BLA Clinical Review Memorandum

Application Type	Supplemental Biologics License Application
STN	STN125592/218
CBER Received Date	04/29/2024
PDUFA Goal Date	02/27/2025
Division / Office	DCTR/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Anne Miranowski, MD
Review Completion Date / Stamped Date	02/26/2025
Supervisory Concurrence	Kathleen Hise, MD Joohee Lee, MD Jay Slater, MD Rebecca Reindel, MD
Applicant	ALK Abelló A/S
Established Name	House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract
(Proposed) Trade Name	Odactra
Pharmacologic Class	Allergenic Extract
Formulation(s), including Adjuvants, etc.	Extract
Dosage Form(s) and Route(s) of Administration	Tablet, Sublingual
Dosing Regimen	One tablet daily (each tablet contains: 12 SQ-HDM: 6 SQ-HDM *Dermatophagoides farinae*, 6 SQ-HDM *Dermatophagoides pteronyssinus*)
Indication(s) and Intended Population(s)	Immunotherapy for house dust mite-induced allergic rhinitis with or without conjunctivitis, confirmed by in vitro testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites or by skin testing to licensed house dust mite allergen extracts. Odactra is approved for use in persons 5 through 65 years of age.
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
AESI	adverse event of special interest
AR/C	allergic rhinitis with or without conjunctivitis
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CMC	Chemistry, Manufacturing, and Controls
COVID-19	coronavirus disease 2019
CSMS	combined symptom-medication score
DMS	daily medication score
DSS	daily symptom score
DU	development unit
EAACI	European Academy of Allergy & Clinical Immunology
eDiary	electronic diary
EEC	environmental exposure chamber
EMA	European Medicines Agency
EoE	eosinophilic esophagitis
EU	European Union
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FEV1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
HDM	house dust mite
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	inhaled corticosteroid
IgE	immunoglobulin E
IP	investigational product
IR	information request
LABA	long-acting β2-agonist
MedDRA	Medical Dictionary for Regulatory Activities
OBPV	Office of Biostatistics and Pharmacovigilance
PeRC	Pediatric Review Committee
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PVP	pharmacovigilance plan
QOL	quality of life
SABA	short-acting beta agonist
SAE	serious adverse event
SAS	safety analysis set
sBLA	supplemental Biologics License Application
SCIT	subcutaneous allergen immunotherapy
SLIT	sublingual allergen immunotherapy
SMQ	standardized MedDRA query
SOC	System Organ Class
SPT	skin prick test
(b) (4)	(b) (4)
TCRS	total combined rhinitis score

TCS	total combined score (rhinoconjunctivitis)
TEAE	treatment-emergent adverse event
TNSS	total nasal symptom score
U.K.	United Kingdom
U.S.	United States
USPI	United States Prescribing Information

1. EXECUTIVE SUMMARY

On April 29, 2024, ALK-Abelló A/S (the Applicant) submitted a supplemental Biologics License Application (sBLA; STN 125592/Amendment 218) to support licensure of House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract (licensed product name: Odactra) for use in children 5 through 11 years of age. The proprietary name for this product, Odactra, will be used in this document. Odactra is a sublingual tablet that contains house dust mite (HDM) allergen extract from *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*; the dose of each tablet is 12 SQ-HDM [6 SQ-HDM *D. farinae* and 6 SQ-HDM *D. pteronyssinus*]. SQ designates the method of standardization based on biological potency, major allergen content, and complexity of the allergen extract.

Odactra was approved for licensure on February 7, 2017 (the original Biologics License Application [BLA] for Odactra was submitted under STN 125592/Amendment 0), for the treatment of HDM-induced allergic rhinitis with or without conjunctivitis (AR/C), confirmed by positive skin test or in vitro testing for immunoglobulin E (IgE) antibodies specific to *Dermatophagoides farinae (Der f)* and *Dermatophagoides pteronyssinus (Der p)* house dust mites or by skin testing to licensed house dust mite allergen extracts, in adults 18 through 65 years of age. On January 20, 2023, the population for use was expanded to include individuals 12 through 65 years of age. The proposed indication is, “Immunotherapy for house dust mite-induced allergic rhinitis, with or without conjunctivitis, confirmed by in vitro testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites or by skin testing to licensed house dust mite allergen extracts. Odactra is approved for use in adolescents and adults 5 through 65 years of age.”

The Pediatric Research Equity Act (PREA) requires that the U.S. Food and Drug Administration (FDA) consider the utility of studying Odactra in pediatric age groups 0 through 16 years of age. At the time of the original BLA approval, a partial waiver from PREA requirements was granted for participants <5 years of age. Per Section 505B(a)(4)(B)(i) of the Federal Food Drug and Cosmetic Act, necessary studies are impossible or highly impracticable due to the small number of children younger than 5 years of age with allergic rhinitis/rhinoconjunctivitis who have been diagnostically confirmed with sensitivity to house dust mite as determined by skin prick test (SPT) or serum specific IgE. This submission has fulfilled the postmarketing requirement (PMR) to conduct a study in children 5-11 years of age evaluating the efficacy and safety of Odactra.

This sBLA included data from 2 clinical studies in children and in adolescents. MT-12 was a double-blind placebo-controlled Phase 3 field efficacy study demonstrating safety and efficacy of Odactra in children 5-11 years of age with symptomatic AR/C and with or without asthma when exposed to house dust mite and were sensitized to *Der f* or *Der p* as determined by house dust mite specific IgE and SPT response to *Der f* and/or *Der p.* MT-11 was a double-blind placebo-controlled Phase 3 study of Odactra in participants 5-17 years of age with HDM allergic asthma and HDM allergic rhinitis that evaluated the safety of Odactra as an add-on treatment for asthma. The primary efficacy endpoint in Study MT-11 was specific to asthma and therefore not relevant to the requested indication reviewed in this sBLA.

Efficacy

Study MT-12 was a randomized, double-blind, placebo-controlled, parallel group Phase 3 study conducted in North America and Europe to evaluate the efficacy and safety of the house dust mite sublingual allergen immunotherapy (SLIT)-tablet (Odactra) in children 5-11 years of age with house dust mite-induced AR/C, with or without asthma. Participants were randomized in a

1:1 ratio to receive either Odactra 12 SQ-HDM (n=729) or a placebo (n=731) once daily for 12 months. The primary objective was to evaluate the efficacy of Odactra compared with placebo in the treatment of HDM-induced allergic rhinitis/rhinoconjunctivitis. The efficacy of Odactra was assessed through self-reporting of symptoms and medication use. Based on these self-assessments, the total combined rhinitis score (TCRS), daily symptom scores (DSS) and daily medication scores (DMS) for rhinoconjunctivitis were calculated. TCRS is the sum of DSS and DMS. For a detailed description of TCRS, DSS, and DMS scoring, see Section 6.1.2. TCRS was chosen as the primary endpoint based on the recommendations of the European Medicines Agency (EMA) and World Allergy Organization (WAO) because the TCRS score includes both the severity of allergic rhinitis symptoms and rescue medication use meant to alleviate those symptoms. The DSS and DMS were evaluated separately as key secondary and secondary endpoints. Daily symptoms included four nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose) and two ocular symptoms (gritty/itchy eyes and watery eyes). Each of these symptoms was individually graded by participants daily on a scale of 0 (none) to 3 (severe) and then summed. Participants in active and placebo arms of this study were allowed to take symptom-relieving allergy medications (including oral and ocular antihistamines and nasal corticosteroids) during the study as needed. The DMS measured the use of these standard symptom-relieving allergy medications. Predefined daily maximum scores were assigned to each class of rhinitis and conjunctivitis medication as 0=none, 6=oral antihistamine, 6=ocular antihistamine, and 8=nasal corticosteroid. The primary efficacy endpoint was the difference in the average TCRS between treatment and placebo groups during the last 8 weeks of one year of treatment. The pre-specified success criteria for efficacy were a point estimate of ≤-15% for the difference in TCRS with Odactra relative to placebo during the last 8 weeks of treatment, with an upper bound of the 95% confidence interval (CI) ≤-10%. MT-12 met these success criteria, with a relative treatment difference based on the average TCRS during the last 8 weeks of treatment of -22.0% (95% CI: -31.1%, -12.0%).

Safety

In Study MT-12, the safety analysis was based on 1458 children 5-11 years of age who received at least 1 dose of the study drug. Of this total, 727 participants received at least 1 dose of Odactra and 731 participants received placebo. The median treatment duration for a participant who received Odactra was 378 days (range 1 to 486 days). Study participants were provided an electronic diary (eDiary; a hand-held electronic device) in which they recorded the occurrence of solicited adverse reactions daily during the first 28 days of treatment. The most common solicited adverse reactions reported in ≥10% of participants were oral pruritus (57% in the Odactra group vs. 24% in the placebo group), throat irritation (55% vs.31%), ear pruritus (33% vs.17%), upper abdominal pain (28% vs. 16%), lip swelling (20% vs. 5%), glossodynia (19% vs. 5%), nausea (16% vs. 9%), dysgeusia (16% vs. 14%), swollen tongue (14% vs. 3%), and mouth swelling (13% vs. 3%). The following unsolicited adverse events (AEs) were reported more frequently with Odactra than with placebo and occurred in ≥1% of participants 5-11 years of age within 28 days after initiation of treatment with Odactra: nasopharyngitis (25.4% vs. 22.4%), tooth loss (5.5% vs. 4.8%), oral pruritus (5.4% vs. 1.2%), COVID-19 (5.4% vs. 5.2%), pharyngitis (5.2% vs. 5.1%), throat irritation (3.6% vs. 1.5%), respiratory tract infection viral (3.6% vs. 3.3%), upper abdominal pain (1.9% vs. 1.1%), headache (1.9% vs. 1.0%), bronchitis viral (1.8% vs. 1.6%), laryngitis (1.7% vs. 1.5%), respiratory tract infection (1.7% vs. 1.2%), varicella (1.7% vs. 1.5%), ear pruritus (1.5% vs. 0.4%), sinusitis (1.5% vs. 0.8%), allergic conjunctivitis (1.5% vs. 0.8%), aphthous ulcer (1.5% vs. 1.0%), pyrexia (1.4% vs. 0.8%), mouth ulceration (1.4% vs. 1.0%), otitis media (1.4% vs. 0.7%), rhinitis (1.2% vs. 0.8%), dyspepsia (1.2% vs. 1.1%), nausea (1.2% vs. 0.3%), gastritis (1.1% vs. 0.5%), oropharyngeal pain (1.1%

vs. 0.7%), and tooth extraction (1.0% vs. 0.8%). There were no cases of confirmed eosinophilic esophagitis (EoE) in either group in the study. The percentage of all enrolled participants who dropped out of the study was higher in the Odactra group (5.4%) compared to the placebo group (3.6%). The rates of serious adverse events (SAEs) were 2.2% in the Odactra group compared to 0.8% in the placebo group. A causal relationship between these SAEs and Odactra was not established. No epinephrine use was reported. No deaths were reported.

In the clinical study provided to support safety of Odactra (MT-11), 270 participants 5-11 years of age were treated with at least one dose of Odactra of whom 238 (88%) completed at least 24 months of therapy. The placebo group had 263 participants. The rate of treatment discontinuation due to an adverse reaction was approximately 2-fold greater in Odactra recipients (1.1%) compared to placebo recipients (0.4%). Of the Odactra recipients, 25.7% of treatment dropouts were due to adverse reactions. SAE rates were 14/270 (5.2%) among Odactra recipients and 12/263 (4.6%) among placebo recipients. One SAE (EoE) was assessed as possibly related to Odactra. There were no other confirmed cases of EoE in the Odactra group. No cases of confirmed EoE occurred in the placebo group. No epinephrine use was reported. No deaths occurred.

