (16)	19 (12)
Dosing every 4 weeks: Assigned dose (mg)			
75	3 (3)	3 (6)	6 (4)
150	11 (10)	4 (7)	15 (9)
225	11 (10)	4 (7)	15 (9)
300	11 (10)	7 (13)	18 (11)
450	7 (6)	4 (7)	11 (7)
600	3 (3)	1 (2)	4 (2)
Dosing every 4 weeks: Total duration of exposure (days)			
Mean (SD)	132 (49)	152 (68)	139 (56)
Median (Min, Max)	119 (57, 324)	124 (96, 311)	119 (57, 324)
Dosing every 4 weeks: Total duration of exposure (weeks)			
[8, 12) weeks	2 (2)	0	2 (1)
[12,16) weeks	5 (5)	3 (6)	8 (5)
[16, 20] weeks	28 (26)	13 (24)	41 (25)
>20 weeks	11 (10)	7 (13)	18 (11)
Dosing every 4 weeks: Duration of exposure after restart from study hold if applicable (days)			
Mean (SD)	121 (19)	123 (14)	122 (18)
Median (Min, Max)	118 (57, 168)	119 (96, 153)	118 (57, 168)

Exposure	Omalizumab (N=110)	Placebo (N=55)	Total (N=165)
Dosing every 4 weeks: Duration of exposure after restart from study hold if applicable (weeks)			
[8, 12) weeks	2 (2)	0	2 (1)
[12, 16) weeks	5 (5)	3 (6)	8 (5)
[16, 20] weeks	30 (27)	17 (31)	47 (29)
>20 weeks	9 (8)	3 (6)	12 (7)

Source: OCS Analysis Studio, Custom Table Tool.
Abbreviations: PSS-S1, Pediatric Safety Set – Stage 1; SD, standard deviation

In the Stage 1 OLE trial, the 59 pediatric subjects (1 to 17 years of age) who progressed from Stage 1 to Stage 1 OLE, with all subjects receiving omalizumab, had a mean exposure of 196 days. Similar to the overall population in Stage 1, 37 (63%) received omalizumab Q2 weeks in the OLE and 22 (37%) received omalizumab Q4 weeks in the OLE (Table 36).

Table 36. Exposure for Pediatric Safety Set During OLE (PSS-S1OLE)

Exposure	Open-Label Omalizumab (N=59)
Received at least one injection of study drug	59 (100)
Dosing schedule	
Every 2 weeks	37 (63)
Every 4 weeks	22 (37)
Total duration of exposure (days)	
Mean (SD)	196 (42)
Median (Min, Max)	186 (161, 352)
Total duration of exposure (weeks)	
>20 weeks	59 (100)
Duration of exposure after restart from study hold if applicable (days)	
Mean (SD)	183 (12)
Median (Min, Max)	183 (161, 215)
Duration of exposure after restart from study hold if applicable (weeks)	
>20 weeks	59 (100)
Dosing every 2 weeks: Assigned dose (mg)	
150	7 (12)
225	7 (12)
300	6 (10)
375	5 (9)
450	10 (17)
600	2 (3)

Exposure	Open-Label Omalizumab (N=59)
Dosing every 2 weeks: Total duration of exposure (days)	
Mean (SD)	196 (40)
Median (Min, Max)	187 (169, 352)
Dosing every 2 weeks: Total duration of exposure (weeks)	
>20 weeks	37 (63)
Dosing every 2 weeks: Duration of exposure after restart from study hold if applicable (days)	
Mean (SD)	184 (11)
Median (Min, Max)	183 (169, 215)
Dosing every 2 weeks: Duration of exposure after restart from study hold if applicable (weeks)	
>20 weeks	37 (63)
Dosing every 4 weeks: Assigned dose (mg)	
75	2 (3)
150	4 (7)
225	5 (9)
300	6 (10)
450	5 (9)
Dosing every 4 weeks: Total duration of exposure (days)	
Mean (SD)	196 (47)
Median (Min, Max)	183 (161, 338)
Dosing every 4 weeks: Total duration of exposure (weeks)	
>20 weeks	22 (37)
Dosing every 4 weeks: Duration of exposure after restart from study hold if applicable (days)	
Mean (SD)	182 (14)
Median (Min, Max)	181 (161, 212)
Dosing every 4 weeks: Duration of exposure after restart from study hold if applicable (weeks)	
>20 weeks	22 (37)

Source: OCS Analysis Studio, Custom Table Tool.
Abbreviations: PSS-S1OLE, pediatric safety set – Stage 1 open-label extension; SD, standard deviation

8.2.4. Adequacy of the Safety Database

While the safety database is small (n=165), it is of sufficient size and duration to assess the safety of omalizumab for the IgE-mediated food allergy indication. The safety of omalizumab for other approved indications, including those ≥6 years of age, is well characterized and can be partially extrapolated to support safety of omalizumab for the new indication.

Since this will be the first approval for children 1 to <6 years of age, safety in this age subgroup (n=61) is reviewed separately; the safety database in this age subgroup is sufficient to assess safety for the new indication. There are no safety findings from prior studies in subjects ≥6 years of age that are expected to be of special significance in younger children. In addition, there are no on-target or off-target effects of omalizumab that are expected to influence development, including immune development, in the younger age cohort.

Only 3 adults were enrolled in OUtMATCH (18 to 28 years of age); safety in adults is supported by extrapolation of safety from the pediatric population in OUtMATCH (n=165) and the extensive safety database for omalizumab use in adults ≥18 years of age, including in the postmarketing setting, for currently approved indications. There are no safety findings from prior studies in subjects ≥6 years of age and no on-target safety concerns that are expected to be of special significance in adults treated for IgE-mediated food allergy.

8.2.5. Adequacy of Applicant's Clinical Safety Assessments

The clinical safety assessments provided by the Applicant are adequate to support the safety review.

8.2.6. Issues Regarding Data Integrity and Submission Quality

No data integrity issues were identified. The submission quality was sufficient to support the assessment of safety for the new indication. Additional details are discussed under the "Data Quality and Integrity" heading in Section 8.1.12.

8.2.7. Categorization of Adverse Events

Adverse events were captured by observing subjects, interviewing subjects (e.g., using checklists, structured questioning, diaries, etc.), receiving unsolicited complaints from subjects, and identifying abnormal values or results from clinical or laboratory evaluations. AEs were captured from the time of consent until a subject completed trial participation, defined as receiving the first injection of omalizumab in Stage 1 OLE, the first injection of omalizumab in Stage 2, or the final follow-up visit for those not enrolled in either.

The Applicant provided appropriate definitions for adverse events and treatment-emergent adverse events in the trial protocol and CSR. Adverse events were defined as any untoward or unfavorable medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related, in accordance with *21 CFR 312.32(a)*. Pre-existing diseases or conditions present or detected during the first time an assessment or laboratory measurement was done during the Screening Visit were considered AEs only if they changed in severity of grade from that timepoint. Vitals or laboratory measurements repeated for confirmation of the pre-existing disease or condition were not considered a different timepoint. Treatment-emergent adverse events (TEAEs) were defined as any AE that was newly developed

or that increased in severity following the first exposure to study drug through completion of Stage 1 participation. For purposes of this review, all summary tables present TEAEs.

Severe dose-limiting symptoms (Section 8.1.8) occurring during OFCs were considered adverse events; however, moderate dose-limiting symptoms (Section 8.1.8), since they defined the threshold at which most OFC were considered positive, were not considered adverse events to avoid artificially diluting AE incidence from OFCs.

Adverse events were mapped by system, organ, class (SOC) or preferred term (PT), according to the MedDRA dictionary, Version 22.0 terms. The Applicant's coding of verbatim terms to PTs was appropriate. Adverse events of special interest included anaphylactic reactions to omalizumab, potential drug-induced liver injury, suspected transmission of an infectious agent by the study drug, and any occurrences of overdose, medication errors, drug abuse, and drug misuse related to investigational product administration. The Applicant analyzed standardized MedDRA queries during their analyses.

PIs graded the severity of all nonallergic AEs experienced by the trial subjects according to the Grading Table for Non-Allergic Adverse Events Version 2.0, provided in the trial protocol. This grading table was based on the *FDA Guidance-Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* and adapted to make it applicable for the population under study. The modifications were drawn from grading scales from NIAID's Division of AIDS and Division of Microbiology and Infectious Diseases, the CTCAE Version 5.0, and the 2017 American Academy of Pediatrics updated Clinical Practice Guideline for Screening and Management of High Blood pressure in Children and Adolescents. Grading, according to the *Grading Table for Non-Allergic Adverse Events Version 2.0* is as follows:

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Life-Threatening
- Grade 5 = Death

Anaphylaxis was graded using the *CoFAR Grading Scale for Systemic Allergic Reactions Version 3.0*, provided in the trial protocol.

Serious adverse events were defined as:

- Death
- A life-threatening event: An AE or serious adverse reaction is considered "life-threatening" if, in the view of either the PI or Sponsor, Division of Allergy, Immunology, and Transplantation/NIAID, its occurrence places the subject at immediate risk of death. It does not include an AE or serious adverse reaction that, had it occurred in a more severe form, might have caused death.
- In-patient hospitalization or prolongation of existing hospitalization.

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly or birth defect
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

8.2.8. Routine Clinical Tests

Routine clinical tests for safety, including complete blood count, complete metabolic panel, and urinalysis, were obtained every 3 months. A pregnancy test was collected monthly in women of childbearing age.

8.2.9. Safety Results

The safety review provided by the Applicant was thoroughly evaluated by the clinical review team. The following sections summarize the safety results of the OUtMATCH trial (Stage 1 and Stage 1 OLE) from our review.

8.2.10. Overview

An overview of subjects with TEAEs in the primary safety pool (PSS-S1, OUtMATCH) is provided in Table 37. The percentage of subjects with reported treatment-emergent adverse events was greater in the placebo treatment group (43 reports, 78%) compared to omalizumab group (69 reports, 63%); the 69 subjects in the omalizumab arm experienced 216 TEAEs, and the 43 subjects in the placebo arm experienced 130 TEAEs. In the omalizumab arm, most subjects with reported AEs experienced Grade 1 or Grade 2 AEs.

Table 37. Overview of Treatment-Emergent Adverse Events From Stage 1 (PSS-S1, OUtMATCH)

Event Category	Omalizumab N=110 n (%)	Placebo N=55 n (%)
AEs reported	69 (63)	43 (78)
SAE	3 (3)	1 (2)
SAEs with fatal outcome	0	0
AE leading to permanent discontinuation of study drug	1 (1)	0(0)
AE leading to study drug interruption	3 (3)	0 (0)

Event Category	Omalizumab N=110 n (%)	Placebo N=55 n (%)
AE	69 (63)	43 (78)
Death	0	0
Grade 5	0	0
Grade 4	2 (2)	1 (2)
Grade 3	2 (2)	10 (18)
Grade 2	31 (28)	18 (33)
Grade 1	34 (31)	14 (26)

Source: CSR and OCS Analysis Studio, Safety Explorer.
Abbreviations: AE, adverse event; PSS-S1, Pediatric Safety Set – Stage 1; SAE, serious adverse event

8.2.11. Deaths

There were no deaths reported during Stage 1 or Stage 1 OLE of the OUtMATCH trial.

8.2.12. Serious Adverse Events

During Stage 1 of the OUtMATCH trial, there were 4 serious adverse events (SAEs) reported, 3 in the omalizumab arm (3%) and 1 in placebo arm (2%) (Table 38). All SAEs were single reports, involving different SOCs.

Table 38. Summary of SAEs by SOC and PT – PSS-S1

System Organ Class Preferred Term	Omalizumab N=110 n	(%)	Placebo N=55 n	(%)
Any SAE	3	(3)	1	(2)
General disorders and administration site conditions	**1**	**(1)**	**0**	**(0)**
Systemic inflammatory response syndrome	1	(1)	0	(0)
Infections and infestations	**1**	**(1)**	**0**	**(0)**
Infectious mononucleosis	1	(1)	0	(0)
Investigations	**1**	**(1)**	**0**	**(0)**
Liver function test increased	1	(1)	0	(0)
Immune system disorders	**0**	**(0)**	**1**	**(2)**
Hypersensitivity	0	(0)	1	(2)

Source: OCS Analysis Studio, Safety Explorer.
Abbreviations: PSS-S1, pediatric safety set – Stage 1; PT, preferred term; SAE, serious adverse event; SOC, system organ class

Descriptions of the three SAEs reported in the omalizumab arm are provided:

(1) A 23-month-old male randomized to receive omalizumab 150 mg Q4 weeks was noted to have increased liver function test results, grade 2. He received his first dose of omalizumab on (b) (6) On (b) (6) increased liver function tests were detected during a routine comprehensive metabolic panel: alanine aminotransferase (ALT) 171 u/L, alkaline phosphatase (ALP) 457 u/L. At the time, the subject was recovering from a recent episode of croup that had been treated with Decadron, racemic epinephrine, and prednisolone, prior to the laboratory evaluation; the PI/Protocol Chair and Medical Monitor discussed the elevated laboratory values, thought they could be related to the croup, and recommended repeating the liver function tests prior to the next injection (injection #4). On (b) (6), repeat labs demonstrated improvements in results- ALT 87 u/L, ALP 591 u/L. Due to the downward trend, the Investigator allowed another injection. The final injection was administered on (b) (6). On (b) (6), repeat complete metabolic panel revealed ALT 121 u/L, ALP 564 u/L, aspartate aminotransferase (AST) 85 u/L. Upon review and discussion with the PI/Protocol Chair, Co-PI and the Medical Monitor, it was felt that the liver function tests were moving in a concerning direction and the decision was made to withdraw the study drug and unblind the treatment. The event did not meet the definition for an adverse event of special interest (AESI) of drug-induced liver injury. The SAE of increased liver function tests was considered to be grade 2 (moderate) and recovered/resolved on (b) (6). The event was considered by the investigator to be possibly related to study treatment.

(2) A 12-year-old female randomized to receive omalizumab 300 mg Q4 weeks was reported with systemic inflammatory response syndrome, grade 4. She received her first dose of omalizumab on (b) (6), and was diagnosed with COVID-19 on (b) (6) (she had received the Pfizer SARS-CoV-2 vaccine on (b) (6) (b) (6) She received her second dose of omalizumab on (b) (6) On (b) (6) she developed systemic symptoms of fever and swollen lymph nodes. She eventually was admitted to the Pediatric Emergency Department and Pediatric Intensive Care Unit and was diagnosed with multisystem inflammatory syndrome (MIS-C). She was discharged from the hospital on (b) (6), on daily low dose aspirin and rivaroxaban, and the event was considered resolved. The event was considered by the investigator to be not related to study treatment; rather, a previous COVID-19 infection was considered a contributing factor to the SAE. The subject remained in the trial and restarted treatment on (b) (6), and completed Stage 1 on (b) (6)

(3) A 7-year-old female randomized to receive omalizumab 225 mg Q4 weeks was reported with infectious mononucleosis, grade 4, that met AESI criteria and resulted in discontinuation. She received her first dose of omalizumab on (b) (6). On (b) (6) safety labs were drawn which demonstrated elevated liver function tests- AST 289 u/l, ALT 422 u/L, with normal bilirubin and no change in ALP from

baseline- white blood cell count 5.0, with 22% atypical lymphocytes (noted as suspect benign reactive). Repeat bloodwork done on (b) (6), revealed continued elevation of liver function tests- ALT 659 u/L, AST 353 u/L- white blood cell count 11.6, with 31% atypical lymphocytes. She developed fever and sore throat a few days later and was diagnosed with infectious mononucleosis. The subject discontinued from the trial due to this event. The investigator considered that this event was not related to study treatment.

Reviewer comment: It is unclear whether the increased liver function tests (LFTs) are due to mononucleosis versus treatment arm, as the increased in LFTs preceded mononucleosis diagnosis.

Of note, there was an additional SAE reported in the trial; however, since this was in an 18-year-old, it was not included the primary safety analysis:

An 18-year-old male randomized to receive omalizumab 300 mg Q4 weeks was reported with suicidal ideation, grade 4 and depression, grade 4. He reported an SAE of hypersensitivity (systemic allergic reaction) during a screening oral food challenge, which is not included in our safety analysis, since it occurred before the first dose of omalizumab was administered. He received his first dose of omalizumab on (b) (6); his most recent dose prior to the event was on (b) (6) On (b) (6) the subject was admitted to an in-patient psychiatric hospital for suicidal ideation. Family reported subject has had a steady change in behavior and had a past history of Prozac and Ritalin use. The event was considered by investigator not to be related to study treatment, but the subject discontinued from the trial on (b) (6), due to subject decision.

8.2.13. Dropouts and/or Discontinuations Due to Adverse Effects

There was one AE that led to discontinuation (PT: liver function increased)- SAE case #3 discussed in Section 8.2.12.

8.2.14. Adverse Events and Adverse Reactions

For AEs reported in ≥5% in either treatment group in Stage 1, not restricted to those occurring more commonly in the omalizumab arm that the placebo arm, the most common AEs reported were hypersensitivity, injection site reaction, coronavirus infection, pyrexia, upper respiratory tract infection, urticaria, viral infection, asthma, diarrhoea, gastroenteritis, and vomiting (Table 39). Among the hypersensitivity AEs, 19 subjects experienced AEs that met Sampson's criteria for anaphylaxis; however, all episodes occurred prior to DBPCFC or during DBPCFC and were considered not related to study treatment. No episodes of anaphylaxis consistent with Sampson's criteria were reported in Stage 1 OLE.

Table 39. Treatment-Emergent AEs (≥5% in Either Treatment Group), Stage 1 Pediatric Population

System Organ Class Preferred Term	Omalizumab N=110 n	 (%)	Placebo N=55 n	 (%)
Hypersensitivity	17	(16)	18	(33)
Injection site reaction	11	(10)	5	(9)
Corona virus infection	8	(7)	3	(6)
Pyrexia	7	(6)	2	(4)
Upper respiratory tract infection	5	(5)	3	(6)
Urticaria	4	(4)	3	(6)
Viral infection	4	(4)	3	(6)
Asthma	4	(4)	3	(6)
Diarrhoea	4	(4)	3	(6)
Gastroenteritis	2	(2)	3	(6)
Vomiting	5	(5)	1	(2)

Source: Clinical Reviewer, OCS Analysis Studio, Safety Explorer.
Abbreviations: AE, adverse event

Among the AEs that occurred in ≥3% and more frequently in the omalizumab arm than in the placebo arm, the most common were injection site reaction, coronavirus infection, pyrexia, atopic dermatitis, and vomiting (Table 40).

Table 40. Treatment-Emergent AEs Occurring ≥3% Frequency and Occurring More Frequently in Treatment Arm Than Placebo, Primary Safety Population, Stage 1

System Organ Class Preferred Term	Omalizumab N=110 n	 (%)	Placebo N=55 n	 (%)
Injection site reaction	17	(16)	6	(11)
Corona virus infection	8	(7)	3	(6)
Pyrexia	7	(6)	2	(4)
Dermatitis atopic	7	(6)	2	(4)
Vomiting	5	(5)	1	(2)
Viral upper respiratory tract infection	3	(3)	0	(0)
Nasal congestion	3	(3)	1	(2)
Tooth extraction	3	(3)	0	(0)

Source: Clinical Reviewer, OCS Analysis Studio, Safety Explorer.
* Injection site reactions terms: 'injection site reaction','injection site urticaria','injection site discomfort','injection site erythema','injection site pain' and 'injection site rash'
* Dermatitis atopic terms: 'dermatitis atopic' and 'eczema'

Adverse reactions were characterized based on suspected causal relationship, following assessment of seriousness, severity, frequency, and strength of causal relationship. When linking causality, common adverse reactions that occurred in ≥3% of subjects, and greater in the

treatment arm than in placebo, included only injection site reaction and pyrexia, and are included in labeling.

8.2.15. Laboratory Finding

Laboratory tests (complete metabolic panel and complete blood count) were obtained at baseline and routinely during the trial. No significant differences were identified between treatment arms. An evaluation of drug-induced serious hepatotoxicity was performed and no subjects in the treatment groups met criteria as a possible Hy's law case. Two subjects in the omalizumab group ALT values >3x the upper limit of normal. These narratives were discussed in the SAE discussion in Section 8.2.12.

8.2.16. Vital Signs

Vital signs were collected during the trial. Mean and median values and changes from baseline were comparable between the omalizumab and placebo arms.

8.2.17. Stage 1 OLE

The first 60 subjects who completed Stage 1 were enrolled in the open label extension stage of the trial. The PSS-S1OLE consists of the 59 subjects ≤17 years of age enrolled in the OLE trial. Overall, the safety results from the OLE were comparable to the TEAE reports from the Stage 1 portion. Data interpretation is limited as there is no placebo comparator. Forty-two subjects (71%) reported at least one AE during the OLE portion (126 TEAEs total), which is similar to the overall incidence in Stage 1. The most common AEs reported during the OLE portion are noted in Table 41. There were no deaths, SAEs, AESIs, or AEs leading to discontinuation during the OLE trial.

Table 41. Most Common AEs (≥5%), PSS-S1OLE

System Organ Class Preferred Term	Open-Label Omalizumab N=59 n	(%)
Any AE	42	(71)
Hypersensitivity	9	(15)
Injection site reaction	8	(14)
Nasopharyngitis	3	(5)
Upper respiratory tract infection	3	(5)
Epistaxis	3	(5)
Vaccination complication	3	(5)
Diarrhoea	3	(5)
Vomiting	3	(5)

Source: Clinical Reviewer, OCS Analysis Studio, Safety Explorer
Abbreviations: AE, adverse event; PSS-S1OLE, pediatric safety set – Stage 1 open-label extension

8.2.18. Analysis of Submission-Specific Safety Issues

Adverse events of special interest for omalizumab included:

- Suspected anaphylactic reactions to omalizumab, identified based on Sampson's criteria (Sampson et al. 2006).
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.
- Suspected transmission of an infectious agent by the study drug, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a subject exposed to a medicinal product. This term applies only when contamination of the study drug is suspected.
- Any occurrences of overdose, medication errors, drug abuse and drug misuse related to omalizumab administration.

8.2.19. Anaphylactic Reactions to XOLAIR

There were no anaphylactic reactions reported secondary to omalizumab administration. Although anaphylactic and hypersensitivity adverse events were reported, most occurred during the DBPCFCs, and none were considered causally related to omalizumab administration by the investigator.

8.2.20. Drug-Induced Liver Injury

There were no drug-induced liver injury events reported secondary to omalizumab administration.

8.2.21. Suspected Transmission of an Infectious Agent by the Study Drug

There was one subject who reported infectious mononucleosis in the omalizumab treatment arm. The AE was considered not related to study treatment and was graded as a grade 4 AE.

8.2.22. Overdose/Medication Errors/Drug Abuse or Misuse

There were no occurrences of overdose, medication errors, drug abuse, and drug misuse related to omalizumab administration.

8.2.23. Safety Analyses by Demographic Subgroups

IgE-mediated food allergy is the first indication for omalizumab approved for children <6 years of age; therefore, safety data for the 1 to 5-year-old subgroup of subjects was reviewed. In addition, safety in adults will also be briefly addressed since only three adults were enrolled in the trial, and, therefore, the primary safety population was solely in the pediatric population.

8.2.24. Safety in the 1 to 5 Years of Age Subgroup

Sixty-one children 1 to 5 years of age were enrolled in the OUtMATCH trial, with 41 subjects randomized to the omalizumab group and 20 subjects assigned to placebo group. Overall, 44 subjects (72%) <6 years of age experienced at least one AE, with 28 of 41 subjects (68%) in the omalizumab group experiencing at least 1 AE (99 total AEs in the 28 subjects) and 16 of the 20 subjects (80%) in the placebo group experiencing at least 1 AE (55 total AEs in the 16 subjects). Overall, 38% of AEs in this population were classified as grade 1, 30% as grade 2, and 5% as grade 3. No grade 4 or grade 5 AEs were reported in this population, and the occurrence of AEs by grade was similar between treatment groups. One of the 44 subjects receiving omalizumab experienced an SAE (grade 2)- a 23-month-old with increased liver function tests that resulted in trial withdrawal (Section 8.2.12).

When assessing AEs by SOC and PT in subjects <6 years old, compared to those ≥6 years old, there is an increase in AEs under: Infections and infestations; Respiratory, thoracic and mediastinal disorders; Gastrointestinal disorders; and Skin and subcutaneous disorders. Review of the PTs under these SOCs demonstrated a general increase in common disorders that affect the lower age group, such as viral infections, ear infection, gastroenteritis, cough, and pyrexia (Table 42). No AESIs or deaths were reported for either the omalizumab or placebo group. The frequency and severity of AEs for subjects <6 years old after randomization was similar to the frequency and severity of AEs for all subjects in the Stage 1 population.