Across the 2 clinical studies (MT-12, MT-11) submitted to the sBLA, 997 participants received at least one dose of Odactra 12DU and 994 participants received placebo. Rates of deaths, nonfatal SAEs, systemic allergic reactions, and EoE were less than 1% for each of these outcomes in Odactra recipients.

Risk-Benefit Assessment

The data submitted to this sBLA support approval of Odactra for the treatment of HDM-induced allergic rhinitis, with or without conjunctivitis in persons 5-11 years of age with confirmed HDM allergy. One field efficacy study in North American and European populations demonstrated a decrease in allergic symptoms and medication use with daily administration of Odactra for 52 weeks.

Among the 997 children 5-11 years of age who received at least one dose of Odactra, the most frequent adverse reactions (>10%) during the first 28 days of treatment were oral pruritus (58%), throat irritation (55%), ear pruritus (34%), upper abdominal pain (29%), lip swelling (22%), glossodynia (21%), nausea (18%), dysgeusia (16%), mouth swelling (16%), and swollen tongue (15%).The estimated rates of anaphylaxis (4/997), EoE (1/997) and symptoms requiring use of epinephrine (0/997) were each less than 1%.

Taken together, these data support a favorable risk-benefit assessment of Odactra for use in persons 5-11 years of age with confirmed HDM-induced AR/C.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The demographics for participants in Study MT-12 were balanced between the two study arms with respect to race, sex, age, and 95.0% White, 3.1% Hispanic, <1% Black or African American, <1% Asian, <1% American Indian or Alaska Native, and <1% Other. Subgroup analyses by race were not performed for this study due to the limited interpretability of results from such small numbers of non-White participants. The higher percentage of male participants (66%) is consistent with the greater prevalence of allergic rhinitis among males in childhood. The mean age of study participants was 8 years with a range of 5-11 years and participants had HDM-induced AR/C for a mean of 2.8 years. In terms of allergen sensitization, 47.8% of participants were sensitized to HDM only while the remaining participants in the study were

sensitized to at least one allergen in addition to HDM at baseline. Approximately 38% of participants had asthma. Subgroup analyses with respect to race, sex, age group, geographic region, polysensitization status, and asthma status did not demonstrate any difference in treatment effect. Similarly, adverse events of special interest were balanced across race, sex, age group, and geographic region and do not seem to disproportionately affect a specific subpopulation.

Clinical Reviewer Comment: While the vast majority of participants in Study MT-12 are from Europe, the data from this study are generalizable to individuals in the United States (U.S.) because of the common pathophysiology of allergic rhinitis/rhinoconjunctivitis due to HDM (an IgE mediated hypersensitivity reaction to allergens contained in airborne HDM body fragments and feces). Furthermore, HDM is an allergen present in humid geographical regions worldwide. The common species found in temperate regions in both North America and Europe are Dermatophagoides farinae and Dermatophagoides pteronyssinus (Portnoy et al. 2013).

1.2 Patient Experience Data

No patient experience data were submitted as part of this application.

Data Submitted in the Application

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

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

AR/C is a worldwide disease affecting over 500 million people, including up to 60 million people in the U.S (Meltzer et al. 2009), with prevalence estimates between 10% and 30% for children and adults in the U.S. and other high-income countries (Schuler IV and Montejo 2021). AR/C is among the most common chronic conditions affecting both children and adults. Many children are diagnosed with AR/C by 6 years of age, and 80% of all individuals with AR/C develop symptoms before 20 years of age (Meltzer et al. 2009). Among adolescents 13-14 years of age, an AR/C prevalence greater than 14% has been reported globally (Mallol et al. 2013), and data

from a cross-sectional study in the U.S. estimated an AR/C prevalence of 25% in adolescents (14-17 years of age) (Hill et al. 2016). Thus, although many patients may develop symptoms at an older age, AR/C is a disease of childhood that can present early in life.

AR/C can potentially impact asthma and is often associated with rhinosinusitis. AR/C can have a major impact on quality of life (QOL). These issues include disturbed sleep; daytime somnolence and fatigue; irritability; depression; impairment of physical and social functioning; and attention, learning, and memory deficits. Between 35 and 50% of adults reported that nasal allergies have at least a moderate effect on their daily life.

Sleep disturbances associated with rhinitis include difficulty falling asleep, staying asleep, and awakening refreshed (Dykewicz et al. 2020). The burden of allergic rhinitis in Europe is also substantial. In a 2004 study, approximately 23% of adults (19% in Spain, 29% in Belgium) were found to have clinically confirmed allergic rhinitis (Bauchau and Durham 2004).

AR/C falls within a spectrum of chronic diseases driven by allergen-induced IgE-mediated and cell-mediated immune responses. AR/C presents as a constellation of nasal and non-nasal symptoms including sneezing, anterior and posterior rhinorrhea, congestion, and ocular itching and congestion. Common environmental triggers include perennial allergens, such as house dust mites and cat dander, and seasonal allergens, such as grass and ragweed pollens.

Polysensitization is common among individuals with AR/C; reported rates of polysensitization in populations seeking medical care for allergic rhinitis range between 31% to 74% (Migueres et al. 2014). Allergic rhinitis commonly coexists with asthma, which typically develops after allergic rhinitis. Between 20 and 40% of individuals with allergic rhinitis also have asthma, and 30 to 80% of individuals with asthma have allergic rhinitis (Compalati et al. 2010).

House dust mites are eight-legged, sightless arthropods that live on host skin cells and other debris. These arthropods live in upholstery, carpet, and mattresses. Humid environments are ideal for house dust mite survival because they cannot seek out water. Instead, house dust mites absorb water through their bodies (Adkinson et al. 2014).

House dust mites, particularly two species, *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*, are ubiquitous in human habitats and are a significant factor underlying perennial allergic rhinitis (Calderón et al. 2015). House dust mite allergen is an important allergy trigger among children and adolescents. In the U.S., the prevalence of HDM sensitivity has been reported to be 30% among adolescents (10-19 years of age) and 28% in the general population (6-59 years of age) based on the National Health and Nutrition Examination Survey (NHANES), with age identified as a predictor of HDM sensitization (Arbes et al. 2005), and HDM sensitization rates across 7 low-income metropolitan areas in the U.S. showed an average of 62% of children 5-11 years of age from low-income metropolitan areas with moderate to severe asthma sensitized to HDM (Gruchalla et al. 2005).

HDM-induced AR/C is a chronic condition which accounts for a significant proportion of the overall health care costs in North America (Schatz 2007). These include both direct expenditures and indirect costs associated with complications resulting from the basic allergic disease and loss of productivity. In addition, the disease may result in a lower QOL for patients (Meltzer et al. 2012). In the adolescent population, this impact on QOL involves both physical and mental components such as impaired sleep and a negative impact on school attendance, performance, and academic achievement (Blaiss et al. 2018).

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

Treatment for house dust mite-induced AR/C includes allergen avoidance measures, saline nasal rinses, and combined pharmacologic therapy regimens of oral, intranasal, and ocular antihistamines, intranasal steroids, and intranasal anticholinergics. Avoidance measures may not minimize allergen levels enough to impact clinical symptoms. Antihistamines, steroids, and anticholinergics treat symptoms associated with house dust mite-induced AR/C but do not modify the course of disease.

2.3 Safety and Efficacy of Pharmacologically Related Products

Allergen-specific immunotherapy is unique compared with avoidance measures and symptomatic therapy in offering the potential to reduce the occurrence and/or severity of symptoms of AR/C and thereby decrease the need for symptomatic treatment with medication by increasing an individual's tolerance of a specific allergen. While the exact mechanism has not been established, allergen-specific immunotherapy is intended to modify the immune response to the allergen to suppress allergic symptoms upon exposure to the inciting allergen. Licensed allergen-specific immunotherapy for aeroallergens includes both subcutaneous allergen immunotherapy (SCIT) and SLIT tablets.

Four SLIT products are approved in the U.S. Oralair is a SLIT product composed of five Northern grass species for the treatment of grass pollen-induced AR/C in persons 5-65 years of age. Grastek is a SLIT product composed of Timothy grass (or cross-reactive grass) pollen-induced AR/C in persons 5-65 years of age. Ragwitek is a SLIT product composed of short ragweed pollen for the treatment of short ragweed pollen-induced AR/C in persons 5-65 years of age. Odactra is a SLIT product composed of house dust mites for the treatment of house dust mite-induced AR/C in persons 12-65 years of age.

The most common adverse reactions reported in ≥5% of adult participants taking SLIT include ear pruritus, oral pruritus, tongue pruritus, mouth edema, throat irritation, and oral paresthesia. The most common adverse reactions reported in ≥5% of children and adolescents 5-17 years of age were throat irritation, oral pruritus, ear pruritus, lip swelling, glossodynia, nausea, oral pain, pharyngeal edema, tongue swelling, abdominal pain upper, stomatitis, and enlarged uvula. Participants also experienced treatment-related systemic allergic reactions for which epinephrine administration was required. Therefore, a boxed warning is present on the package inserts of these SLIT products warning of the risk of severe allergic reactions. EoE has been reported with the use of grass pollen SLIT products. The package inserts of Grastek, Ragwitek, and Oralair include information about EoE under Contraindications, Warnings and Precautions, and Adverse Reactions.

The Cochrane Review of sublingual immunotherapy for allergic rhinitis (Radulovic S et al., 2010) reviewed 60 randomized controlled clinical trials of SLIT. Forty-nine were suitable for pooling in meta-analyses which included 2333 SLIT and 2256 placebo participants). Symptom and medication scores were both improved with little difference in overall efficacy compared to SCIT. And in contrast to SCIT, none of the trials reported severe systemic reactions or anaphylaxis, and none of the systemic reactions that were reported required the use of epinephrine. When compared directly with SCIT, SLIT appeared to be associated with fewer SAEs.

For additional details regarding the safety and efficacy data to support each of the SLIT products listed above, please refer to the package insert for each of these products, which can be retrieved at: http://www.fda.gov/BiologicsBloodVaccines/Allergenics/ucm391505.htm.

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

Odactra was licensed in the U.S. in February 2017 for the treatment of HDM-induced AR/C in adults 18-65 years of age and in January 2023 for the treatment of AR/C in adolescents 12-17 years of age. In the U.S., the licensed dose of the extract is 12 SQ-HDM which is administered daily. The HDM SLIT-tablet is also approved as allergen immunotherapy in adolescents 12-17 years of age and adults for the treatment of HDM-induced AR/C in Canada, Europe, Japan, Australia, Hong Kong, Israel, Lebanon, Macao, Malaysia, Philippines, Qatar, Russia, Saudi Arabia, South Korea, Taiwan, Thailand, Turkey, and United Arab Emirates. It is also approved in these countries for the treatment of HDM-induced asthma in adults 18 years of age and older. It is approved in New Zealand for the treatment of HDM-induced allergic rhinitis and asthma in adults 18 years of age and older. Additionally, it is approved in Japan for treatment of HDM-induced AR/C in children (age not specified).

U.S. Experience

Data from 8 clinical studies were submitted in support of licensure of Odactra for treatment of HDM-induced AR/C in adults 18-65 years of age. Demonstration of efficacy for U.S. licensure of Odactra was based on 3 studies: a Phase 2 environmental exposure chamber (EEC) study (P003) and two Phase 3 field efficacy studies (P001 and P015). Participants in all 3 of these studies had a history of symptomatic AR/C with or without asthma when exposed to house dust and were sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by HDM-specific IgE and SPT response to *D. farinae* and/or *D. pteronyssinus*. Data from all 8 clinical studies were evaluated to establish safety of the product. However, the pivotal data to support safety of Odactra were derived from these 3 clinical studies (Studies P001, P003 and P015) as well as Study P014. The latter was a randomized, double-blind placebo-controlled study that included participants ≥18 years of age with mild to moderate asthma and AR/C.

Data from 3 clinical studies were submitted in support of licensure of Odactra for treatment of HDM-induced AR/C in adolescents 12-17 years of age. Demonstration of efficacy of U.S. licensure of Odactra was based on 1 study: a Phase 3 field efficacy study (P001). Participants in this study had a history of symptomatic AR/C with or without asthma when exposed to house dust and were sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by HDM-specific IgE and SPT response to *D. farinae* and/or *D. pteronyssinus*. Data from all 3 clinical studies were evaluated to establish safety of the product. The pivotal data to support safety of Odactra were derived from Study MT-18, a Phase 3, single-arm, open-label study that evaluated the safety and tolerability of daily treatment with Odactra over 28 days in 253 adolescents (12-17 years of age) with HDM-induced AR/C with or without asthma. Safety data from Studies TO-203-3-2 and P001 were considered supportive of the safety data from Study MT-18.

Efficacy

Study P001 was a randomized, double-blind, placebo-controlled, parallel assignment Phase 3 study conducted in North America to evaluate the efficacy and safety of the HDM SLIT-tablet (Odactra) in adult and adolescent participants ≥12 years of age (N=1482) with HDM-induced AR/C with or without asthma. Participants were randomized in a 1:1 ratio to receive either Odactra 12 SQ-HDM (n=741) or a placebo (n=741) once daily for 12 months. The primary objective of Study P001 was to evaluate the efficacy of Odactra compared to placebo in the treatment of HDM-induced AR/C. The efficacy of Odactra was assessed through self-reporting of symptoms and medication use. Based on these self-assessments, the TCRS, DSS, and DMS for rhinoconjunctivitis were calculated. The primary efficacy endpoint was measured by TCRS

(which is the sum of the rhinitis DSS and rhinitis DMS). Key secondary and secondary endpoints were measured by DSS and DMS. Daily symptoms included four nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose) and two ocular symptoms (gritty/itchy eyes and watery eyes). Each symptom was individually graded by participants daily on a scale of 0 (none) to 3 (severe) and then summed. Participants in active and placebo arms of this study were allowed to take symptom-relieving allergy medications (including oral and ocular antihistamines and nasal corticosteroids) during the study as needed. The DMS measured the use of these standard symptom-relieving allergy medications. Predefined daily maximum scores were assigned to each class of rhinitis and conjunctivitis medication as 0=none, 6=oral antihistamine, 6=ocular antihistamine, and 8=nasal corticosteroid. The primary efficacy endpoint was the difference in the average TCRS between treatment and placebo groups during the last 8 weeks of treatment. The pre-specified success criterion was that the treatment difference relative to placebo of the TCRS during the last 8 weeks of treatment should be ≤-15% for the point estimate with an upper bound of the 95% CI ≤-10% in order to demonstrate efficacy. The relative treatment difference based on the average TCRS during the last 8 weeks of treatment was -17.2% (95% CI: -25.0%, -9.7%).

Study P015 was a Phase 3 randomized, double-blind, placebo-controlled, parallel assignment study conducted in Europe to evaluate the efficacy and safety of the HDM SLIT-tablet in adults ages 18-65 years with HDM-induced AR/C with or without asthma. 992 participants were randomized in a 1:1:1 ratio to receive either Odactra (12 SQ-HDM or 6 SQ-HDM) or placebo for 12 months. The primary endpoint was the treatment difference relative to placebo of the average TCRS during the last 8 weeks of treatment. This study did not pre-specify an upper bound for study success. The relative treatment difference between the placebo and 12 SQ-HDM group in the average TCRS during the last 8 weeks of treatment based on the full analysis set (FAS) was -18.1% (95%CI, -27.6%, -7.7%).

Study P003 was a Phase 2 randomized, double-blind, placebo-controlled, parallel-assignment study. The primary objective of the study was to evaluate the safety and efficacy of Odactra compared to placebo in treatment of HDM-induced AR/C following challenge in an EEC in participants with HDM-induced AR/C with or without asthma. The study enrolled 124 participants ≥18 years of age. The study was conducted at a single center located in Austria. Participants were randomized 1:1:1 to receive either Odactra 12 SQ-HDM (n=42), Odactra 6 SQ-HDM (n=41), or placebo (n=41). Participants received daily dosing with Odactra for 24 weeks prior to a 6-hour challenge in an EEC. In the EEC, participants were challenged with a continuous high concentration of HDM allergen (approximately 0.3 grams HDM allergen mixture containing 10:10:1 *D. farinae* whole bodies, *D. pteronyssinus* whole bodies, and feces from both species), which reflects the composition of mite material during natural exposure. Prior to the challenge sessions, participants were required to stop their medications to treat allergic rhinitis and conjunctivitis symptoms but were allowed to use rescue medications while in the EEC. Each session was monitored, and participants were provided medical treatment if warranted. While in the EEC, participants recorded the presence of nasal symptoms (itchy nose, blocked nose, runny nose, and sneezing) every 15 minutes in electronic diaries. Scores were assigned for each symptom based on a 4-point rating scale (0=none to 3=severe) and summed in order to calculate the total nasal symptom score (TNSS). The primary efficacy endpoint was to evaluate the difference in the average TNSS between treatment and placebo group during the chamber session at Week 24. No pre-specified criteria for success were defined. The primary efficacy analysis (the TNSS) in the EEC at Week 24 showed that the treatment difference relative to placebo was -48.6% (95% CI: -60.2%, -35.3%) in the 12 SQ-HDM group.

Safety
In Study P001, the safety analysis was based on 1482 participants who received at least 1 dose of the study drug. Of these 1482 participants, 640 participants 18-65 years of age received at least 1 dose of Odactra and 631 participants received placebo. The median treatment duration for participants who received Odactra was 267 days (range 1 to 368 days). Study participants were provided side effect report cards in which they recorded the occurrence of solicited adverse reactions daily during the first 28 days of treatment. The most common solicited adverse reactions reported in ≥10% of participants were throat irritation/tickle (67%), itching in the mouth (61%), itching in the ear (52%), swelling of the uvula/back of the mouth (20%), swelling of the lips (18%), and swelling of the tongue (16%), throat swelling (14%), nausea (14%), tongue pain (14%), tongue ulcer/sore on the tongue (12%), stomach pain (11%), mouth ulcer/sore on the mouth (10%), and taste alteration (10%). The following unsolicited AEs were reported more frequently with Odactra than with placebo and occurred in ≥1% of participants 18-65 years of age within 28 days after initiation of treatment with Odactra: paresthesia oral (9.2% vs. 3.2%), tongue pruritus (4.7% vs. 1.1%), oral pain (2.7% vs. 0.6%), stomatitis (2.5% vs. 1.1%), pharyngeal erythema (2.0% vs. 0.3%), eye pruritus (1.7% vs. 1.4%), oral mucosal erythema (1.7%), upper respiratory tract infection (1.6% vs. 1.1%), sneezing (1.6% vs. 0.3%), lip pruritus (1.4% vs. 0.3%), dysphagia (1.4% vs. 0.0%), fatigue (1.3% vs. 1.0%), hypoesthesia oral (1.3% vs. 1.0%), oropharyngeal pain (1.3% vs. 0.6%), chest discomfort (1.3% vs. 0.3%), dry throat (1.3% vs. 0.3%), pruritus (1.1% vs. 1.0%), and urticaria (1.1% vs. 0.3%). Dyspepsia was reported in 2.2% of Odactra recipients compared to 0% of placebo recipients. One case of EoE was diagnosed in an adolescent Odactra recipient on Day 204 of treatment confirmed by biopsy which resolved with treatment. No cases of confirmed EoE occurred in the placebo group. The percentage of all enrolled participants who dropped out of the study was higher in the Odactra group (24.2%) compared to the placebo group (17.3%). The rates of SAEs were 1.5% in the Odactra group compared to 0.9% in the placebo group. A causal relationship between these SAEs and Odactra was not established. No deaths were reported.

Across the 4 clinical studies that provided data to support safety of Odactra (Studies P001, P015, P003 and P014), 1279 participants 18-65 years of age were treated with at least one dose of Odactra, 1104 (86%) of whom completed at least 4 months of therapy. The placebo group had 1277 participants. The percentages of participants in these studies who discontinued treatment because of an adverse reaction while exposed to Odactra or placebo were 8.1% and 3.0%, respectively. The most common adverse reactions (≥1.0%) that led to study discontinuation in participants who received Odactra were throat irritation (1.5%), oral pruritus (1.3%), ear pruritus (1.1%), and mouth swelling (1.0%). SAE rates were 16/1279 (1.3%) among Odactra recipients and 23/1277 (1.8%) among placebo recipients. A causal relationship between these SAEs and Odactra was not established. No deaths occurred.

Of 1279 participants who received Odactra, 34 (2.7%) reported dyspepsia compared to 0/1277 (0%) of participants who received placebo. Twenty participants who received Odactra (1.6%) reported symptoms of gastroesophageal reflux disease compared to 3/1277 (0.2%) of participants who received placebo.

Epinephrine use was reported in 5/1279 (0.4%) participants who received Odactra compared to 3/1277 (0.2%) of participants who received placebo. Of these participants, 1 experienced a systemic allergic event related to Odactra, using epinephrine on the day of treatment initiation, compared with 2 placebo recipients who used epinephrine 6 and 25 days after treatment initiation, respectively.

Across 8 clinical studies submitted to the original BLA (MT-01/P011, P008, MT-03/P013, P003, MT-02/P012, P001, MT-06/P015, MT-04/P014), 1458 participants received at least one dose of Odactra 12 SQ-HDM, 727 received Odactra 6 SQ-HDM, and 1793 received placebo. Rates of deaths, SAEs, systemic allergic reactions, and EoE were less than 1% for each of these outcomes in Odactra recipients. Across 8 clinical studies conducted with different doses of Odactra, EoE was reported in 2/2737 (0.07%) participants who received Odactra compared with 0/1636 (0%) participants who received placebo.

In open-label Study MT-18, the safety analysis was based on 253 participants who received at least 1 dose of the study drug. The median treatment duration was 28 days (range 11 to 32 days). Study participants were provided side effect report cards in which they recorded the occurrence of solicited adverse reactions daily during the first 28 days of treatment. The most common solicited adverse reactions reported in ≥10% of participants were itching of the mouth (68.4%), throat irritation/tickle (62.1%), itching in the ear (40.7%), mouth ulcer/sore in the mouth (25.7%), tongue ulcer/sore on the tongue (22.5%), swelling in the back of the mouth (21.3%), swelling of the lips (21.3%), tongue pain (19.0%), nausea (feel like throwing up) (17.4%), stomach pain (16.6%), swelling of the tongue (15.4%), throat swelling (14.6%), and diarrhea (10.3%). The following unsolicited AEs occurred in ≥1% of participants 12-17 years of age within 28 days after initiation of treatment with Odactra: oral pain (3.2%), oral pruritus (2.8%), throat irritation (1.6%), ear pruritus (1.2%), and mouth ulceration (1.2%). No events of EoE were reported in Study MT-18. There were no reports of treatment-emergent adverse events (TEAEs) requiring treatment with epinephrine or SAEs in this study. No deaths were reported.

The safety data from Study P001 and Study TO-203-3-2 were comparable to that of Study MT-18 (with the exception that Study P001 identified one case of EoE in an adolescent participant). In these studies, no new safety signals were identified that would require additional evaluation in the adolescent age group and the overall safety profile of Odactra in the adolescent population was deemed to be acceptable.

The number of adults >65 years of age (N=11) who received Odactra and were enrolled in the pivotal studies was too small to support a labeled indication for this age group at the time of original BLA submission.