Table 42. Treatment Emergent Adverse Events Occurring ≥3% Frequency and Occurring More Frequently in Subjects <6 Year of Age Compared to Subjects ≥6 Year of Age

System Organ Class Preferred Term	<6 yo (N=61)	≥6 yo (N=104)
Infections and infestations	23 (38)	22 (21)
Viral Infection	21 (34)	15 (14)
Ear infection	4 (7)	0
Gastroenteritis	6 (10)	2 (2)
Molluscum contagiosum	2 (3)	0
Impetigo	2 (3)	1 (1)
Otitis media	2 (3)	2 (2)
Respiratory, thoracic and mediastinal disorders	14 (23)	13 (13)
Cough	6 (10)	0
Asthma	3 (5)	4 (4)
Nasal congestion	3 (5)	1 (1)
Respiratory disorder	2 (3)	0
General disorders and administration site conditions	13 (21)	21 (20)
Pyrexia	5 (8)	4 (4)
Gastrointestinal disorders	8 (13)	11 (11)
Diarrhoea	5 (8)	2 (2)
Vomiting	3 (5)	3 (3)
Skin and subcutaneous tissue disorders	9 (15)	11 (11)
Dermatitis	5 (8)	2 (2)

Source: Clinical Reviewer, OCS Analysis Studio, Custom Table Tool.
*viral infection: upper respiratory tract infection, viral infection, coronavirus infection, viral upper respiratory tract infection, coxsackie viral infection, influenza, infectious mononucleosis, conjunctivitis viral
*gastroenteritis: gastroenteritis, gastroenteritis viral, gastrointestinal viral infection
*injection site reaction: injection site reaction, injection site erythema, injection site rash, injection site discomfort, injection site pain, injection site swelling, injection site urticaria

A total of 19 subjects <6 years of age were enrolled in the Stage 1 OLE trial. In this subgroup, 16 subjects (82%) experienced 59 AEs; 76% of the AEs were classified as grade 1 and 24% classified as grade 2, with no grade 3, 4, or 5 AEs reported. There were no deaths, no SAEs, no AESIs, and no TEAEs leading to trial withdrawal in this age subgroup. The frequency and severity of AEs in the <6-year-old cohort in the OLE phase was similar to that seen in the Stage 1 portion.

Given the small number of subjects <6 years of age enrolled in OUtMATCH, pediatric safety can be extrapolated from the subjects ≥6 years of age enrolled in OUtMATCH, and prior characterization of safety in children ≥6 years of age, since the central role of signaling through allergen-specific IgE is shared across the age spectrum and the since PK in the <6 years of age subpopulation is similar to the older age subgroups. There are no safety findings from prior studies in subjects ≥6 years of age that are expected to be of special significance in younger children, and there are no on-target or off-target effects of omalizumab that are expected to influence development, including immune development, in the younger age cohort.

8.2.25. Safety in Adults

Only three adults were enrolled in OUtMATCH, with two adult subjects randomized to receive omalizumab and one to placebo. Only one of the adult subjects (omalizumab arm) went on to the Stage 1 OLE as the other adult did not complete end of Stage 1 food challenges. Of the three subjects, 9 AEs were reported, including 2 serious AEs (depression and suicidal ideation-described in Section 8.2.12). Additional AEs reported include anaphylaxis (during OFC), hypersensitivity, asthma, ligament rupture, and ankle operation. None of the AEs led to trial withdrawal. Given the limited number of adults enrolled, safety review for this population is very limited.

Since the mechanism of IgE-mediated food allergy is similar in pediatric and adult populations, along with the known mechanism of action of omalizumab, extrapolation of safety can be made from the pediatric and adolescent population to adults. Extrapolation is also supported by the PK comparability in adults in comparison to the younger cohorts. There are no omalizumab safety findings from prior studies in subjects ≥6 years of age and no on-target safety concerns that are expected to be of special significance in adults treated for IgE-mediated food allergy.

8.2.26. 90-Day Safety Update

For the supplemental BLA submission, subjects randomized on or before July 8, 2022 (database freeze date February 2, 2023) were included from in the Interim Clinical Study Report and Summary of Clinical Safety. The Applicant aligned with the Agency during the pre-sBLA meeting on the proposed 90-day Safety Update Report. The Safety Update Report presents following safety results as of database freeze date of September 21, 2023:

- Safety data from the 12 subjects from Stage 1 who were randomized after July 8, 2022
- Safety data of 115 subjects from Stage 2 (8-week open-label omalizumab)

Stage 1

Of the 12 subjects randomized after July 8, 2022, eight were randomized to omalizumab and four to placebo. The median age of the 12 subjects was 4.5 years of age, with the majority under 6 years old (58%). Nine of the subjects experienced an AE. The most common (experienced by ≥2 subjects) AEs by preferred term in the omalizumab and placebo groups were hypersensitivity, eczema, nasopharyngitis, and rhinorrhea. These results are consistent with the AEs seen in Stage 1. The AEs that were reported in a greater percentage in the omalizumab arm than the placebo arm, and in more than one subject, include: ear infection and respiratory tract infection viral. The AEs were reported as mild (grade 1 or grade 2), except for one Grade 3 which was a PT of hypersensitivity that occurred during Stage 1 food challenge in the placebo arm. There were no deaths or SAEs.

Stage 2

A total of 180 subjects were randomized in the Stage 1 trial: 60 subjects entered the Stage 1 OLE. Of the remining 120 subjects, at total of 5 subjects did not complete Stage 1. 115 subjects entered the Stage 2 OLE omalizumab trial. Approximately 41% of the subjects were under 6 year of age, 38% 5 to <12 years of age, and 20% were 12 to <18 years of age, and one subject was 18 years of age or older. A total of 38 subjects reported an AE (total 60 AEs reported). The most common AE per PT reported were respiratory tract infection, coronavirus infection, gastroenteritis viral, and hypersensitivity. There were no deaths or SAEs. The majority of the AEs were grade 1 and grade 2, with only 2 reported as Grade 3. As this is an open label extension, safety data are limited given no compactor arm.

The 90-day safety report was limited given the small numbers and the open label extension design in Stage 2. However, no new safety signals were identified and were consistent with the safety review from Stage 1.

8.2.27. Integrated Assessment of Safety

The safety data submitted with this supplement were sufficient to assess the safety of omalizumab in the proposed IgE-mediated food allergy population. The safety data for omalizumab was provided by the single adequate and well controlled trial, OUtMATCH- Stage 1, that enrolled 165 children 1 to 17 years of age, of which 110 received omalizumab during the 16 to 20-week treatment period. A separate review assessed uncontrolled safety data from the 59 subjects (1 to 17 years of age) who were enrolled in the 24- to 28-week OLE trial, all of whom received omalizumab. Of note, 38 subjects in the OLE trial had been treated with omalizumab in the preceding 16-to-20-week Stage 1 trial.

To investigate submission-specific safety issues, this review performed safety analyses for known and potential safety signals identified during the review and from the known safety profile of omalizumab from development programs for the other approved indications and post marketing reports. There were no deaths in the development program. There were three SAEs that occurred in the omalizumab arm, with two possibly related to omalizumab (increase in LFTs that did not result in drug induced liver toxicity). There were no cases of anaphylaxis related to omalizumab administration. The most common adverse events that occurred more often in treatment group compared to placebo were injection site reactions, coronavirus infection, pyrexia, atopic dermatitis, and vomiting.

As this indication will be the first approved for subjects 1 to 5 years old, safety of this population was carefully reviewed. Only 41 omalizumab-treated subjects were in this cohort, limiting interpretation of safety for this age group, but results were consistent with those for subjects ≥6 years of age. As only 3 adults were enrolled in this trial, safety for the adult population was fully extrapolated from the pediatric and adolescent population for this trial, as well as from the safety results from development programs for other indications.

Overall, the safety of omalizumab in this trial aligned with the previous safety seen with omalizumab for the other approved indications. Given the benefit of omalizumab, the safety profile in subjects ≥1 year of age with food allergies is favorable.

8.3. Statistical Issues

There were a few minor statistical-related issues in this application, none of which substantially impacted our decision-making:

(1) In the Applicant's interim CSR (dated June 30, 2023), the population defined in the estimands for the primary and key secondary endpoints in Stage 1 was comprised of pediatric patients only, while the study objective specified by the Applicant was targeting pediatric and adult patients aged 1 year and older. Although the trial enrolled both adult and pediatric subjects, at the time of the prespecified interim analysis, only 3 adults were enrolled (aged 18, 20, and 28 years), though the Applicant planned to enroll adults up to less than 56 years of age. As discussed in Section 1.2 and Section 6.1, the mechanism of action of omalizumab in the treatment of IgE-mediated food allergy extends across the age spectrum; as a result, extrapolation of efficacy data from subjects 1 to 17 years of age to the >18 years of age population, with PK matching, is supported.

(2) While there was only a small amount of missingness for the primary (peanut: 2%) and key secondary (cashew: 4%; milk: 4%; egg: 2%) endpoints, the Applicant's analyses of the impact of the missing-not-at-random (MNAR) assumption on the primary and key secondary efficacy results were limited. The Applicant conducted completer analyses (excluding subjects with missing data for any reason) for the primary and key secondary endpoints, but these did not adequately evaluate the robustness of trial results to the MNAR assumption. Although the Applicant prespecified a tipping point analysis for the primary endpoint under the MNAR assumption in the SAP (version 2.0 [dated October 26, 2022]), this was not completed, as the Applicant stated in their interim CSR (dated June 30, 2023) that this analysis was not needed based on the interim results.

(3) Details and justification of the interim analysis, including the alpha allocation choices for the primary and key secondary endpoints, were not clearly specified in the Applicant's SAP. The alpha selections for the interim and final analyses were discussed with the Applicant during a Type B meeting with the Agency on June 27, 2023, under IND 005369. While the Applicant's alpha selections are not statistically problematic, they remain unclear. An information request was sent to the Applicant on October 25, 2023, but no clarity was provided in the Applicant's response received on October 27, 2023.

8.4. Conclusions and Recommendations

This supplement for omalizumab supports the addition of the following indication for IgE-mediated food allergy to labeling:

> *"IgE-mediated food allergy in adult and pediatric patients aged 1 year and older for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods. To be used in conjunction with food allergen avoidance."*

This supplement is supported by the results from a prespecified interim analysis of a single adequate and well-controlled trial that enrolled 168 participants (1 to 28 years of age) with DBPCFC-confirmed IgE-mediated food allergy to peanut (moderate-severe dose-limiting symptoms at ≤100 mg of peanut protein) and at least 2 other foods, including milk, egg, wheat, cashew, hazelnut, or walnut (moderate-severe dose-limiting symptoms at ≤300 mg of food protein). Following 16 to 20 weeks of treatment with omalizumab or placebo, the primary and key secondary endpoints were met:

Results of the post-treatment DBPCFCs demonstrated a higher proportion of responders who were able to consume a single dose of ≥600 mg of peanut protein without moderate-severe dose-limiting symptoms in the omalizumab arm compared to placebo:

- Peanut: 68.2% vs 5.5% (Difference: 62.7%, 95% CI: [50.4%, 72.1%], p<0.0001)

Results for the key secondary endpoints using the proportion of subjects able to consume ≥1000 mg of food protein to define responders similarly demonstrated a higher proportion of responders in the omalizumab arm compared to placebo:

- Cashew: 42.2% vs 3.3% (Difference: 38.9%, 95% CI: [22.6%, 52%], p<0.0001)
- Milk: 65.8% vs 10.5% (Difference: 55.3%, 95% CI: [29.8%, 71.9%], p<0.0001)
- Egg: 67.4% vs 0% (Difference: 67.4%, 95% CI: [48.5%, 79.2%], p<0.0001)

The trial design of OUtMATCH was robust, with objective primary and key secondary endpoints; the results were highly statistically significant and clinically meaningful, providing strong support for the efficacy of omalizumab for the proposed indication. There is an unmet need for treatments for patients with allergy to one or more foods to reduce the risk for serious outcomes, most notably fatal anaphylaxis. Given the strength of OUtMATCH trial design and the persuasiveness of the trial results, along with the strength of the mechanistic evidence, SEE has been demonstrated.

Omalizumab was first approved for asthma in 2003 and safety has been extensively studied in randomized controlled trials for other indications, specifically in subjects ≥6 years of age, as well as in the postmarketing setting, with an estimated cumulative exposure of 1,991,779 patient treatment years, as of December 31, 2022. No new safety signals were identified in the OUtMATCH trial, including no anaphylaxis events related to omalizumab administration. The

most common (≥3%) adverse reactions noted were injection site reactions and pyrexia. Since this will be the first approval of omalizumab for children 1 to 5 years of age, safety in this age cohort (n=61) was carefully reviewed and identified no new safety signals.

Overall, there is a favorable benefit-risk assessment for omalizumab in the treatment of IgE-mediated food allergy in adult and pediatric patients aged 1 year and older for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods. Approval of omalizumab for this new indication provides a treatment option for patients ≥1 year of age with allergy to one or more foods, particularly for those patients at highest risk for severe anaphylaxis, such as those with a prior history of anaphylaxis from accidental food ingestions, those with low food allergen thresholds for reactivity, and those with comorbid conditions, such as poorly controlled asthma.

9 Advisory Committee Meeting and Other External Consultations

Although approval of omalizumab for the IgE-mediated food allergy indication has the potential to have a significant impact on patient management, the review team did not identify questions regarding the clinical trial design, conduct of the trial, analysis of the data, or safety issues that required discussion at an Advisor Committee meeting.

10 Pediatrics

This sBLA submission includes data from children 1 to 17 years of age that supports approval for children ≥1 year of age. An Agreed iPSP (submitted on July 8, 2019) between FDA and the Applicant determined that a waiver in children <1 year of age was acceptable as the necessary studies are impossible or highly impracticable to conduct.

An Amended iPSP was submitted on April 17, 2023, in which it updated the filing plans for the sBLA. These amendments were agreed upon on August 2, 2023.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Table 43. Prescription Drug Labeling

Full Prescribing Information Sections	Rationale for Major Changes Incorporated Into the Finalized Prescribing Information (PI)
BOXED WARNING	N/A
1 INDICATIONS AND USAGE	Addition of a new subsection for the following new indication: XOLAIR is indicated for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods in adult and pediatric patients aged 1 year and older with IgE-mediated food allergy. XOLAIR is to be used in conjunction with food avoidance. <u>Limitations of Use:</u> XOLAIR is not indicated for the emergency treatment of allergic reactions, including anaphylaxis. *The team discussed the term, 'reduction' vs* [redacted] (b) (4) *in the indication statement and found 'reduction' to be a more meaningful term for healthcare professionals although* [redacted] (b) (4) *is the term used in the regulation.*
2 DOSAGE AND ADMINISTRATION	Addition of recommended dosage for IgE-mediated food allergy based on total serum IgE level (IU/mL), measured before the start of treatment, and by body weight, which are presented in a table.
4 CONTRAINDICATIONS	N/A

Continued

Table 43, continued

Full Prescribing Information Sections	Rationale for Major Changes Incorporated Into the Finalized Prescribing Information (PI)
5 WARNINGS AND PRECAUTIONS	In the [redacted] (b) (4) subsection, the team did not include Applicant's proposed new language for [redacted] (b) (4) Added a new subsection, **5.9 Potential Medication Error Related to Emergency Treatment of Anaphylaxis**, with the following language: XOLAIR should not be used for the acute treatment of allergic reactions, including anaphylaxis. In studies to [redacted] (b) (4) The safety and effectiveness of XOLAIR for treatment of allergic reactions, including anaphylaxis have not been established. Instruct patients that XOLAIR is for maintenance use to reduce allergic reactions, including anaphylaxis, while avoiding food allergens. *The 'Potential Medication Error Related to Emergency Treatment of Anaphylaxis' was added in this Section because the use-related risk analysis (URRA) showed there was risk of death if the user required emergency treatment of allergic reactions but administers XOLAIR instead of epinephrine. Please refer to Human Factors Validation Results review dated February 2, 2024.*
6 ADVERSE REACTIONS	**Clinical Trials Experience** subsection updated with safety data from Food Allergy clinical study with the following heading: 'Adverse Reactions from a Clinical Study in Patients with IgE-Mediated Food Allergy.' *The safety data presented in this section is based on pediatric patients (n=165) because the safety data obtained from adults (n=3) was limited.*

Continued

Table 43, continued

Full Prescribing Information Sections	Rationale for Major Changes Incorporated Into the Finalized Prescribing Information (PI)
7 DRUG INTERACTIONS	N/A
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	**Pediatric Use** subsection updated with pediatric use statement, supportive evidence, and a summary sentence that supports the use of XOLAIR in pediatric patients 1 year and older with IgE-mediated Food Allergy.
12 CLINICAL PHARMACOLOGY	**Pharmacodynamics** updated with data for serum free IgE and total IgE levels from the Food Allergy clinical study. **Pharmacokinetics** updated with population pharmacokinetic data from patients with IgE-mediated food allergy. **Immunogenicity** updated with language that indicate ADA samples were not measured in studies for CRSwNP and IgE-mediated Food Allergy so that immunogenicity information is available for all approved indications.
13 NONCLINICAL TOXICOLOGY	N/A
14 CLINICAL STUDIES	Added a new subsection for the new indication for IgE-Mediated Food Allergy that describes the study, study population, and results. The clinical study included 165 pediatric patients and 3 adults. Efficacy was assessed from pediatric patients and the effectiveness of XOLAIR in adults was supported by the adequate, well-controlled study in pediatric patients and the disease similarity in pediatric and adult patients. *Language for open-label extension study was added in this section for the IgE-mediated food allergy indication because the primary endpoint was assessed at 16-20 weeks, the efficacy endpoint assessed was objective, and the results are meaningful without a concurrent control group given the known natural history of the disease. A sentence, 'Efficacy cannot be established from uncontrolled, open-label study' was added to convey the limitations of the study design and interpretability of the findings.*

Continued

Table 43, continued

Full Prescribing Information Sections	Rationale for Major Changes Incorporated Into the Finalized Prescribing Information (PI)
17 PATIENT COUNSELING INFORMATION	N/A
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	N/A

Abbreviations: ADA, antidrug antibody; CRSwNP, chronic rhinosinusitis with nasal polyps; IgE, immunoglobulin E; N/A, not applicable

12 Risk Evaluation and Mitigation Strategies

The Division did not find any safety issues that requires a risk evaluation and mitigation strategy. The safety findings that were identified can be adequately addressed through labeling and will be followed with routine pharmacovigilance.

13 Postmarketing Requirements and Commitment

The Division did not find any issues that necessitate postmarketing requirements.

14 Division Associate Director (Clinical) Comments

IgE-mediated food allergy is a common, potentially life-threatening disorder that affects approximately 33 million people in the United States, including 8% of children and 10% of adults. Current standard of care requires strict avoidance of food allergens, with prompt administration of epinephrine to treat allergic reactions occurring from accidental exposures. Avoidance of food allergens requires careful reading of food labels; however, despite best efforts at avoidance, accidental exposures may be unavoidable. The requirement for constant vigilance in avoiding food allergens and fear of accidental exposures can have significant detrimental psychosocial, nutritional, and financial impacts.

Palforzia (peanut allergen powder) was approved in 2020 for oral immunotherapy to mitigate allergic reactions that may occur with accidental exposure to peanut, but it is limited to peanut allergy, requires administration in an observed setting for the first several months of administration, is approved only for children 4-17 years of age, and is associated with significant adverse events. Due to the significant risk of anaphylaxis, it is only available through a Risk

Evaluation and Mitigation Strategy. As discussed by patients and caregivers at the September 9, 2021, Externally-Led Patient-Focused Drug Development meeting, organized by the Food Allergy Collaborative, patients are eager to have more treatment options available, including treatments that address multiple food allergies and that have an improved safety profile.

Genentech, in partnership with Novartis, submitted this sBLA to support approval of omalizumab for adults and children ≥1 year of age with one or more IgE-mediated food allergies to reduce allergic reactions, including anaphylaxis, that may occur with accidental exposure. Omalizumab was first approved in 2003 and has a well-characterized safety profile, with post-marketing exposure estimated at 1,992,779 patient treatment years as of December 31, 2022. Signaling through allergen-specific IgE bound to FcεR1 on the surface of mast cells and basophils, upon exposure to offending food allergens, is central to the pathophysiology of IgE-mediated food allergy. Omalizumab selectively binds to IgE, agnostic to specificity, and inhibits IgE binding to high-affinity IgE receptors (FcεRI) on the surface of mast cells and basophils.

The pivotal trial submitted to support this application, the OUtMATCH trial, was conducted by the NIAID Consortium for Food Allergy Research (CoFAR). Participants ≥1 year of age with peanut allergy and allergy to two additional foods (milk, egg, wheat, cashew, hazelnut, or walnut), confirmed by DBPCFCs at screening, were randomized 2:1 to receive omalizumab or placebo for 16-20 weeks. The planned trial population size was 225, but at a pre-specified interim analysis, after 168 participants (165 in the 1 to 17 years of age group) had completed the post-treatment DBPCFCs, highly statistically significant results for the primary and key secondary endpoints were obtained and Stage 1 data was locked. Both the primary and key secondary endpoints were met, persuasively demonstrating that omalizumab treatment was superior to placebo. The shift in dose tolerated without moderate-severe dose-limiting symptoms, via DBPCFCs, that was required to meet the primary endpoint (≤100 mg at screening and ≥600 mg during Stage 1) and key secondary endpoints (≤300 mg at screening and ≥1000 mg during Stage 1) was sufficiently large to control for variability in thresholds and to provide sufficient protection to reduce the risk of an allergic reaction, including anaphylaxis, from an accidental exposure to food allergen. The primary and key secondary results were statistically significant (all p-values <0.0001) and clinically meaningful. In Stage 1, 68.2% in the omalizumab arm tolerated a single dose of ≥600 mg of peanut protein vs 5.5% in the placebo arm. For the key secondary endpoints, the proportion tolerating a single dose of ≥1000 mg of food protein in the omalizumab arm, compared to the placebo arm, were: 42.2% vs 3.3% for cashew; 65.8% vs 10.5% for milk; and 67.4% vs 0% for egg. The proportion of subjects who were able to consume at least two or all three foods during DBPCFCs demonstrated that:

- 71% of omalizumab-treated participants were able to consume a single dose of ≥600 mg of at least two foods versus 5% in the placebo arm
- 67% of omalizumab-treated participants were able to consume a single dose of ≥1000 mg of at least two foods versus 4% in the placebo arm

- 48% of omalizumab-treated participants were able to consume a single dose of ≥600 mg of all three foods versus 4% in the placebo arm
- 39% of omalizumab-treated participants were able to consume a single dose of ≥1000 mg of all three foods versus 0% in the placebo arm

Of note, however, 17%, 8%, 13%, and 25% were not able to consume >100 mg of peanut, milk, egg, and cashew protein, respectively, without moderate-severe dose-limiting symptoms. This result demonstrates that, while the primary and key secondary endpoints were met, there is variability in response and continued food allergen avoidance is needed.

The results from OUtMATCH, including use of carefully conducted DBPCFCs, provides robust evidence of effectiveness from an adequate and well-controlled trial. Benefits were similar across pediatric age groups (1-5 years of age, 6-11 years of age, 12-17 years of age), and extrapolation to adults is appropriate given the shared mechanism for IgE-mediated reactions and similar PK results. Although real-world exposures to food allergen were not assessed as an endpoint, there is an unmet need for treatments for patients with allergy to one or more foods to reduce the risk for serious outcomes, most notably fatal anaphylaxis. Given the strength of trial design and the persuasiveness of the results from the OUtMATCH trial, along with the strength of the mechanistic evidence, substantial evidence of effectiveness has been demonstrated.

On review of safety, there were no cases of anaphylaxis related to omalizumab administration. There were no deaths in the development program. There were three SAEs that occurred in the omalizumab arm, with two possibly related to omalizumab (increase in liver function tests). Adverse reactions occurring in ≥3% of participants receiving omalizumab were injection site reactions and pyrexia and are included in labeling. Results from the 41 omalizumab-treated subjects 1-5 years of age were consistent with those for subjects ≥6 years of age. As only 3 adults were enrolled in this trial, safety for the adult population was fully extrapolated from the pediatric and adolescent population for this trial, as well as from the safety results from development programs for other indications. Overall, the safety of omalizumab in this trial aligned with the previous safety seen with omalizumab for the other approved indications.