Foreign Experience

The HDM SLIT-tablet was approved by the EMA decentralized procedure comprising 11 European Union (EU) countries (Austria, Czech Republic, Denmark, Finland, France, Germany, Italy, Norway, Poland, Slovakia, and Sweden) on August 30, 2015, and marketed in those 11 EU countries under the name Acarizax. During this time, the tablet was also approved in Belgium and Australia. In these countries Acarizax was approved for the treatment of persistent moderate to severe HDM-induced allergic rhinitis and allergic asthma not well-controlled by inhaled corticosteroids (ICS) and associated with mild to severe HDM-induced allergic rhinitis in adults 18-65 years of age. Acarizax was approved for the indication of allergic asthma not well controlled by ICS based on one Phase 3 study (P014/MT-06) with supportive evidence from a Phase 2 study. The Phase 3 study included 834 adults with HDM-associated allergic asthma not well-controlled by daily use of ICS corresponding to 400-1200 µg budesonide. Participants were initially treated for 7-12 months with one of two doses of Acarizax (6 or 12 SQ-HDM) or placebo. ICS were reduced and withdrawn over a 6-month period. Efficacy was assessed as the time to first moderate or severe asthma exacerbation in participants treated with Acarizax versus those treated with a placebo SLIT-tablet. A 31-34% risk reduction (estimated by hazard ratio) in moderate or severe asthma exacerbations was reported in participants treated with 12 SQ-HDM

of Acarizax. The Phase 2 supportive study included 604 adolescents and adults with HDM-associated allergic asthma controlled by ICS (100-800µg budesonide). Participants were treated with one of three doses of Acarizax (1, 2, or 6 SQ-HDM) or placebo for 1 year. Efficacy was evaluated over the last 4 weeks of the study by the mean change from baseline of the daily ICS dose. Participants taking 6 SQ-HDM experienced a relative mean ICS reduction from baseline of 42% versus 15% for the placebo group.

In foreign postmarketing data, 1,281 postmarketing serious allergic reactions have been reported in patients (all ages) taking Odactra which includes 118 events of anaphylactic reactions and 5 events of EoE (4 in adults and 1 in a patient of unknown age). Of these, 77 postmarketing systemic allergic reactions have been reported in children (<12 years) treated with Odactra which includes 21 events of anaphylactic reactions. All 21 events were reported in Japan where Odactra is approved for the treatment of children. Eleven (11) of the 21 events of anaphylactic reactions were treated with epinephrine. After submission of this sBLA, the Application also submitted a 120-days safety update report on August 26, 2024. In this report, 4 additional cases of anaphylaxis from Odactra were reported in children 5 through 11 years of age in Japan. Two (2) of 4 events were treated with epinephrine. Two (2) of these events occurred after a treatment interruption and it is unknown if epinephrine was administered for these events. No systemic allergic reactions of EoE were reported in children (<12 years).

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

Pre-Submission

- March 1, 2017: (Odactra) House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract was licensed for immunotherapy for HDM-induced allergic rhinitis, with or without conjunctivitis, confirmed by in vitro testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or skin testing to licensed HDM allergen extracts in adults 18-65 years of age. The primary efficacy endpoint was the treatment difference of Odactra compared to placebo of the average TCRS during the last 8 weeks of treatment between Visit 10 and Visit 11. The primary efficacy endpoint was calculated as the treatment difference relative to placebo by [(treatment - placebo) / placebo * 100]. The pre-specified criteria for efficacy were demonstration of a point estimate difference between treatment and placebo of ≤-15% and an upper bound of the 95% CI of that difference of ≤-10%. The studies submitted in support of this BLA contained efficacy data for adolescents but insufficient safety data. The number of adolescent participants in which treatment with Odactra was investigated at the time of original BLA submission for licensure in the adult population was too small to adequately support safety in the adolescent population (n=94 adolescent participants 12-17 years of age on active treatment randomized in Study P001). Deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act were outlined in the Approval Letter:
    - Deferred pediatric study (Study 1) under PREA to evaluate safety and efficacy of Odactra in pediatric participants 5-17 years of age with HDM-induced allergic rhinitis/rhinoconjunctivitis with or without asthma.
    - Deferred pediatric study (Study 2) under PREA to evaluate the safety of Odactra in pediatric participants 5-17 years of age with HDM-induced allergic rhinitis/rhinoconjunctivitis with or without asthma.
- July 30, 2018: Type C Meeting Briefing Package was submitted with a revised pediatric plan. The Center for Biologics Evaluation and Research (CBER) advised that additional

efficacy data for a sBLA submission in adolescents 12 through 17 of age would not be required.

- September 11, 2019: Type C Meeting Briefing Package was submitted. CBER determined that study MT-18, an open-label, 28-day safety study, would be sufficient support the adolescent safety database. CBER agreed that for the age group 12-17 years of age, efficacy data from Study P001 reviewed under STN 125592/0 are sufficient for the evaluation of effectiveness in this age group. CBER also determined that the Applicant could proceed to study efficacy and safety in pediatric participants 5-11 years of age in Study MT-12. CBER concurred with a revised, staged development approach. Study MT-18: an open-label 28-day safety study to evaluate safety and tolerability of Odactra in adolescents 12-17 years of age with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma over 28 days of treatment.
    - Study MT-12: a Phase 3, double-blind, parallel-group, placebo-controlled study to evaluate safety, tolerability, and efficacy of Odactra in children 5-11 years of age with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma.
- July 9, 2020: The Applicant submitted a Type C Meeting Request. CBER agreed the data package [Study MT-18 results as well as existing clinical data from completed studies involving adolescent participants exposed to the 12 SQ-HDM dose [Studies P013, P008, P001 which were included in the original BLA submission (STN 125592/0) and Study TO-203-3-2 which was not previously submitted)] would be sufficient to support the submission of an sBLA to extend the indication to include the adolescent population 12-17 years of age.
- December 13, 2022: A meeting with the Pediatric Review Committee (PeRC) was held in conjunction with the submission of the sBLA for the 12-17-year-old age group in which the results of the data analyses in the adolescent population from Study MT-18, Study TO-203-3-2, and Study P001 were discussed. The Division also proposed the following to PeRC (PeRC agreed with this proposal):
    - Release of the Applicant from PMR#1 and PMR#2 (listed in the March 1, 2017 Approval Letter).
    - Issuance of new PREA PMR for Study MT-12 (a Phase 3, double-blind, parallel-group, randomized, placebo-controlled study to evaluate safety, tolerability, and efficacy of Odactra in children 5-11 years of age with HDM-induced allergic rhinitis/rhinoconjunctivitis with or without asthma).
- January 20, 2023: Odactra was licensed for immunotherapy for the same indication in adolescents 12-17 years of age using supplementary safety data.
- There were no meetings prior to the submission of this efficacy supplement.

Post submission, a total of 12 amendments were submitted in response to CBER clinical information requests (IRs). These amendments satisfactorily addressed all clinical IRs sent during the review period and have been incorporated into this memorandum.

2.6 Other Relevant Background Information

Not applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The Applicant attested that the studies submitted in support of this application were conducted in compliance with Good Clinical Practices (GCP) through provision of the following statements:

- Clinical Study Report for Study MT-12: "The trial was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP (ICH 2016)."
- Clinical Study Report for Study MT-11: "The trial was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013) and ICH GCP (ICH, 2016)."

3.3 Financial Disclosures

Covered clinical study (name and/or number): Study MT-12
Was a list of clinical investigators provided? x Yes ☐ No (Request list from Applicant)
Total number of investigators identified: 441 (including sub-investigators; 9 persons were investigators/sub-investigators at 2 study sites)
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0
Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>There were no investigators for whom a certification of due diligence was required</u> Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant) NA

Covered clinical study (name and/or number): MT-11
Was a list of clinical investigators provided? x Yes ☐ No (Request list from Applicant)
Total number of investigators identified: 332 (including sub-investigators; 4 persons were investigators/sub-investigators at 2 study sites)
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0
Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>There were no investigators for whom a certification of due diligence was required</u> Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from Applicant) NA

Clinical Reviewer Comment: An IR was sent to the Applicant to clarify the number of investigators with certification of due diligence. The numbers presented in the above tables reflect the information that we received from the Applicant in response to our request.

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

4.1 Chemistry, Manufacturing, and Controls

This submission did not include new Chemistry, Manufacturing, and Controls (CMC) data. Please see the CMC Review Memorandum for STN 125592/0 for a review of the data submitted under the original BLA.

Allergen potency in Odactra is described by the development unit (DU). DU is equivalent to SQ-HDM, which is the unit of allergen potency used in the United States Prescribing Information (USPI). The potency of the tablet is determined using the (b) (4)

Stability data determined the dating period for Odactra to be 36 months from the date of manufacture when stored at 20-25°C (68-77°F). The date of manufacture will be defined as the date when the drug substance is added to the excipient solution.

4.2 Assay Validation

Not applicable.

4.3 Nonclinical Pharmacology/Toxicology

This submission did not include new nonclinical pharmacology/ toxicology data. Please see the Clinical Review Memorandum for STN 125592/0 for a review of the data submitted under the original BLA.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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

Clinical Reviewer Comment: Pharmacokinetic studies have demonstrated that sublingually delivered allergen extracts are captured by mucosal dendritic cells and transported to local draining lymph nodes (Frati F, 2007). A recent review of animal and human data has presented molecular and cellular changes associated with allergen immunotherapy in a temporal framework. Early on, there is suppression of mast cell and basophil degranulation. This is followed by induction of regulatory T and B cells and suppression of pro-allergic Th2 cells in peripheral blood. Late effects include reduction in numbers of pro-allergic cells (i.e., mast cells, eosinophils) residing in mucosal tissues (Akdis M, 2014 and Akdis CA, 2014).

4.4.2 Human Pharmacodynamics (PD)

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

Not applicable.

4.5 Statistical

A complete statistical review of the data submitted to the sBLA was conducted by Dr. Zhong Gao within CBER's Office of Biostatistics and Pharmacovigilance (OBPV)/ Division of Biostatistics/ Therapeutics Evaluation Branch 2 who verified the efficacy data and conclusions submitted to the sBLA. Please see the Biostatistical Review Memorandum for a detailed discussion of these analyses.

4.6 Pharmacovigilance

A revised pharmacovigilance plan (PVP) was submitted with this sBLA. The Applicant summarized the changes from the previous PVP.

1. Systemic allergic reactions including anaphylactic reactions, local allergic reactions with potential compromise the airway, acute worsening of asthma symptoms, and anaphylactic shock were removed from important identified risks. The Applicant was released from the postmarketing commitment regarding the study of incidence of systemic allergic reactions and EoE among patients exposed to Odactra in amendment STN: BL 125592/192 dated January 17, 2024. The Applicant considers these risks to be known risks related to the use of Odactra addressed in the product information and followed up via routine pharmacovigilance activities. EoE was kept as an important identified risk in order to keep focus on the risk during routine pharmacovigilance activities.
2. Use in children (5-11 years of age) was removed from important missing information after completion of the pediatric phase 3 trial, MT-12.

A complete review of the PVP (submitted to STN 125592/218) was conducted by Dr. Jonathan Reich, MD within CBER's OBPV/Division of Pharmacovigilance. Please see the pharmacovigilance review memorandum for details.

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

5.1 Review Strategy

Assessment of the efficacy and safety of Odactra in children 5-11 years of age was based primarily on review of Phase 3 Study MT-12 (the focus of this clinical review, see Section 6.1 Discussion of Individual Studies/Clinical Trials; Study MT-12 was a randomized, parallel-group, double-blinded, placebo-controlled, multi-center, phase 3 trial conducted in Europe and North America evaluating the efficacy and safety of a one-year treatment course of Odactra in children 5-11 years of age).