The omalizumab dosing for IgE-mediated food allergy is similar to that approved for (b) (4) CRSwNP, with dose (75 to 600 mg) and dosing frequency (Q2 weeks or Q4 weeks) determined using a dosing table that is dependent on the patient's weight (kg) and pre-dose total serum IgE level (IU/mL). A new dosing table is proposed for IgE-mediated food allergy that expands IgE categories to accommodate patients with pre-dose total IgE levels up to 1850 IU/mL (previous maximum was 1500 IU/mL for the CRSwNP indication) or a body weight down to 10 kg (previous minimum 20 kg for asthma) to allow for dosing in younger children. The algorithm used to generate the dosing table targets delivery of 0.016 mg/kg of omalizumab for every IU/mL of total IgE in a 4-week interval and does not exceed a 20 mg/kg dose for a single administration, consistent with the dosing tables for other indications. The proposed dosing table was used in the pivotal trial, OUtMATCH, and enabled dosing in patients down to 1 year of

age. Patients with pre-dose total serum IgE levels >1850 IU/mL are not candidates for omalizumab treatment for the IgE-mediated food allergy indication.

Omalizumab was approved for home administration by patients or caregivers, including for patients ≥6 years of age with asthma, on April 9, 2021. As reviewed by the Applicant in their submitted Clinical Overview, no new safety signals have been identified following approvals of omalizumab for home use. Selection of patients for home administration requires careful selection to mitigate risk, particularly related to anaphylaxis. While omalizumab carries a boxed warning for anaphylaxis, other biologics approved for home use have similar rates of anaphylaxis. Approval for home use of omalizumab in children as young as 1 year of age follows the approval of dupilumab for home administration in children as young as 6 months of age with atopic dermatitis. Based on the favorable safety profile in the OUtMATCH trial, the preference of patients and caregivers to have this option, and the experience many patients and caregivers for young children with food allergy have with the management of anaphylaxis, home administration is not restricted by age with this approval. Initiation of home administration should use an individualized, risk-based approach with shared-decision making between providers and patients.

Review of human factors study results by the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology identified several use errors and use difficulties with critical tasks, most notably risk for administration of XOLAIR to treat an acute allergic reaction, including anaphylaxis. DMEPA identified additional risk mitigations to address the use errors with labels and labeling that have been implemented by the Applicant and are acceptable.

Overall, there is a favorable benefit-risk assessment and I agree with the recommendation for approval of this omalizumab supplement for the IgE-mediated food allergy indication:

> IgE-mediated food allergy in adult and pediatric patients aged 1 year and older for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods. To be used in conjunction with food allergen avoidance.

IgE-mediated food allergy is an area of unmet need, especially for patients with multiple food allergies. Approval of omalizumab for this new indication provides a treatment option for patients ≥1 year of age with allergy to one or more foods that can reduce allergic reactions, including anaphylaxis, from accidental exposures.

15 Appendices

15.1. References

Literature

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15.2. Financial Disclosure

The financial disclosure information from this trial does not impact the interpretation of the safety or efficacy results. There was one investigator who had a financial disclosure: [redacted] disclosed payments >$15,000/year for participation [redacted]. In review of the Sunshine Act data, the Applicant observed that [redacted] has been a [redacted] and a total of $103,942 was paid to [redacted] for speaking and consulting fees. The site at which [redacted] serves as a subinvestigator enrolled [redacted] of the [redacted] subjects enrolled. [redacted] serves as one of [redacted] subinvestigators at the site. The Applicant believes there is limited risk of bias given his role as subinvestigator and the number of subjects at the site. Review of the individual trial sites did not show deviation of efficacy results.

Covered Clinical Study (Name and/or Number): OUtMATCH

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 166		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Applicant of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.3.1. OUtMATCH Trial

Trial Design

The OUtMATCH trial is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial conducted in subjects aged 1 to <56 years who are allergic to peanut and at least two other foods including milk, egg, wheat, cashew, hazelnut, or walnut. The trial is designed to include three stages. However, only data from an interim analysis of Stage 1 and an OLE were provided in the present submission. Therefore, Stage 2 and Stage 3 of the trial will not be discussed.

The planned enrollment to be randomized at the beginning of Stage 1 included 225 subjects, including at least 50 subjects aged 1 year to <6 years, about 160 subjects aged 6 to <18 years, and about 15 subjects aged 18 to <56 years. Throughout enrollment, subjects will be instructed to strictly avoid all foods to which they are allergic.

During Screening, all subjects completed a set of double-blind placebo-controlled food challenges (DBPCFCs), which consisted of four blinded OFCs that could be conducted over separate visits. These included three active OFCs (peanut and two additional foods), and one placebo OFC (oat). Subjects experiencing dose-limiting symptoms to a single dose of ≤100 mg of peanut protein and ≤300 mg protein for each of the other two foods, with no dose-limiting symptoms during the placebo OFC moved to Stage 1.

In Stage 1, subjects were randomized 2:1 to treatment with omalizumab or placebo. Doses were given either every 2 or 4 weeks based on the subject's screening IgE levels (IU/mL) and body weight (kg) using a dosing table based on the same dosing algorithm approved for the treatment of moderate to severe asthma, and CRSwNP. The algorithm targets 0.016 mg/kg omalizumab for every IU/mL of predose total IgE within a 4-week interval. Across all body weight groups, the dosing does not exceed 20 mg/kg. The dosing table is shown below.

Note that total IgE values were measured at the initial Screening visit, and at the Screening DBPCFC. Only values measured at the initial Screening visit were used to determine the omalizumab dosage.

Table 44. Subcutaneous Omalizumab Doses Every 2 or 4 Weeks for Subjects 1 Year of Age and Older for IgE-Mediated Food Allergies

	Body Weight (kg)												
Baseline IgE (IU/mL)	≥10-12	> 12-15	>15-20	>20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30-100	75	75	75	75	75	75	150	150	150	150	150	300	300
>100-200	75	75	75	150	150	150	300	300	300	300	300	450	600
>200-300	75	75	150	150	150	225	300	300	450	450	450	600	375
>300-400	150	150	150	225	225	300	450	450	450	600	600	450	525
>400-500	150	150	225	225	300	450	450	600	600	375	375	525	600
>500-600	150	150	225	300	300	450	600	600	375	450	450	600	
>600-700	150	150	225	300	225	450	600	375	450	450	525		
>700-800	150	150	150	225	225	300	375	450	450	525	600		
>800-900	150	150	150	225	225	300	375	450	525	600			
>900-1000	150	150	225	225	300	375	450	525	600				
>1000-1100	150	150	225	225	300	375	450	600					
>1100-1200	150	150	225	300	300	450	525	600	DO NOT DOSE				
>1200-1300	150	225	225	300	375	450	525						
>1300-1500	150	225	300	300	375	525	600						
>1500-1850		225	300	375	450	600							

Dosing frequency:

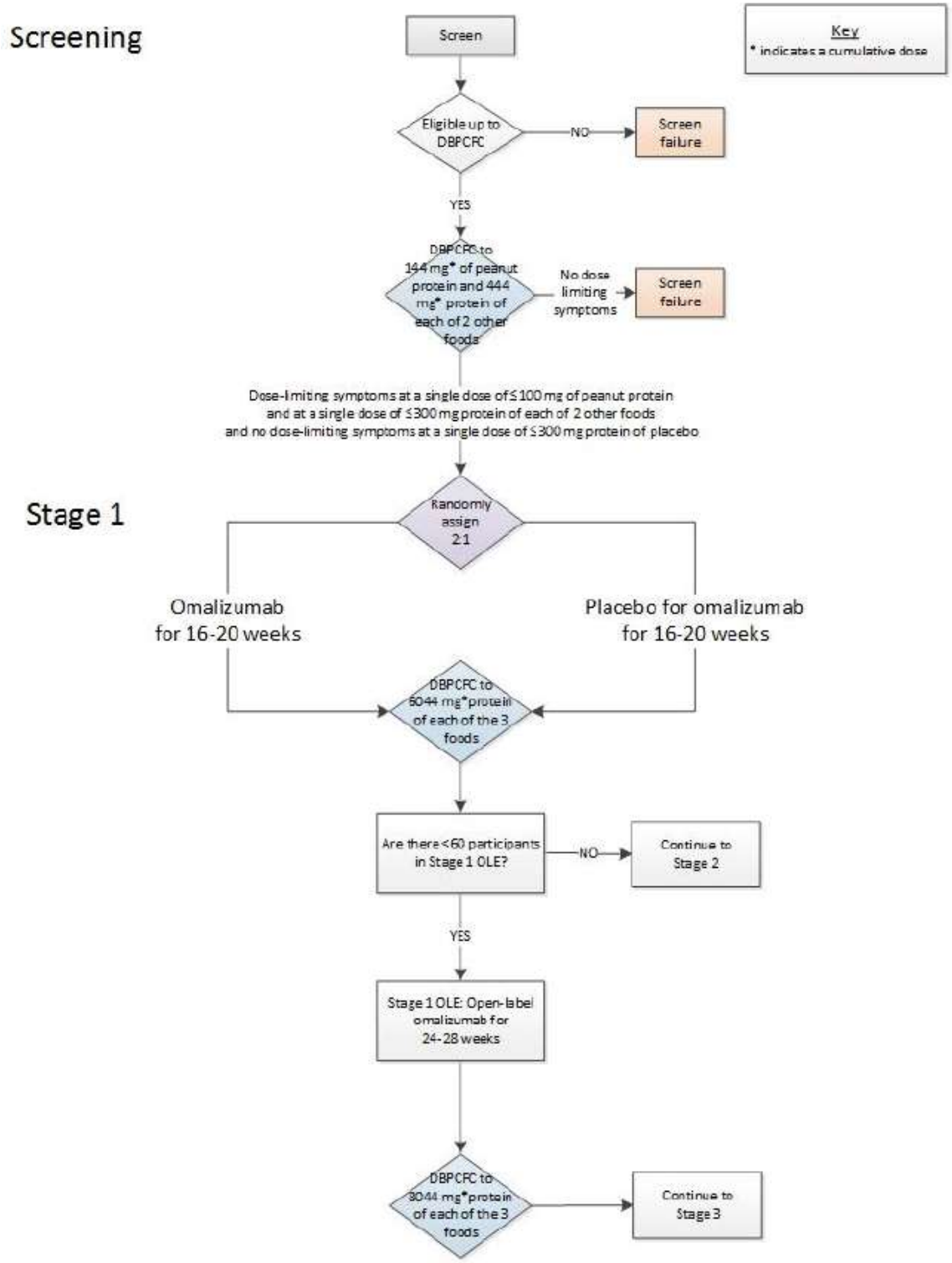
	Dose every 4 weeks
	Dose every 2 weeks
	Do not dose

Source: Appendix 2, Protocol v7.0 for Trial OUtMATCH
Abbreviations: IgE, immunoglobulin E

Treatments were given for 16 to 20 weeks. After 16 weeks of treatment, subjects completed another set of DBPCFCs to placebo, peanut, and two other subject-specific foods. DBPCFCs could occur over four separate visits with a maximum period of 28 days to complete all blinded OFCs. As subjects continued to receive omalizumab or placebo while OFCs were completed, Stage 1 could last as long as 20 weeks.

The trial schema for Screening and Stage 1 is shown in Figure 7.

Figure 7. Trial Schema for Screening and Stage 1, OUtMATCH Trial



Source: Figure 1, Clinical Study Report for Trial OUtMATCH
Abbreviations: DBPCFC, double-blind, placebo-controlled food challenge; OLE, open-label extension

The first 60 subjects who completed Stage 1 moved on to the Stage 1 OLE. During the OLE, each subject received treatment with open-label omalizumab followed by a set of DBPCFCs to assess the safety and efficacy of either 24 or 40 weeks of treatment with omalizumab (for subjects in Stage 1 in the placebo and omalizumab treatment groups, respectively). DBPCFCs began after 24 weeks of treatment and, as before, could occur over four separate visits with a maximum period of 28 days to complete all blinded OFCs. As subjects continued to receive omalizumab while OFCs were completed, Stage 1 OLE could last as long as 28 weeks.

Omalizumab was provided as XOLAIR prefilled syringes containing 75 or 150 mg.

Noteworthy Inclusion and Exclusion Criteria

Inclusion Criteria

- Male or female, 1 year to less than 56 years of age at Screening
- Peanut allergic
- Allergic to at least two of the six other foods (milk, egg, wheat, cashew, hazelnut, walnut)
- Body weight and total serum IgE level suitable for omalizumab dosing

Exclusion Criteria

- Dose-limiting symptoms during the blinded OFC to placebo during the Screening DBPCFC
- Past or current history of any immunotherapy to any of the foods being treated in this trial
- Treatment with monoclonal antibody therapy, or other immunomodulatory therapy within six months of Screening
- Use of investigational drugs within 24 weeks of Screening

Other prohibited medications included use of oral β-blockers, tricyclic antidepressants, systemic corticosteroids or other systemic immunomodulatory drugs (e.g., cyclosporine, methotrexate, azathioprine, mycophenolate mofetil).

Subject Disposition and Demographics

A total of 168 subjects were enrolled in Stage 1, including 165 pediatric subjects with median (range) age of 7 (1, 17) years, and 3 adult subjects. The interim analysis for efficacy were conducted on all pediatric subjects (aged 1 year to <18 years) randomized into Stage 1 on or before July 8, 2022 (n=165). Analysis was conducted after all subjects either completed or discontinued from Stage 1.

A total of 160/165 (97%) pediatric subjects completed Stage 1. Five subjects, all of whom were assigned to receive omalizumab treatment, withdrew from the trial. Two subjects withdrew due to adverse events, and 1 subject each withdrew due to withdrawal by subject, withdrawal by parent or guardian, and failure to meet continuation criteria. All 160 subjects completed the Stage 1 DBPCFC to peanut. Other subject-specific foods evaluated during Stage 1 included milk (n=57, 34.5%), egg (n=65, 39.4%), wheat (n=18, 10.9%), cashew (n=94, 57.0%), hazelnut (n=23, 13.9%), and walnut (n=73, 44.2%).

A total of 60 pediatric subjects from Stage 1 continued on to the Stage 1 OLE, including 39 subjects who were randomized to omalizumab treatment during Stage 1, and 21 subjects who were randomized to placebo during Stage 1.

Of the 165 pediatric subjects enrolled in Stage 1, most subjects were male (n=92, 55.8%) and White (n=104, 63.0%). Out of 165 subjects, 61 (37.0%) were <6 years of age, 62 (37.6%) were 6 to <12 years of age, and 42 (25.5%) were 12 to <18 years of age. Among pediatric subjects randomized to receive omalizumab (n=110), the median (range) body weight was 25.2 (10.1, 85.5) kg.

PK, PD and ADA Sample Collection

Blood samples for PK, assessment of free IgE, and total IgE were collected at the first Screening DBPCFC visit, Week 16 (Stage 1), and during the Stage 1 OLE at Week 24. Total IgE samples to determine the omalizumab dosage were also measured at an initial Screening visit separate from the Screening DBPCFC.

Samples to assess immunogenicity were not collected. Per the Applicant, omalizumab concentration levels during the treatment period exceeded the level that would allow for detection of ADA due to drug interference.

PK and PD Analysis

Serum trough omalizumab concentrations measured in Stage 1 and the Stage 1 OLE were summarized descriptively. Summaries included subjects who received any injection of omalizumab in Stage 1 or Stage 1 OLE and was grouped by the omalizumab dosing frequency (i.e., every 2 weeks or every 4 weeks) and by age group (i.e., <6 years, 6 to <12 years, or 12 to <18 years).

Pharmacodynamic biomarkers of free IgE and total IgE measured in Stage 1 and the Stage 1 OLE were summarized descriptively. Each summary included the measurements taken during the Screening DBPCFC, during the first DBPCFC visit at the end of Stage 1 or the Stage 1 OLE, and the percent change in PD biomarkers from Screening. Summaries for both Stage 1 and Stage 1 OLE were grouped by Stage 1 treatment arm, dosing frequency, and age group.

Pharmacokinetic and PD analyses for Stage 1 used two analysis sets: 1) PSS-S1 and 2) Pediatric Per-Protocol Set – Stage 1 (PPP-S1). Analyses for Stage 1 OLE used the PSS-S1OLE.

- PSS-S1 (n=165) included all randomized subjects aged <18 years who received at least one dose of omalizumab or placebo in Stage 1
- PPP-S1 (n=143) included all randomized subjects aged <18 years who completed at least 75% of scheduled injections in Stage 1 and completed the blinded OFC to peanut during the DBPCFC at the end of Stage 1. Subjects with major protocol deviations that could affect efficacy were excluded.
- PSS-S1OLE (n=59) included all subjects who moved to the Stage 1 OLE who received any dose of open-label omalizumab during Stage 1 OLE.

15.3.2. Bioanalytical Methods

Serum omalizumab concentrations were determined with the method described in validation report 94-01-1560-571 (Genentech, Inc., South San Francisco, CA). The assay was then partially validated as described in report NBx RS602700a (b) (4) Several amendments to the bioanalytical method have been made (validation by (b) (4) The current bioanalytical method used to quantitate omalizumab concentrations has previously been reviewed during review of BLA 103976/S-5242. Method validation and in-study bioanalytical performance were determined to be acceptable. Refer to the clinical pharmacology review in DARRTS dated June 13, 2023 (Reference ID: 5189864).

Total omalizumab (defined as the sum of free [unbound] and IgE-bound omalizumab) is determined using a sandwich-ELISA procedure. Microtiter plates are coated with human IgE antibody. Samples containing omalizumab are then incubated with the microtiter plate to capture omalizumab to the microtiter plate bound IgE. After a wash step, a horseradish peroxidase conjugated anti-omalizumab antibody is then added. This anti-omalizumab antibody targets the complementarity-determining regions of omalizumab. The reaction is then initiated through the addition of QuantaRed Enhanced Chemifluorescent horseradish peroxidase substrate solution for detection of the bound analyte. The assay is excited at 530 to 575 nm with emission detected at 585 to 630 nm on a fluorometer. The validated assay range in human serum is 40 to 1000 ng/mL.

Table 45. Method Performance in the OUtMATCH Trial (Report SPI_S_19026)

Parameter	Observations	Acceptable?
Assay passing rate	• Omalizumab concentrations from Stage 1 were determined in 25 assay runs • 19/25 (76%) runs met the method acceptance criteria • 6 runs were rejected due to QCs not meeting criteria	Yes
Standard curve performance	• Cumulative accuracy (% bias) range: -0.8 to 0.4% • Cumulative precision (% CV): ≤1.4%	Yes
QC performance	• Cumulative accuracy (% bias) range: 11.4 to 12.0% • Cumulative precision (% CV): ≤8.3% • Percent total error: ≤19.7%	Yes
Repeat analysis	Samples were reanalyzed for the following reasons: • BLQ of diluted sample • Greater than ULOQ	Yes
Method reproducibility	• Incurred sample reanalysis was performed for 41/428 samples (9.6%) • 41/41 samples (100%) met acceptance criteria based on percent difference ≤30% of the mean • Study is still ongoing and additional samples for ISR are planned • Acceptance criteria would be met even if 10% of samples were analyzed and remaining samples needed to reach a 10% sample size did not meet acceptance criteria (i.e., 41/43=95%)	Yes
Study sample analysis/ stability	Samples were stored at -75 °C until analysis. The report indicates that all samples were analyzed within the established stability of three years and nine months at -75 °C.	

Source: In-study bioanalysis report SPI_S_19026
Abbreviations: BLQ, below the limit of quantitation; CV, coefficient of variation; ISR, incurred sample reanalysis; QC, quality control samples; ULOQ, upper limit of quantitation

Bioanalytical performance for quantitation of total serum omalizumab concentrations in the OUtMATCH trial is acceptable.

PD Bioanalytical Method

Free IgE

In the OUtMATCH trial, free IgE in human serum was measured at the first Screening DBPCFC visit, Week 16 (Stage 1) and Week 24 (OLE) using an ELISA-based method. Note that free IgE refers to IgE that is not bound to omalizumab.

Samples were incubated on plates precoated with an IgE receptor fusion protein to capture IgE not bound to omalizumab. Bound samples were detected by incubation with an antibody to human IgE conjugated to biotin. Following a wash step, streptavidin conjugated β-galactosidase is added to the wells, followed by a substrate solution (4-methylumbelliferyl-β-D-galactoside). The reaction results in cleavage of the substrate, releasing the fluorochrome 4-methylumbelliferyl in proportion to the amount of free IgE in the samples. Fluorescence is measured to quantify the amount of free IgE in the samples. The quantitation range for the assay in native human serum is between 2 and 150 ng/mL (0.83 and 62.5 IU/mL). Note that dilution of the samples is limited to 1:2 in order to avoid disruption of omalizumab-IgE complexes.

A validation report for measurement of free IgE was provided: P331: The validation history of the method for the qualification of the free IgE in human serum by fluorimetric ELISA. The method was originally performed at Genentech (South San Francisco, CA) before being transferred to Novartis Biologics (Basel, Switzerland), and later to (b) (4) Select validation results derived from report NBx RS602700 (report detailing validation after transfer to (b) (4) are provided below:

Table 46. Partial Validation Results for Measurement of Free IgE

Validation Parameters	Partial Validation Summary	
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to ULOQ: concentration range of 1.563 to 200 ng/mL exceeds the quantitation range	8
	Cumulative accuracy (%bias) from 1.563 to 200 ng/mL	-3.7 to 8.4%
	Cumulative precision (%CV) from LLOQ to ULOQ	≤6.5%
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 4 QCs (includes three QCs and a complex control)	-11.9 to -10.5%
	Interbatch %CV	≤9.4%
Cross-validation	30 human clinical serum samples were evaluated and compared to the method established at another laboratory	27/30 (90%) samples with % difference <30%

Source: Method validation report P331
Abbreviations: CV, coefficient of variation; IgE, immunoglobulin E; LLOQ, lower limit of quantitation; QC, quality control samples; ULOQ, upper limit of quantitation

Table 47. Method Performance in the OUtMATCH Trial (Report SPI_S_19027)

Parameter	Observations	Acceptable?
Assay passing rate	• Omalizumab concentrations from Stage 1 were determined in 17 assay runs • 17/17 (100%) runs met the method acceptance criteria	Yes
Standard curve performance	• Cumulative accuracy (% bias) range: -5.6 to 10.0% • Cumulative precision (% CV): ≤6.8%	Yes
QC performance	• Cumulative accuracy (% bias) range: 2.2 to 14.8% • Cumulative precision (% CV): ≤7.4% • Percent total error: ≤18.3%	Yes
Repeat analysis	No sample repeat analysis was performed	Yes
Method reproducibility	Incurred sample reanalysis was not performed	N/A
Study sample analysis/ stability	Samples were stored at -75 °C until analysis. The report indicates that all samples were analyzed within the established stability of four years and two months at -75 °C.	

Source: In-study bioanalysis report SPI_S_19027
Abbreviations: CV, coefficient of variation; QC, quality control samples

The data suggest that the method used to quantitate free IgE in samples from the OUtMATCH trial performed acceptably.

Total IgE

In OUtMATCH, total IgE in human serum was measured at the first Screening DBPCFC visit, Week 16 (Stage 1) and Week 24 (OLE). Note that total IgE refers to the sum of IgE that is bound to omalizumab and free IgE (i.e., IgE not bound to omalizumab).

The method uses a commercial ImmunoCAP platform to measure levels of total IgE in human serum samples. The ImmunoCAP solid phase consists of a cellulose-derivate coated with anti-IgE antibodies. After incubation of the sample and a washing step, a β-galactosidase-coupled anti-IgE conjugate binds specifically to IgE. The presence of total IgE was measured by a fluorometric reaction.

Validation and in-study reports were not provided for measurement of total IgE. However, the method described is the same as that used to analyze samples in study K12101 (submitted under BLA 103976/S-5242). The in-study PD analysis report for study K12101 indicates that analysis was done per the method described in report DMPK-R1701204-PD: Quantitative determination of total IgE in human serum on the Phadia ImmunoCAP platform.

The Applicant used a commercial system (b) (4) to measure serum total IgE. Calibrators (b) (4) and quality control samples (b) (4) were provided as ready-to-use

reagents. The quantitation range for the assay is between 2.00 and 5000 IU/mL in 100% human serum.