Safety data in children from Study MT-11, a randomized, double-blinded, placebo-controlled phase 3 study evaluating the efficacy and safety of the HDM SLIT-tablet in children and adolescents (5-17 years of age) with HDM allergic asthma and from Study MT-03, a randomized, double-blinded, placebo-controlled phase 1 study investigating the safety of the HDM SLIT-tablet in children and adolescents (5-14 years of age) with HDM allergic asthma (with or without rhinitis) are considered supplemental to safety data from Study MT-12. The primary efficacy endpoint in Study MT-11 wase specific to asthma and are not relevant to the requested indication reviewed in this sBLA. Study MT-11 safety data are summarized in this

clinical review (see Section 6.2 Discussion of Individual Studies/Clinical Trials). Study MT-03 is included in Section 8.2.2 Overall Exposure, Demographics of Pooled Safety Populations.

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

The following files served as the basis for the clinical review of STN 125592/218:

- 125592/218/0:
  - Module 1.2 Cover Letters
  - Module 1.3.4 Financial Certification and Disclosures
  - Module 1.11.4 Multiple Module Information Amendment – Children Indication
  - Module 1.14 Labeling
  - Module 2
    - Module 2.2 Introduction
    - Module 2.5 Clinical Overview
    - Module 2.7 Clinical Summary (Summary of Clinical Efficacy, Summary of Clinical Safety, Synopses of Individual Studies)
  - Section 5 Clinical Study Reports (Studies MT-12, MT-11)
- 125592/218/1: Applicant Response to FDA IR
- 125592/218/2: Summary of Clinical Safety Addendum – Children Indication – 120-day Safety Update Report
- 125592/218/4: Applicant Response to FDA IR
- 125592/218/5: Applicant Response to FDA IR
- 125592/218/6: Applicant Response to FDA IR
- 125592/218/8: Applicant Response to FDA IR
- 125592/218/10: Applicant Response to FDA IR
- 125592/218/12: Applicant Response to FDA IR
- 125592/218/14: Applicant Response to FDA IR
- 125592/218/15: Applicant Response to FDA IR
- 125592/218/16: Applicant Response to FDA IR

5.3 Table of Studies/Clinical Trials

Table 1. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of Odactra

Study	Design (Length of Study)	Participants Per Treatment Arm	Age (Years)	Countries (Number of Sites)
MT-12	Randomized, parallel group, double-blind, placebo-controlled Phase 3 (approx. 12 months)	12DU (729), placebo (731)	5-11	Bulgaria (10), Canada (8), France (1), Germany (5), Lithuania (5), Poland (12), Russia (17), Slovakia (4), Spain (3), Ukraine (13), U.S. (17)
MT-11	Randomized, parallel-group, double-blind, placebo-controlled Phase 3 (24-30 months)	12DU (270), placebo (263)	5-17	Bulgaria (8), France (5), Germany (3), Hungary (7), Poland (15), Russia (10), Spain (7), U.K. (2), U.S. (7)
MT-03	Randomized, double-blind, placebo- controlled Phase 1 (28 days)	0.5DU (9), 1DU (9), 3DU (9), 6DU (9), 9DU (9), 12DU (9), placebo (18)	5-14	Spain (4)

Source: FDA-generated table
Abbreviations: DU=development unit, which is equivalent to standardized quality house dust mite (SQ-HDM); EU=European Union

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

Not applicable.

5.4.2 External Consults/Collaborations

Not applicable.

5.5 Literature Reviewed

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study MT-12

NCT04145219
Study title: “A one-year placebo-controlled phase III trial evaluating the efficacy and safety of the house dust mite (HDM) SLIT-tablet in children (5-11 years of age) with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma”

6.1.1 Objectives (Primary, Secondary, etc.)

Primary Objective

To demonstrate the efficacy of the HDM SLIT-tablet compared to placebo in the treatment of HDM AR in children (5-11 years of age) based on total combined rhinitis symptoms and medication use (TCRS) during the primary efficacy assessment period.

Key Secondary Objectives

To demonstrate the efficacy of the HDM SLIT-tablet compared to placebo during the primary efficacy assessment period based on:

- Rhinitis symptoms (based on DSS)
- Rhinitis medication use (based on DMS)
- Combined rhinoconjunctivitis symptoms and medication use (based on total combined score [TCS])

Secondary Objectives

To evaluate the HDM SLIT-tablet compared to placebo during the primary efficacy assessment period based on:

- Safety and tolerability
- Rhinoconjunctivitis symptoms
- Rhinoconjunctivitis medication use
- Rhinoconjunctivitis QoL

- Asthma symptoms and medication use
- Changes in immunological parameters

6.1.2 Design Overview

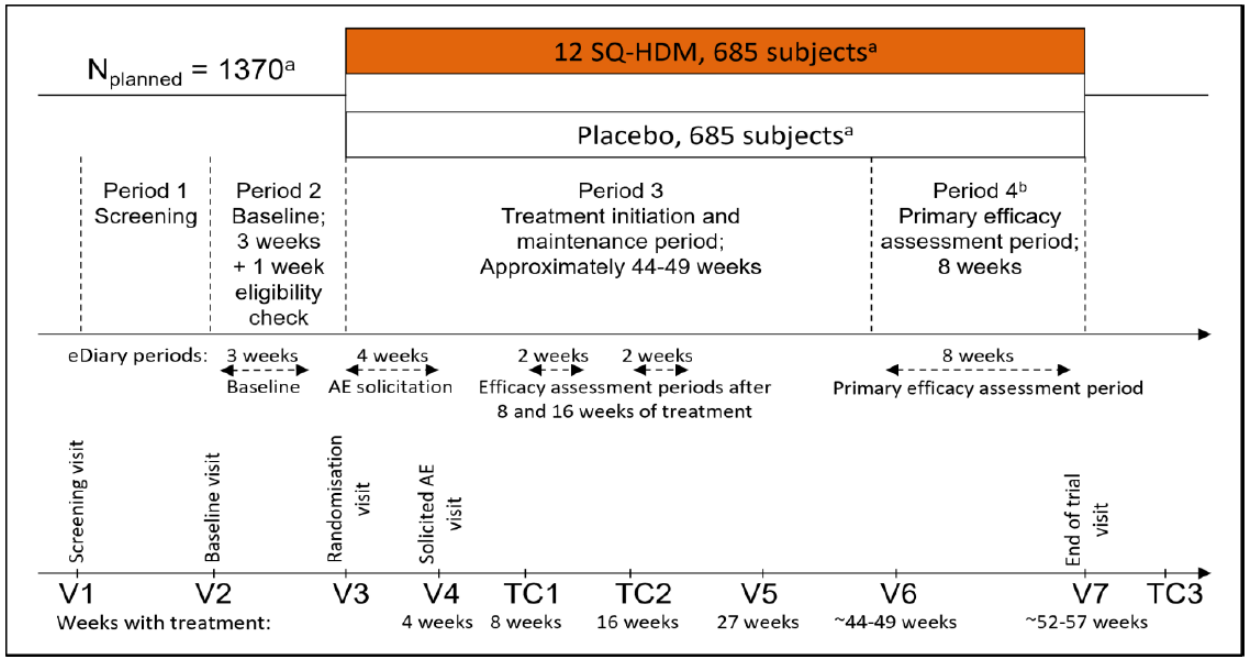
Study MT-12 was a randomized, parallel-group, double-blind, placebo-controlled, multi-center, phase 3 trial conducted in Europe and North America evaluating the efficacy and safety of 12-SQ-HDM in children (5-11 years of age) with HDM AR/C with or without asthma.

The trial was conducted at 95 sites, 17 of which were located in the U.S. and 8 in Canada. The study population consisted of 1458 participants 5-11 years of age with HDM-induced AR/C with or without asthma. Participants were randomized in a 1:1 ratio to receive Odactra (727 participants) or placebo (731 participants).

Participants were treated with one 12DU sublingual tablet of Odactra or placebo each day for 52 to 57 weeks. A baseline run-in period of 4 weeks was performed first. During this period, participants were allowed to take rhinoconjunctivitis and asthma rescue medication provided by the Applicant and their rhinoconjunctivitis symptoms and use of rescue medication was rated daily in their eDiary by the parent/caregiver together with the participant. To be eligible for inclusion, participants were required to have a rhinitis DSS of at least 6, or a score of at least 5 with one symptom being severe, on 8 of the last 14 days of the baseline period and were required to use rescue medication for treatment of HDM allergic rhinitis during at least 8 of the last 14 days of the baseline period. The baseline period ended 1 week before randomization to check for eligibility for the trial. The induction period was 44-49 weeks before treatment effects were measured. Including the 8-week efficacy assessment period, participants were on treatment for a minimum of approximately 12 months and a maximum of approximately 13 months. Participants were continued to be allowed to take rescue medication provided by the Applicant at the baseline visit during the induction and efficacy assessment periods.

Primary efficacy assessments were performed during the last 8 weeks of treatment and at a time when seasonal allergens would not interfere with the allergic rhinoconjunctivitis symptom assessment which was based on symptom and medication usage. Participants' primary efficacy assessment period was required to be between September 1st and April 1st.

Figure 1. Trial Design



Source: Applicant CSR Study MT-12, pg. 33, Figure 1
Abbreviations: HDM=house dust mite, $N_{planned}$=planned number of participants, SQ-HDM=dose unit for the HDM SLIT-tablet, TC=telephone call, V=visit
Notes:
a. The actual number of randomized participants was 1460; 729 in 12 SQ-HDM group and 731 in placebo group.
b. Participants' primary efficacy assessment period had to be between 01-Sep and 01-Apr and include the dates of the 3-week baseline period from previous year. For pollen allergic participants, the primary efficacy assessment period had to be outside of the season of their pollen allergy.

Symptom scores included 4 rhinitis (runny nose, stuffy nose, sneezing, itchy nose) and 2 conjunctivitis (itchy eyes, and watery eyes) scores which were recorded daily in the morning during the baseline period, for 2 weeks at Week 8 and Week 16, and from Visit 6 through Visit 7 on a scale of 0 (no symptoms) to 3 (severe symptoms). Asthma DSS were also reported (cough, wheeze, and chest tightness/shortness of breath, scored from 0 to 3 for a total of 9), but were not part of the scoring system for the primary endpoint.

Table 2. Participant's Symptom Scoring

Scored by Participant	Definition of Score	Numerical Score[a]
No symptoms	No sign/symptom evident	0
Mild symptoms	Symptom clearly present, but minimal awareness; easily tolerated	1
Moderate symptoms	Definite awareness of symptom that is bothersome but tolerable	2
Severe symptoms	Symptoms that are hard to tolerate; causes interference with activities of daily living and/or sleeping	3

Source: Applicant CSR MT-12, Appendix 16.1.1, pg. 340, Table 9
a. Scoring scales are not seen by the participants

Medication scores were tabulated as shown in Table 3.