15.3.3. Population PK Analysis

The FDA's Assessment

In this application, the Applicant submitted a population PK report entitled *Population Pharmacokinetic-Immunoglobulin E (PK IgE) Response Analysis for Omalizumab in Food Allergy* to characterize the kinetics of total omalizumab, total and free IgE in subjects with food allergy (FA) and explore potential new covariate relationships. In addition, the Applicant explored the free IgE-allergy response with 600 mg of peanut proteins, 1000 mg of cashew proteins, 1000 mg of egg proteins and 1000 mg of milk proteins in subjects treated with omalizumab.

Omalizumab, total IgE and free IgE concentrations from a single FA trial (OUtMATCH) were added to a large pool of previously analyzed data from non-FA subjects across nine studies. In total, 178, 451 and 168 omalizumab, total IgE and free IgE concentrations, respectively, from 133 FA subjects were added to 9797, 16916 and 9268 omalizumab, total IgE and free IgE concentrations, respectively, from 2342 non-FA subjects, to create the updated population PK-IgE analysis dataset.

The previously developed omalizumab-IgE binding model (Honma et al. 2016) was refined with the updated pooled dataset including the OUtMATCH data. The existing age covariate effects (fractional changes in the rate of synthesis of free IgE (R_E), the apparent equilibrium binding constant (K_D) and the apparent volume of omalizumab (V_X/F) parameters for subjects younger than 12 years) in the model remained statistically significant. The inclusion of an additional three covariate effects for the fractional changes in the apparent clearance of omalizumab (CL_X/F), R_E and k_D were found to be statistically significant. There was a 22% decrease and 34% and 45% increases in CL_X/F, RE and K_D, respectively, estimated for FA subjects compared to non-FA, with other PK-IgE model parameters and covariate effects comparable to those estimated prior to the inclusion of OUtMATCH.

For peanut, cashew, milk and egg, FA response efficacy endpoints, steady-state trough free IgE concentrations were generally comparable between responder and nonresponder subjects. Steady-state free IgE concentrations was not a statistically significant predictor of response in the logistic regression models.

In general, the Applicant's population PK IgE and response analysis is considered acceptable for the purpose of predicting kinetic parameters of omalizumab, total and free IgE concentrations in FA subjects and non-FA subjects. The Applicant's analyses were independently verified by the reviewer, with no significant discordance identified.

15.3.3.1. Population PK Assessment Summary

The Applicant's Analysis is summarized in Table 48.

Table 48. Applicant's Analysis

General Information	
Objectives of population PK analysis	To use a PK-IgE binding model previously developed in nonfood allergy (predominantly asthma, (Honma et al. 2016) to describe the kinetics of total omalizumab, total and free IgE in subjects with food allergy (FA) and explore potential new covariate relationships. To describe the free IgE-allergy response with 600 mg of peanut proteins, 1000 mg of cashew proteins, 1000 mg of egg proteins and 1000 mg of milk proteins in subjects treated with omalizumab.
Studies included	OUtMATCH, CIGE0250008, CIGE0250009, CIGE0250011, CIGE025A2306. CIGE0250010; CIGE025AIA05, CIGE025A2204, CIGE025A2208, CIGE025A2210.
Dose(s) included	**Figure 8. Omalizumab Dosing Tables Used in OUtMATCH**

Baseline IgE (IU/mL)	Body Weight (kg)												
	≥10-12	>12-15	>15-20	>20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30-100	75	75	75	75	75	75	150	150	150	150	150	300	300
>100-200	75	75	75	150	150	150	300	300	300	300	300	450	600
>200-300	75	75	150	150	150	225	300	300	450	450	450	600	375
>300-400	150	150	150	225	225	300	450	450	450	600	600	450	525
>400-500	150	150	225	225	300	450	450	600	600	375	375	525	600
>500-600	150	150	225	300	300	450	600	600	375	450	450	600	
>600-700	150	150	225	300	225	450	600	375	450	450	525		
>700-800	150	150	150	225	225	300	375	450	450	525	600		
>800-900	150	150	150	225	225	300	375	450	525	600			
>900-1000	150	150	225	225	300	375	450	525	600				
>1000-1100	150	150	225	225	300	375	450	600					
>1100-1200	150	150	225	300	300	450	525	600					
>1200-1300	150	225	225	300	375	450	525						
>1300-1500	150	225	300	300	375	525	600						
>1500-1850		225	300	375	450	600							

DO NOT DOSE

Source: Applicant's Population PK Report 125019 P12

Continued

Table 48, continued

General Information		
Population included		**Table 49. Demographics of Subjects Included in the PopPK-IgE Analysis That Treated With Omalizumab**

Demographic	Statistic	Non-food Allergy	Food Allergy	Overall
Number of Subjects (%)	.	2493 (95)	133 (5)	2626
Age (yrs)	Mean (SD)	31 (18.4)	7.96 (4.85)	29.8 (18.7)
	Median (Min-Max)	32 (5-79)	7 (1-20)	30 (1-79)
Baseline Weight (kg)	Mean (SD)	65.6 (25.1)	31.7 (19.0)	63.9 (26.0)
	Median (Min-Max)	67.0 (19.3-150)	25.3 (10.1-87.5)	66.0 (10.1-150)
Baseline BMI (kg/m2)	Mean (SD)	25.1 (6.81)	17.5 (3.26)	24.8 (6.89)
	Median (Min-Max)	24.6 (9.56-62.9)	16.8 (7.00-29.9)	24.2 (7.00-62.9)
Baseline IgE (ng/mL)	Mean (SD)	652 (621)	1902 (1200)	715 (717)
	Median (Min-Max)	445 (46.0-4238)	1670 (339-7502)	469 (46.0-7502)
Gender N (%)	Female	1302 (52)	55 (41)	1357 (52)
	Male	1191 (48)	78 (59)	1269 (48)
Race N (%)	Asian / Orient	21 (1)	17 (13)	38 (1)
	Black / African American	228 (9)	8 (6)	236 (9)
	Other / Unknown	284 (11)	23 (17)	307 (12)
	Caucasian/White	1960 (79)	85 (64)	2045 (78)
Age group N (%)	1-5 years	1 (0)	52 (39)	53 (2)
	6-11 years	696 (28)	45 (34)	741 (28)
	≥12 years	1796 (72)	36 (27)	1832 (70)
Adult N (%)	Adult (>=18 years)	1673 (67)	2 (2)	1675 (64)
	Pediatric (<18 years)	820 (33)	131 (98)	951 (36)

Source: Applicant's Population PK Report 125019 P21
Abbreviations: IgE, immunoglobulin E; popPK, population pharmacokinetic; SD, standard deviation

Population characteristics	General	Overall, the proportion of male and female subjects was 48% and 52%, respectively, being 59% and 41%, respectively in FA subjects. Of the 2626 subjects included in the PK-IgE analysis, 2045 (78%) of the population were Caucasian (64% of FA subjects).
	Organ impairment	No information regarding hepatic and renal impairment in the analysis.
	Pediatrics	The median age of FA subjects was 7 years (range: 1-20) with median weight of 25.3 kg (range: 10.1-87.5). These were lower than the non-FA subjects previously analyzed for which the median age was 32 years (range: 5-79) and weight 67.0 kg (19.3-150). Of the non-FA subjects, 72% were aged 12 years or older and 28% between 6 and 11 years, compared to 27% and 34%, respectively in FA subjects. In FA, 39% of subjects were aged 1-5 years, with only 1 non-FA subject (<0.05%) in this age group.
No. of subjects, PK samples, and BLQ		In total, 178, 313 and 168 omalizumab, total IgE and free IgE concentrations, respectively, from 133 FA subjects were included in the PK-IgE analysis in addition to 9797, 16916 and 9268 omalizumab, total IgE and free IgE concentrations, respectively, from 2342 non-FA subjects.

Continued

Table 48, continued

General Information		
Sampling schedule	Rich sampling	There were three clinical pharmacology studies with rich sampling but a shorter duration period: • Study A2204, a single-dose, parallel-group study to investigate omalizumab bioequivalence between the lyophilized drug product and a liquid formulation (150 and 300 mg SC) in stable atopic individuals (including those with mild to moderate asthma and/or rhinitis) with total IgE above normal levels (30–300 IU/mL) at the screening visit[CIGE025A2204]. • Study A2208, a single-dose study in mild to moderate asthmatics with IgE/body weight combinations above that in the currently licensed dosing table to determine safety, tolerability, pharmacokinetics, and pharmacodynamics of omalizumab [CIGE025A2208]. • Study A2210, a randomized, double-blind, placebo-controlled study to demonstrate the efficacy of XOLAIR in an allergen bronchoprovocation study in asthmatic populations defined by serum IgE concentrations; this study included an arm with subjects recruited to have baseline IgE in the range 700-2000 IU/mL, above the currently approved dosing table [CIGE025A2210].
	In ITT population	In the OutMATCH trial, sparse trough PK, total IgE, free IgE samples were to be collected at Screening, Week 16 in Stage 1, and for subjects participating in Stage 1 OLE, an additional Week 24 sample in Stage 1 OLE was collected (approximately equivalent to week 40 since the start of the Stage 1).
Covariates Evaluated	Static	Population PK modeling: Indication (non-FA vs FA), age, body weight, baseline IgE groups. IE-Response analysis: MTD of proteins at screening, number of allergies, age (as categorical (1-5 years, 6-11 years, and 12 years and older) or continuous variable), sex, race, comorbidities asthma/atopic dermatitis/allergic rhinitis.
	Time-varying	None.

Continued

Table 48, continued

Final Model	Summary
Software and version	Nonlinear mixed effects modeling was performed using NONMEM (version 7.5), installed on a computer running under the Red Hat Enterprise Linux version 7. NONMEM executable files were compiled using the Intel Visual FORTRAN Compiler Professional (for IA 64, version 11.). NONMEM was run through PDx-Pop (version 5.3). Within NONMEM, the First-Order method was used in the previous population PK-IgE analyses (Honma et al. 2016) and was again used for the present analysis. Data preparation, graphical exploration, goodness-of-fits plots and other model diagnostics along with the logistic regression for the IgE-response analysis, were performed using R (version 4.1.2) through RStudio (version 1.2.5019).
Model structure	**Figure 9. Omalizumab PK/IgE Model Structure**  S is the amount of omalizumab in the absorption compartment, X is the amount of omalizumab in the central volume V_X/F, E is the amount of free IgE in the central volume V_E/F, and C is the amount of omalizumab-IgE complex in the central volume V_C/F. k_a is the absorption rate constant, CL_X/F and V_X/F are the apparent clearance and volume of omalizumab, CL_C/F and V_C/F are the apparent clearance and volume of complex, CL_E and V_E/F are the apparent clearance and volume of free IgE, R_E is the rate of synthesis of free IgE, K_D is the apparent equilibrium binding constant. The model assumes that V_X=V_E, consistent with the model for patients with allergic asthma. Source: Modified from Wada DR, Le K (2013). Population Pharmacokinetics/Pharmacodynamics of Omalizumab in Chronic Idiopathic Urticaria. Population Pharmacokinetics Report 13-0627 [internal]. 2013-05-28_Omalizumab_PPKPD_ Report_Final.docx. Figure A, p. 12

Continued

Table 48, continued

Final Model	Summary
Model parameter estimates	**Table 50. Final PopPK-IgE Model Parameter Values (af0013)**

Structural Parameter	Estimate	%RSE	Lower 95% CI	Upper 95% CI		
CL_X/F (L/Day)	0.203	2.28	0.194	0.212		
CL_E/F (L/Day)	2.07	7.15	1.78	2.36		
CL_C/F (L/Day)	0.460	6.72	0.399	0.521		
V_X/F and V_E/F (L)	8.10	1.54	7.85	8.34		
V_C/F (L)	1.98	10.9	1.56	2.40		
R_E (µg/Day)	681	7.08	587	775		
ka (Day-1)	0.667	19.6	0.410	0.924		
k_D (nM)	1.53	3.24	1.43	1.63		
Nonlinearity in k_D (α)	0.110	6.45	0.0961	0.124		
Random Effect Parameters and Correlations	**Estimate**	**%RSE**	**Lower 95% CI**	**Upper 95% CI**	**CV%/R***	**Shrinkage (%)**
CL_X/F	0.116	8.79	0.0960	0.136	34.1	28.7
CL_X/F:V_X/F	0.0762	13.1	0.0566	0.0958	0.840	-
V_X/F	0.0706	14.7	0.0502	0.0910	26.6	40.3
CL_C/F	0.0342	33.3	0.0119	0.0565	18.5	44.8
CL_C/F:R_E	-0.0192	54.7	-0.0398	0.00138	-0.410	-
R_E	0.0655	18.3	0.0420	0.0890	25.6	20.4
CL_E/F	0.0392	34.9	0.0123	0.0661	19.8	42.9
V_C/F	1.59	19.4	0.984	2.20	126	62.5
ka	1.42	30.4	0.573	2.27	119	68.6
k_D	0.0515	9.98	0.0414	0.0616	22.7	48.3
Residual Variance	**Estimate**	**%RSE**	**Lower 95% CI**	**Upper 95% CI**	**CV%**	
Omalizumab	0.0611	7.33	0.0523	0.0699	24.7	
Total IgE	0.0768	5.10	0.0691	0.0845	27.7	
Free IgE	0.0819	5.02	0.0738	0.0900	28.6	

*co-efficient of variation (CV%) for random effects and R for correlations
CI=confidence interval, %RSE=percent relative standard error, CV%=percent co-efficient of variation.
Source: ...\PKPDM&S\Pop PK\Analysis\OUtMATCH 06JUN23\af0013.sum & .ext

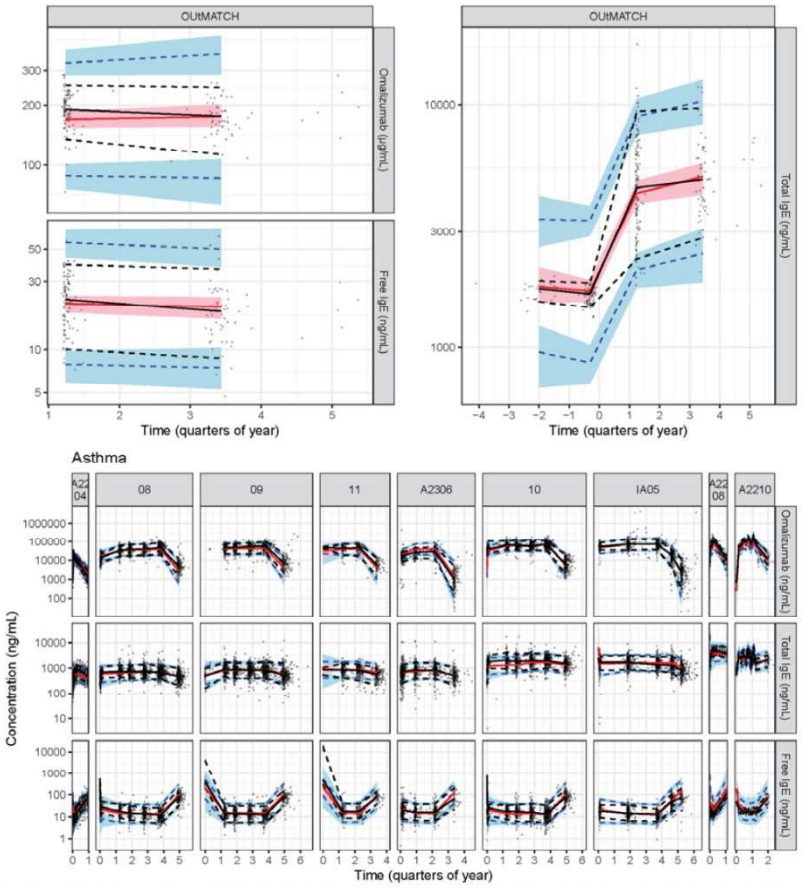
Source: Applicant's Population PK Report 125019 P27

Uncertainty and variability (RSE, IIV, shrinkage, bootstrap)	See Table 50 above
BLQ for parameter accuracy	None

Continued

Table 48, continued

Final Model	Summary
Goodness-of-fit, VPC	**Figure 10. Prediction-Corrected VPC of Each Study Using the Final Model (af0013)**

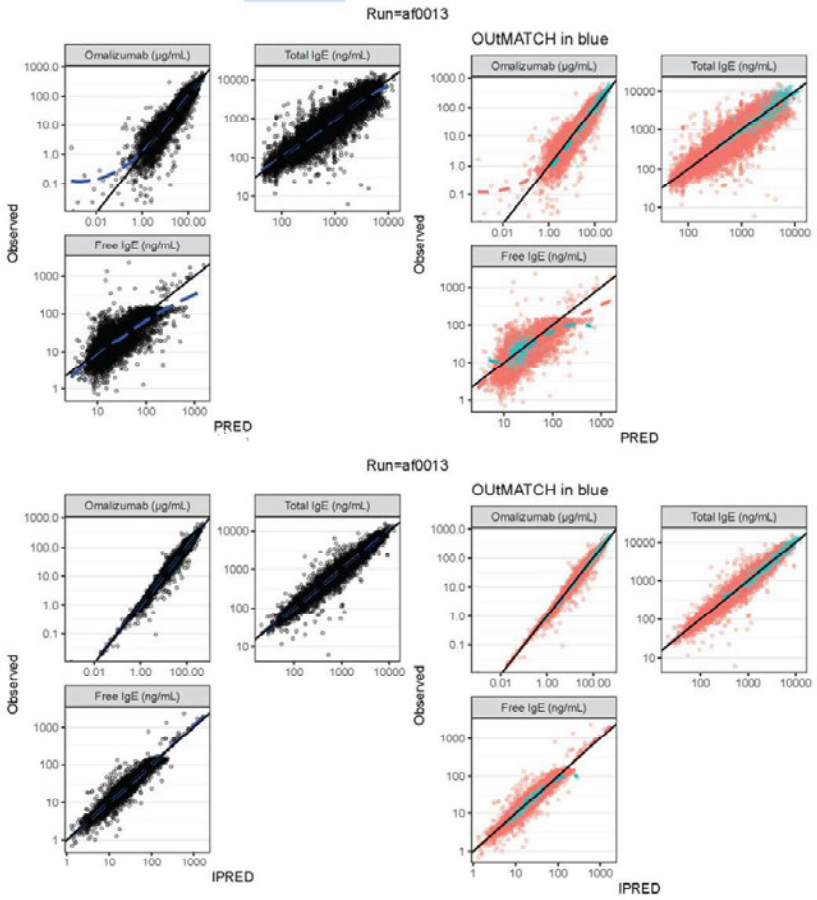


Black lines are the median (solid), 5th and 95th (dashed) percentiles of observations with red lines the median (solid), 5th and 95th (dashed) percentiles of predictions. Bands are the 2.5th and 97.5th percentile for the median (red) and 2.5th and 97.5th percentile (light blue) of the 5th and 95th percentiles.

Source: Applicant's Population PK Report 125019 P29
Abbreviations: VPC, visual predictive check

Continued

Table 48, continued

Final Model	Summary
Goodness-of-fit, VPC (continued)	**Figure 11. Final Model Goodness-of-Fit Plots (af0013)**  Source: Applicant's Population PK Report 125019 P84

Continued

Table 48, continued

Final Model	Summary
Significant covariates and clinical relevance	**Table 51. Final PopPK-IgE Model Covariate Effects (af0013)**

Parameter	Covariate	Estimate	%RSE	Lower 95% CI	Upper 95% CI
CL_X/F, CL_E/F, CL_C/F, R_E	Body weight (median: 70 kg)	0.956[a]	4.75	0.867	1.04
CL_X/F	BMI (median: 20 kg·m^{-2})	0.111[a]	67.8	-0.0366	0.259
CL_X/F	Race: Black	1.06[b]	2.23	1.01	1.11
CL_X/F	Race: Asian / Orient	1.07[b]	4.23	0.981	1.16
CL_X/F	Race: Other	1.10[b]	2.33	1.05	1.15
CL_X/F	Food Allergy[d]	0.784[b]	5.70	0.699	0.873
CL_E/F	Baseline IgE (median: 365 ng·mL^{-1})	0.316[c]	3.96	0.291	0.341
V_X/F, V_E/F, V_C/F	Body weight (median: 70 kg)	1.02[a]	3.00	0.960	1.08
V_X/F	Age: <12 y	0.983[b]	2.63	0.932	1.03
R_E	Age: <12 y	0.891[b]	1.69	0.861	0.921
R_E	Baseline IgE (median: 365 ng·mL^{-1})	0.652[a]	1.93	0.627	0.677
R_E	Race: Black	1.01[b]	2.50	0.960	1.06
R_E	Race: Asian / Orient	1.10[b]	5.49	0.982	1.22
R_E	Race: Other	0.926[b]	2.58	0.879	0.973
R_E	Sex: Female	0.969[b]	1.33	0.944	0.994
R_E	Food Allergy[d]	1.34[b]	2.60	1.27	1.41
k_D	Age: <12 y	1.22[b]	1.84	1.18	1.26
k_D	Baseline IgE (median: 365 ng·mL^{-1})	0.0769[a]	12.1	0.0586	0.0952
k_D	Race: Black	0.940[b]	2.90	0.886	0.994
k_D	Race: Asian / Orient	0.880[b]	7.56	0.750	1.01
k_D	Race: Other	0.946[b]	3.08	0.889	1.00
k_D	Food Allergy[d]	1.45[b]	3.57	1.35	1.55

[a] power model, [b] ratio, [c] inverse power model, [d] new covariate compared to base model
CI=confidence interval, %RSE=percent relative standard error.
Source: ...\PKPDM&S\Pop PK\Analysis\OUtMATCH 06JUN23\af0013.sum & .ext

Source: Applicant's Population PK Report 125019 P28

There was a 22% decrease and 34% and 45% increases in CL_X/F, RE and kD, respectively, estimated for FA subjects compared to non-FA, with other PK-IgE model parameters and covariate effects comparable to those estimated prior to the inclusion of OUtMATCH

Analysis based on simulation (optional)	For each of the dosing table cells in Figure 8, 1000 subjects (≥12 years) were simulated for 24 weeks of treatment (until steady-state) for the FA and non-FA populations. In addition, for cells stratified by a weight less than 50 kg, 1000 younger subjects (<12 years) were also simulated. Model-based simulations indicated steady-state free IgE concentrations were reaching the target free IgE concentration suppression with an average serum free IgE below 25 ng/mL and were generally comparable across multiple adult and pediatric weight and baseline IgE ranges between FA and non-FA subjects using the dosing regimens employed in OUtMATCH
Labeling Language	**Description**
12.3 PK	None

IgE-Response Analysis

For the PK-IgE response primary analysis for omalizumab in FA (OUtMATCH), 110, 64, 38 and 46 subjects (<18 years of age) had evaluable data indicating whether they were able to tolerate ≥600 mg of peanut protein or ≥1000 mg of cashew, milk, or egg protein, respectively, without

dose-limiting toxicity. The median age of FA subjects was 7.5 years (range: 1 to 20) with median weight of 25.6 kg (range: 10.1 to 87.5). Overall, the proportion of male and female subjects was 58% and 42%, respectively in FA subjects. Of the 112 subjects included in the PK-IgE response analyses, 64% were Caucasian.

For peanut, cashew, milk and egg protein FA response efficacy endpoints, steady-state trough free IgE concentrations were generally comparable between responder and nonresponder subjects in treated subjects. Consequently, using steady-state free IgE concentrations as the predictor of response in the logistic regression models was found to be non-statistically significant for all four endpoints.

Reviewer comment: The population PK modeling analyses for omalizumab, total and free IgE are deemed acceptable. The reviewer was able to repeat and verify the Applicant's analyses with no significant discordance identified. Overall, the final population PK models appeared adequate to characterize the kinetic profiles of omalizumab, total and free IgE in FA and non-FA subjects, as indicated in the Applicant's goodness-of-fit plots and VPC plots. Model-based simulations indicated steady-state free IgE concentrations were reaching the target free IgE concentrations suppression with an average serum free IgE below 25 ng/mL and were generally comparable across multiple adult and pediatric weight and baseline IgE ranges between FA and non-FA subjects using the dosing regimens employed in OUtMATCH.

In the IgE-response analysis, for peanut, cashew, milk and egg protein FA response efficacy endpoints, steady-state trough free IgE concentrations were generally comparable between responder and nonresponder subjects in treated subjects. Consequently, using steady-state free IgE concentrations as the predictor of response in the logistic regression models was found to be non-statistically significant for all four endpoints. The analysis should be deemed as exploratory because the data was limited and the analyses might be confounded by other factors.

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/s/

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