Table 3. Scoring of Rhinoconjunctivitis Rescue Medication

Rescue Medication and Participant Dosing	Score/Dose Unit[a]	Maximum Daily Score
Rhinitis medication score	--	--
Desloratadine oral solution, 0.5 mg/ml	--	--
5 years of age: 2.5 ml (1.25 mg) once daily	4	4
6-11 years of age: 5 ml (2.5 mg) once daily	4	4
≥12 years of age: 10 ml (5 mg) once daily	4	4
Loratadine tablets[b], 10 mg		
6-12 years of age and >30 kg: 1 tablet (10 mg) once daily	4	4
>12 years of age: 1 tablet (10 mg) once daily	4	4
Mometasone furoate nasal spray, 50 µg /dose		
<12 years of age: 1 puff in each nostril once daily	4	8
≥12 years of age: 2 puffs in each nostril once daily	2	8
Maximum daily rhinitis medication score[c]	--	**12**
Conjunctivitis medication score	--	--
Desloratadine oral solution 0.5 mg/ml	--	--
5 years of age: 2.5 ml (1.25 mg) once daily	2	2
6-11 years of age: 5 ml (2.5 mg) once daily	2	2
≥12 years of age: 10 ml (5 mg) once daily	2	2
Loratadine tablets[b], 10 mg	--	--
6-12 years of age and >30 kg: 1 tablet (10 mg) once daily	2	2
>12 years of age: 1 tablet (10 mg) once daily	2	2
Olopatadine eye drops, 1 mg/ml	--	--
1 drop in each eye twice daily	1.5	6
Maximum daily conjunctivitis medication score[c]	--	**8**
Maximum daily rhinoconjunctivitis medication score[c]	--	**20**

Source: Applicant CSR MT-12, Appendix 16.1.1, pg. 342, Table 11
Notes:
a. Scoring scales are not seen by the participants
b. Loratadine will count 4 in the rhinitis score and 2 in the conjunctivitis score, based on assumed equal efficacy of antihistamine on the 4 nasal symptoms and 2 eye symptoms (Salmun & Lorber 2002)
c. If any participant exceeds the recommended daily dose of symptomatic medication, the maximum daily score will be used.

The rhinitis DSS is calculated by adding up the scores assigned to each individual rhinitis symptom (runny nose, stuffy nose, sneezing, itchy nose) as in Table 2. The rhinitis DMS is calculated by adding up the scores assigned to the medication taken to manage those symptoms as in Table 3. The TCRS is then calculated by adding together the score for rhinitis symptoms (DSS) and the score for medication used (DMS).

AE solicitation was conducted via an eDiary completed by the parent/caregiver together with the participant during the first 28 days of treatment. Investigators also assessed AEs occurring since the last visit at each scheduled visit and telephone call.

6.1.3 Population

The trial included participants 5-11 years of age with HDM AR/C with or without asthma. Selection criteria are summarized below:

Inclusion Criteria

1. Written informed consent obtained from parents/guardians before any trial related procedures are performed
2. Male or female of any race/ethnicity and weighing 15 kg or more on the day of screening

3. 5-11 years of age at randomization
4. A clinical history of AR/C when exposed to HDM (diagnosed by a physician) of 1 year duration or more (with or without asthma) and with allergic rhinitis symptoms despite having received allergy pharmacotherapy during the previous year prior to the screening visit
5. Have a rhinitis DSS of at least 6, or a score of at least 5 with one symptom being severe, on at least 8 of the last 14 days of the baseline period
6. Use symptomatic medication for treatment of HDM allergic rhinitis during at least 8 of the last 14 days of the baseline period
7. Presence of one or more of the following Allergic Rhinitis Impact on Asthma (ARIA) QOL items due to HDM AR/C during the last 14 days of the baseline period:
    1) Sleep disturbance
    2) Impairment of daily activities, leisure and/or sport
    3) Impairment of school
    4) Troublesome symptoms
8. Positive SPT to *D. pteronyssinus* or *D. farinae* at screening. A positive SPT is defined in the SPT Guideline. Briefly, for participants in North America, a positive SPT is defined as a wheal size ≥5 mm. For participants in Europe, a positive SPT is defined as a wheal size of ≥3 mm.
9. Positive *D. pteronyssinus* or *D. farinae*-specific IgE (defined as ≥class 3, ≥3.5 kU/l) at screening
10. Lung function measured by forced expiratory volume in 1 second (FEV1) ≥70% of predicted value or according to local requirements while on participant's usual asthma medication following at least a 6-hour washout of short-acting beta agonist (SABA) at screening, baseline visit, and at randomization
11. Participant willing and able to comply with trial protocol

Exclusion Criteria

1. A clinically relevant history of symptomatic perennial AR/C caused by a perennial allergen source such as animal hair and dander and/or mold to which the participant is exposed during the baseline and/or efficacy assessment periods
2. A clinically relevant history of symptomatic seasonal allergic rhinoconjunctivitis and/or asthma caused by an allergen to which the participant is exposed, and which could potentially overlap with the baseline and/or efficacy assessment periods
3. Any nasal or pharyngeal condition that could interfere with the safety or efficacy evaluation, (e.g., clinically relevant nasal polyps, a history of paranasal sinus surgery or surgery of nasal turbinates). Surgery of the palatine or pharyngeal tonsils in the past is not an exclusion criterion
4. SLIT treatment with *D. pteronyssinus* or *D. farinae* for more than 1 month within the last 5 years. In addition, any SLIT treatment with *D. pteronyssinus* or *D. farinae* within the previous 12 months
5. SCIT treatment with *D. pteronyssinus* or *D. farinae* reaching the maintenance dose within the last 5 years. In addition, any SCIT treatment with *D. pteronyssinus* or *D. farinae* within the previous 12 months
6. Ongoing treatment with any allergy immunotherapy product
7. Severe chronic oral inflammation

8. A diagnosis or history of EoE
9. Any systemic immunosuppressive treatment, other than glucocorticosteroids, within 130 days prior to Visit 1 (screening). Any oral glucocorticosteroids from 60 days prior to Visit 2 (baseline). Any other systemic glucocorticosteroids (depot or parenteral) from 90 days prior to Visit 2 (baseline)
10. Asthma requiring daily use of more than 400 mcg budesonide or equivalent at screening
11. Any clinical deterioration of asthma that resulted in emergency treatment, hospitalization or treatment with systemic corticosteroids within 3 months prior to randomization
12. Any clinically relevant chronic disease, including malignancy, that in the opinion of the investigator would interfere with the trial evaluations or the safety of the participant
13. A history of chronic urticaria (>6 weeks) and/or chronic angioedema (>6 weeks) within the last 2 years prior to screening that in the opinion of the investigator may constitute an increased safety concern
14. A relevant history of systemic allergic reaction (e.g., anaphylaxis with cardiorespiratory symptoms), generalized urticaria or severe facial angioedema that in the opinion of the investigator may constitute an increased safety concern
15. Active or poorly controlled autoimmune diseases, immune defects, immunodeficiencies, immunosuppression or malignant neoplastic diseases with current disease relevance
16. Treatment with medications with potential impact on efficacy endpoints (e.g., treatment with anti-IgE drugs within 130 days/5 half-lives of the drug (which ever longest) or treatment with antidepressant or antipsychotic medications with antihistaminergic effect)
17. Known history of allergy, hypersensitivity or intolerance to any of the excipients or active substances of the investigational product (IP) (except for *D. pteronyssinus* and/or *D. farinae*) or to any excipient of the rescue medication provided in this trial
18. Female with positive urine pregnancy test
19. Sexually active female of childbearing potential without medically accepted contraceptive method
20. A business or personal relationship with trial staff or sponsor who is directly involved with the conduct of the trial
21. Previously been randomized into this trial, is participating in this trial at another investigational site or is participating or planning to participate in any other clinical trial during the duration of this trial
22. A history or current evidence of any condition, treatment, laboratory values out of range or other circumstance that in the opinion of the investigator are clinically relevant and might expose the participant to risk by participating in the trial, confound the results of the trial, or interfere with the participant's participation for the full duration of the trial
23. Has a condition or requires treatment that may increase the risk of the participant developing severe adverse reactions after adrenaline/epinephrine administration
24. Unable to or will not comply with the use of adrenaline/epinephrine auto-injectors for countries where this is a regulatory requirement

Clinical Reviewer's Comment: The overall inclusion and exclusion criteria in MT-12 were similar to those of prior studies of Odactra in adolescents and adults. By requiring participants to have both a positive SPT to HDM and the presence of HDM-specific IgE antibodies in these studies, participants were more likely to have true allergies to HDM. While the cutoffs for a positive test were at the lower limit for both SPT and specific IgE, the combined requirement of a positive result for both tests decreased the chances of studying non-HDM allergic participants.

Asthmatics were ineligible to enroll in this trial if they required daily use of more than 400 mcg of budesonide or equivalent ICS at screening or had any clinical deterioration of their asthma that resulted in emergency treatment, hospitalization, or treatment with systemic corticosteroids within 3 months prior to randomization. They were also required to have an FEV1 ≥70% of predicted value. In terms of the asthma inclusion criterion, Study P001's asthma population was better controlled as participants in Study P001 had to have a FEV1 of at least 80% of predicted value at the Screening, Run-in, and Randomization Visits. This is in contrast with Study MT-18 in which participant had to have an FEV1 ≥70% of predicted value, similar to MT-12. The asthma inclusion criteria in MT-12 made it less likely that asthmatics with severe or unstable disease enrolled in the trial; however, these also limit the generalizability of the safety data to persons with severe or unstable asthma.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The IPs provided in this study were the HDM SLIT-tablet and placebo, which were manufactured and provided by the Applicant (see Table 4 below). Odactra included 12DU of standardized allergen extract of two species of cultivated house dust mite, *Dermatophagoides pteronyssinus* (*Der p*) and *Dermatophagoides farinae* (*Der f*). (b) (4) are manufactured for each species: (b) (4) (b) (4) The major allergen content in *Der p* and *Der f* (b) (4) (b) (4) is measured in relation to the in-house reference standard.

Table 4. Investigational Products, Administration and Dose, Study MT-12

Administration and Dose	HDM SLIT-tablet	Placebo
Active ingredients	Standardized allergen extract from the HDMs *D. pteronyssinus* and *D. farinae*	None
Dose/strength	12 SQ-HDM	N/A
Dosage form	Oral lyophilisate	Oral lyophilisate
Route of administration	Sublingual	Sublingual
Dosing schedule	1 tablet daily	1 tablet daily

Source: Applicant CSR, Study MT-12, Table 5, pg. 35
Abbreviations: D.=Dermatophagoides, HDM=House dust mite, SLIT=sublingual immunotherapy, SQ-HDM=dose unit for the HDM SLIT-tablet, SQ=SQ is a method for standardization of biological potency, major allergen content and complexity of the allergen extract

6.1.5 Directions for Use

The daily dose of the IP was one 12 SQ-HDM SLIT-tablet or placebo (excipient-only) tablet. Participants took the first dose of the study treatment at the study site and were observed for allergic reactions for 30 minutes. If participants tolerated the first dose in clinic, participants were directed to take one sublingual tablet daily at home. Participants were instructed that the IP should be taken in the morning with dry fingers from the blister unit immediately after opening and placed under the tongue, where it would disperse. Participants were advised not to swallow during the first minute and not to eat or drink for 5 minutes after tablet administration.

6.1.6 Sites and Centers

Study MT-12 was conducted in 11 countries at 83 study sites in North America (U.S. and Canada) and 91 study sites in Europe (Bulgaria, France, Germany, Lithuania, Poland, Russia, Slovakia, Spain, and Ukraine).

Table 5. Number of Study Sites by Country, Including Randomized Participants, Study MT-12

Country	Number of Sites Approved by IEC/IRB (N=174)	Number of Sites with Randomized Participants (N=95)	Number of Randomized and Treated Participants (N=1,458)
Bulgaria	11	10	181
Canada	13	8	38
France	4	1	3
Germany	10	5	17
Lithuania	7	5	94
Poland	12	12	353
Russia	20	17	329
Slovakia	5	4	66
Spain	7	3	7
Ukraine	15	13	330
United States	70	17	40

Source: Applicant CSR, Study MT-12, Table 2, pg. 27
Abbreviations: IEC=Independent Ethics Committee, IRB=Institutional Review Board

6.1.7 Surveillance/Monitoring

The surveillance/ monitoring procedures for Study MT-12 are described in Table 6 below.

Table 6. Study Schedule of Activities, Study MT-12[a]

Visit ID, Visit, Time from Randomization (IMP Initiation)	V1 Screening Max -12w	V2 Baseline -4w -7d	V3 Randomization	V4 Solicited AEs 4w +7d	TC1 8 w ±7d	TC2 16 w ±7d	V5 27 w ±7d	V6 44-49 w ±7d	V7 End of trial 52-57w ±7d[b]	TC3 Follow-up + 2w from V7 +7d	UV
Informed consent	X	-	-	-	-	-	-	-	-	-	-
Demography	X	-	-	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-	-
Assess symptoms of eosinophilic esophagitis	X	X	X	X	X	X	X	X	X	X	(X)
Record previous and concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	-	-	-	-	-	-	-	X	-	(X)
Oropharyngeal examination	-	X	X[c]	X	-	-	X	X	-	-	(X)
Height and weight[d]	X	X	X	X	-	-	X	X	X	-	X
Vital signs	X	X	X	X	-	-	X	X	X	-	(X)
Body temperature	-	-	X	-	-	-	-	-	-	-	
FEV1	-	-	X	-	-	-	-	-	X	-	(X)
Urine pregnancy test, if applicable[e]	X	X	X	X			X	X	X	-	(X)
SPT	X	(X)[f]	-	-	-	-	-	-	-	-	
Inclusion/exclusion criteria	X	X	X	-	-	-	-	-	-	-	
Blood and urine samples for safety laboratory assessments	X	-	-	-	-	-	-	-	X	-	(X)

Visit ID, Visit, Time from Randomization (IMP Initiation)	**V1 Screening Max -12w**	**V2 Baseline -4w -7d**	**V3 Randomization**	**V4 Solicited AEs 4w +7d**	**TC1 8 w ±7d**	**TC2 16 w ±7d**	**V5 27 w ±7d**	**V6 44-49 w ±7d**	**V7 End of trial 52-57w ±7d[b]**	**TC3 Follow-up + 2w from V7 +7d**	**UV**
Blood sample for specific IgE[g]	X[h]	-	-	-	-	-	-	-	-	-	(X)
Assess and record AEs in eCRF	X	X	X	X	X	X	X	X	X	X	X
Randomization			X	-	-	-	-	-	-	-	-
Issue and review local and systemic allergic reaction emergency plan	-	-	X	-	-	-	-	-	-	-	-
PRQLQ	-	-	X				X	X	X	-	-
Record absence from school/work for participant and parent / caregiver	-	-	X	X	X	X	X	X	X	-	(X)
Record health care utilization	-	-	X	X	X	X	X	X	X	-	(X)
Blood sample for pharmacogenetics biobank[i]	-	-	-	-	-	-	-	-	X	-	-
Intake of IMP at clinic	-	-	X	-	-	-	-	-	-	-	(X)
Dispense IMP	-	-	X	X	-	-	X	X	-	-	(X)
Dispense rhinoconjunctivitis and asthma rescue medication and instruct in the use	-	X	X	X	-	-	X	X	-	-	(X)
Dispense adrenaline / epinephrine auto-injectors[j]	-	-	X	X	-	-	X	X	-	-	(X)

Visit ID, Visit, Time from Randomization (IMP Initiation)	**V1 Screening Max -12w**	**V2 Baseline -4w -7d**	**V3 Randomization**	**V4 Solicited AEs 4w +7d**	**TC1 8 w ±7d**	**TC2 16 w ±7d**	**V5 27 w ±7d**	**V6 44-49 w ±7d**	**V7 End of trial 52-57w ±7d[b]**	**TC3 Follow-up + 2w from V7 +7d**	**UV**
Collect unused adrenaline / epinephrine auto-injector	-	-	-	-	-	-	-	-	X	-	-
Collect rescue medication as applicable and perform drug accountability	-	-	X	X	-	-	X	X	X	-	-
Collect IMP, perform drug accountability and IMP compliance check	-	-	-	X	-	-	X	X	X	-	-
Show and discuss trial video	-	X	-	-	-	-	-	X	-	-	-
Issue and instruct parent/caregiver in use and activation of eDiary	-	X	X	-	X	X	-	X	-	-	X
Instruct in the recording of pre-specified symptoms in eDiary	-	-	X	-	-	-	-	-	-	-	-
Review eDiary and record solicited AEs in eCRF	-	-	-	X	-	-	-	-	-	-	-
eDiary recording	-	3 weeks	-4 weeks	-	2 weeks	2 weeks	-	8 weeks	-	-	-
Check eDiary compliance	-	-	X	X	-	-	-	-	X	-	-
Collect eDiary	-	-	-	-	-	-	-	-	X	-	-

Source: Applicant CSR MT-12, Appendix 16.1.1, pg. 295

Abbreviations: ID=identification; IMP=investigational medicinal product; Max=maximum; V=visit; TC=telephone call; w=weeks; d=days; UV=unscheduled visit; eDiary=electronic diary; FEV1=forced expiratory volume in 1 second; AE=adverse event; SPT=skin prick test; IgE=immunoglobulin E; eCRF=electronic case report form; PRQLQ=Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; (X)=the corresponding procedure was optional and should be conducted at the unscheduled visit per investigator's discretion.

Notes:

a. To the extent possible, all examinations scheduled for the final visit must be performed on participants who receive IMP but do not complete the trial according to the protocol. If possible, the TC follow-up (TC 3) should be performed and the corresponding eCRF pages should be filled in
b. V7 to be performed 8 weeks +14 days after V6 and no later than 1st April
c. Oropharyngeal examinations will be done before and 30 ±5 mins after IMP administration at Visit 3
d. If applicable, adjust the local and systemic allergic reaction emergency plan
e. For female participants of childbearing potential
f. SPT to be performed at visit 2, if not possible at visit 1, due to necessary wash-out of concomitant medication
g. IgE against *D. pteronyssinus* and *D. farinae*
h. Inform participants that continued participation in trial depends on the result of the blood sample for specific IgE against *D. pteronyssinus* and *D. farinae*
i. For participants where the participant/parent/guardian has given consent
j. For countries where this is a regulatory requirement

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

- The efficacy of Odactra compared to placebo was determined as the intergroup difference in the average TCRS during the last 8 weeks of treatment between Visit 6 and Visit 7. The analysis was to be performed using a linear mixed effect model (LME). This model uses the square root of the average daily TCRS during the primary efficacy assessment period as response variable. The primary efficacy endpoint was calculated as the treatment difference relative to placebo by [(treatment - placebo)/placebo * 100]. The pre-specified criteria for efficacy were demonstration of a point estimate difference between treatment and placebo of ≤-15% and an upper bound of the 95% CI of that difference of ≤-10%.

Clinical Reviewer Comment: The primary efficacy endpoint used in MT-12 was the same primary efficacy endpoint used to calculate adult and adolescent primary efficacy results for Odactra. Use of TCRS was appropriate for children 5-11 years of age who experience similar symptoms and utilize the same relief medications as adults and adolescents with allergic rhinitis/rhinoconjunctivitis due to IgE-mediated house dust mite allergy.

Key Secondary Efficacy Endpoints

- The average rhinitis DSS during the primary efficacy assessment period (last 8 weeks of treatment)
- The average rhinitis DMS during the primary efficacy assessment period (last 8 weeks of treatment)
- The average daily TCS during the primary efficacy assessment period (last 8 weeks of treatment)

Secondary Efficacy Endpoints

- Safety and tolerability assessments
- Average rhinoconjunctivitis DSS
- Average rhinoconjunctivitis DMS
- Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) score
- Average asthma DSS
- SABA free days
- Weekly number of puffs of as-needed SABA use
- Changes in immunological parameters
- Rhinitis mild days
- Rhinitis exacerbation days
- Average daily rhinitis combined symptom-medication score (CSMS) (recommended by the European Academy of Allergy & Clinical Immunology [EAACI])
- Average daily rhinoconjunctivitis CSMS (recommended by the EAACI)

Exploratory Efficacy Endpoints

The exploratory endpoints during the efficacy assessment period are:

- Average TCCS (the sum of the conjunctivitis DSS and the conjunctivitis DMS)
- Average conjunctivitis DSS
- Average conjunctivitis DMS
- Rhinitis symptom-free days

- Nocturnal awakenings due to asthma requiring SABA use

The exploratory endpoints derived from 2-week-long daily entries into the eDiary collected 8 and 16 weeks after treatment initiation are:

- Average TCRS
- Average TCS
- Average rhinitis DSS
- Average rhinitis DMS
- TCRS during pollen season in spring and summer

6.1.9 Statistical Considerations & Statistical Analysis Plan

The total target sample size was about 1370 with participants randomized 1:1 to receive the study treatment or placebo for up to 52 weeks.

The expected dropout rate was 15% which estimated about 580 participants per treatment group. Unless otherwise stated in the statistical analysis plan, all statistical tests were conducted at $\alpha = 0.05$ (2-sided) level. The primary and key secondary endpoints were tested in a stepwise procedure, where statistical conclusions were made on the key secondary efficacy endpoints only if statistical significance was demonstrated in the primary efficacy endpoint.

The randomization list was generated by a trial-independent statistician and was not accessible to trial personnel involved in the conduct of the trial until the database had been locked.

Please see the statistical review for a detailed description of the statistical analyses.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Below are the definitions of each population to be analyzed. The FAS was used for all efficacy analyses and baseline characteristics. The safety analysis set (SAS) was used for safety summaries and listings, and study drug exposure.

Full analysis set (FAS)

This population served as the primary population for the evaluation of efficacy data. The FAS population includes all randomized participants who received at least one dose of study drug. Participants were analyzed as randomized (i.e., according to their randomized assignment of treatment). There were 1458 participants in the FAS (Odactra N=731; placebo N=727).

Below is a list of major protocol violations/deviations that led to exclusion of a participant:

- Participants who were not 5-11 years of age at the time of randomization
- Participants who were randomized in error due to violation of inclusion or exclusion criteria
- Participants who are siblings included in the same cohort
- Participants in Ukraine who were temporarily without study drug due to the Ukrainian crisis

Safety analysis set (SAS)

The population served as the primary population for the evaluation of safety data. The SAS includes all randomized participants who received at least one dose of study drug. Participants

were analyzed as treated (i.e., according to treatment they received). There were 1458 participants in the SAS (Odactra N=731; placebo N=727).

6.1.10.1.1 Demographics

The demographics of Study MT-12 are shown below in Table 7.

Table 7. Demographics and Baseline Characteristics, Full Analysis Set, Study MT-12

Characteristic	Placebo (N=731)	Odactra (N=727)
Age (years)[a]	--	--
Mean (SD)	8.0 (1.9)	8.0 (1.9)
Median	8.0	8.0
Min – Max	4 - 11	4 - 11
Sex, n (%)	--	--
Female	254 (34.7%)	241 (33.1%)
Male	477 (65.3%)	486 (66.9%)
Race, n (%)	--	--
Asian	3 (0.4%)	1 (0.1%)
Black or African American	4 (0.5%)	1 (0.1%)
White	714 (97.7%)	722 (99.3%)
American Indian or Alaska Native	-	1 (0.1%)
Multiple	3 (0.4%)	1 (0.1%)
Other	7 (1.0%)	1 (0.1%)
Ethnicity, n (%)	--	--
Hispanic or Latino	19 (2.6%)	26 (3.6%)
Not Hispanic or Latino	697 (95.3%)	688 (94.6%)
Not Reported	15 (2.1%)	13 (1.8%)
Country, n (%)	--	--
Bulgaria	90 (12.3%)	91 (12.5%)
Canada	20 (2.7%)	18 (2.5%)
Lithuania	47 (6.4%)	47 (6.5%)
Poland	177 (24.2%)	176 (24.2%)
Russia	166 (22.7%)	163 (22.4%)
Slovakia	33 (4.5%)	33 (4.5%)
Ukraine	165 (22.6%)	165 (22.7%)
United States	19 (2.6%)	21 (2.9%)
France	1 (0.1%)	2 (0.3%)
Germany	9 (1.2%)	8 (1.1%)
Spain	4 (0.5%)	3 (0.4%)

Source: Applicant CSR MT-12, Table 13, pg. 62
Abbreviations: SD=standard deviation; min=minimum, max=maximum; N=number of participants in FAS; n=number of participants with observation; %=percentage of participants in full analysis set
Notes:
a. Age at screening

Clinical Reviewer Comment: There were more males (66.0%) than females in this study of young children, which reflects the skewed prevalence of allergic rhinitis in childhood.

The majority of participants enrolled in this study were White (98.5%). In comparison, the racial demographics in Study P001 were 76.3% White, 10.5% African American, 5.7% multi-racial, 0.7% American Indian or Alaskan Native, and 6.7% Asian). The racial demographics of Study MT-18 were 99.6% White and 0.4% Native Hawaiian or Other Pacific Islander, very similar to those of Study MT-12. While the source of the racial demographic imbalance in this study is unclear, it may be due to participant enrollment at study sites outside of the U.S. that are

ethnically less diverse. The generalizability of the data from this study to non-White populations may be limited given the small number of non-White participants studied. While the vast majority of participants in Study MT-12 are from Europe, the data from this study are generalizable to individuals in the U.S. because of the common pathophysiology of allergic rhinitis/rhinoconjunctivitis due to HDM (an IgE-mediated hypersensitivity reaction to allergens contained in airborne HDM body fragments and feces). Furthermore, HDM is an allergen present in humid geographical regions worldwide. The common species found in temperate regions in both North America and Europe are Dermatophagoides farinae and Dermatophagoides pteronyssinus (Portnoy et al. 2013).

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The mean duration of the diagnosis of allergic rhinitis/rhinoconjunctivitis in all randomized participants was 2.8 years. In terms of sensitization profiles, 47.8% were sensitized only to HDM while the remaining participants were sensitized to HDM as well as other environmental aeroallergens). Asthma was present in 38.2% of participants (36.7% in the treatment group and 39.7% in the placebo group).

Clinical Reviewer Comment: This population is representative of individuals with allergic rhinitis in both sensitivity to other aeroallergens and diagnosis of asthma (Burks et al., 2020). A slight majority of participants enrolled in this study were polysensitized (to additional allergens other than HDM), which can confound assessment of efficacy of HDM desensitization. The Applicant attempted to mitigate the impact of concomitant allergies to seasonal allergens by performing the efficacy assessments in pollen allergic participants outside of the season of their pollen allergy.

6.1.10.1.3 Participant Disposition

The table below outlines participant disposition.

Table 8. Participant Disposition, Total Analysis Set, Study MT-12

Disposition	Placebo n	Placebo %n	Odactra n	Odactra %n	Overall n	Overall %n
Randomized not treated[b]	--	--	2	--	2	--
Randomized and treated	731	100%	727	100%	1458	100%
Safety set[c]	731	100%	727	100%	1458	100%
Full analysis set (FAS)[d]	731	100%	727	100%	1458	100%
FAS, observed[e]	706	96.6%	693	95.3%	1399	96.0%
Completed trial	707	96.7%	691	95.0%	1398	95.9%
Discontinued trial	24	3.3%	36	5.0%	60	4.1%
Reason for trial discontinuation	--	--	--	--	--	--
Adverse event	6	0.8%	14	1.9%	20	1.4%
Lost to follow-up	3	0.4%	2	0.3%	5	0.3%
Severe or persistent symptoms of esophagitis	--	--	1	0.1%	1	0.1%
Withdrawal of consent	8	1.1%	12	1.7%	20	1.4%
Other	7	1.0%	7	1.0%	14	1.0%
Completed IMP	705	96.4%	688	94.6%	1393	95.5%
Discontinued IMP but completed trial	2	0.3%	3	0.4%	5	0.3%
Reason for IMP discontinuation[f]	--	--	--	--	--	--

Disposition	Placebo n	Placebo %n	Odactra n	Odactra %n	Overall n	Overall %n
Adverse event	--	--	3	0.4%	3	0.2%
Physician's decision	2	0.3%	--	--	2	0.1%
Discontinued IMP[h]	26	3.6%	39	5.4%	65	4.5%
Reason for IMP discontinuation[g]	--	--	--	--	--	--
Adverse event	6	0.8%	16	2.2%	22	1.5%
Lost to follow-up	3	0.4%	2	0.3%	5	0.3%
Other	7	1.0%	7	1.0%	14	1.0%
Physicians' decision	2	0.3%	--	--	2	0.1%
Severe or persistent symptoms of esophagitis	--	--	2	0.3%	2	0.1%
Withdrawal of consent	8	1.1%	12	1.7%	20	1.4%

Source: Applicant CSR MT-12, Table 15.1.1, pgs. 126-127
Abbreviations: FAS=full analysis set, n=Number of participants, %n=Percentage of participants in FAS, IMP=Investigational medicinal product; AE=adverse event
Notes:
a. Rescreened participants are counted once as participants screened and once as screen failures whether or not they failed rescreening.
b. Two participants randomized to the Odactra group were not treated.
c. Participants are counted in the arm according to the treatment they actually received.
d. Participants are counted in the arm to which they were randomized.
e. Participants in FAS with at least 1 eDiary record during the primary efficacy assessment period.
f. Participants discontinuing IMP but completing the trial.
g. All participants discontinuing IMP.
h. Discontinued IMP includes those participants who discontinued IMP but completed the trial.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary efficacy analysis was based on the TCRS during the last 8 weeks of treatment using the FAS population. The pre-specified criteria for efficacy were demonstration of a point estimate of ≤-15% and an upper bound of the 95% CI of that difference of ≤-10%.

Table 9. Analysis of Average Daily TCRS During the Primary Efficacy Period, Observed Case (FAS), Study MT-12

Treatment	N_{FAS}	n_{obs}	Adjusted Mean (SE)	Estimate [95% CI]	p-value
Placebo	731	706	4.4 (0.3)	--	--
12 SQ-HDM	727	693	3.4 (0.3)	--	--
12 SQ-HDM - Placebo	--	--	--	-1.0 [-1.4, -0.5]	<.0001
(12 SQ-HDM - Placebo)/Placebo (%)	--	--	--	-22.0 [-31.1, -12.0]	--

Source: Applicant Response to FDA IR dated 10/24/2024, pg. 5, Table 1
Abbreviations: FAS=full analysis set, SE=standard error, CI=confidence interval, N_{FAS}=number of participants in FAS, n_{obs}=number of participants with observations contributing to the analysis, TCRS=total combined rhinitis score
The endpoint was square root transformed and analyzed as the response variable in an LME which includes treatment and cohort as fixed factors, the square root of the baseline value as a covariate, country/region within cohort as a random effect, and with different residual errors specified for each treatment. Denominator degrees of freedom was calculated using the Kenward and Roger's approximation. The p-value for the absolute difference is reported as the test result. The results were back-transformed as follows; from the LME, estimated least square means on the square root transformed scale were output along with associated covariance matrix. For the adjusted means and absolute difference, the SE was approximated by using the first order Delta method (first order Taylor approximation), and from this the 95% CI was calculated. For the relative difference, Fieller's theorem was first used to calculate the 95% CI, and then this was back-transformed by applying a monotone transformation.

Clinical Reviewer Comment: The primary efficacy analysis met the pre-specified criteria for success with respect to the point estimate (≤-15%) as well as the upper bound of the 95% CI of that difference of ≤-10%. In comparison, the treatment difference relative to placebo in Study P001 for adults was -16.0%. The higher degree of response to treatment with Odactra reported in children 5-11 years of age may, in part, be due to a difference in the immunologic plasticity or tolerogenic capacity in younger children compared to adults.

Table 10. Overview of Analyses of the Primary Endpoint, Average Daily TCRS During the Primary Efficacy Period (FAS), Study MT-12

Analysis Frame, Analysis Name	Absolute Treatment Difference [95% CI]	Relative Treatment Difference (%) [95% CI]	p-value
Observed case	--	--	--
Primary analysis	-1.0 [-1.4, -0.5]	-22.0 [-31.1, -12.0]	<.0001
Sensitivity analysis (potential data issues)	-1.0 [-1.5, -0.5]	-22.6 [-31.7, -12.7]	<.0001
Trial product estimand	--	--	--
Main analytical approach	-1.0 [-1.5, -0.5]	-22.2 [-31.2, -12.2]	<.0001
Sensitivity 1	-1.0 [-1.4, -0.5]	-21.9 [-30.9, -11.9]	<.0001
Sensitivity 2[a]	-0.9 [-1.4, -0.5]	-21.4 [-30.5, -11.4]	<.0001
Treatment policy estimand	--	--	--
Main analytical approach	-1.0 [-1.4, -0.5]	-21.8 [-30.8, -11.8]	<.0001
Sensitivity	-0.9 [-1.4, -0.5]	-21.1 [-30.2, -11.0]	0.0001

Source: Applicant 1.11.3 Response to FDA IR dated 11/8/2024, pg. 4, Table 1 (original CSR MT-12, pg. 69, Table 19)
Abbreviations: TCRS=total combined rhinitis score; FAS=full analysis set; CI=confidence interval
Notes: p-value=p-value for test of superiority (an absolute difference of 0) TCRS=total combined rhinitis score
Absolute difference=12 SQ-HDM - Placebo, relative difference=(12 SQ-HDM - Placebo)/Placebo, Penalty=penalty that had to be added to imputed values for the 12 SQ-HDM treatment group in order for the conclusion to change

Additional sensitivity and supportive analyses of the primary efficacy endpoint were conducted as shown in Table 10 above. These additional analyses were conducted to exclude participants with potential data issues including participants randomized in error, siblings in the same cohort, and participants in Ukraine who were unable to take the study treatment). Analysis of the primary endpoint using estimands was conducted to determine the impact of missing data on the outcome. While both estimands contained all data for participants who completed the study, the trial product estimand contained data until discontinuation of treatment for those participants who discontinued treatment whereas the treatment product estimand contained all observed data for those participants who discontinued treatment. The sensitivity analysis results were similar to the primary efficacy analysis.

Clinical Reviewer Comment: The primary efficacy analysis and the additional sensitivity and supportive analyses of the primary endpoint yielded consistent positive improvements in the average daily TCRS compared to placebo during the primary efficacy assessment period. The lack of significant difference between the primary efficacy analysis and the sensitivity analysis makes it unlikely that missing data impacted the results of the primary efficacy analysis.

6.1.11.2 Analyses of Secondary Endpoints

Key secondary analyses include the Rhinitis DSS, Rhinitis DMS, and the Total Combined Rhinoconjunctivitis Score (TCS).

Rhinitis Daily Symptom Score (DSS)

The nonparametric analysis of the average rhinitis DSS for the FAS population during the last 8 weeks of treatment is presented in the table below.

Table 11. Analysis of Average Rhinitis DSS During the Primary Efficacy Period, Observed Case (FAS), Study MT-12

Treatment	N_{FAS}	n_{obs}	Adjusted Mean (SE)	Estimate [95% CI]	p-value
Placebo	731	706	1.9 (0.1)	--	--
12 SQ-HDM	727	693	1.5 (0.1)	--	--
12 SQ-HDM - Placebo	--	--	--	-0.4 [-0.6, -0.2]	<.0001
(12 SQ-HDM - Placebo)/Placebo (%)	--	--	--	-22.2 [-30.8, -12.8]	

Source: Applicant Response to FDA IR dated 10/24/2024, pg. 19, Table 16
Abbreviations: FAS=full analysis set, SE=standard error, CI=confidence interval, N_{FAS}=number of participants in FAS, n_{obs}=number of participants with observations contributing to the analysis, DSS=daily symptom score
Notes: The endpoint was square root transformed and analyzed as the response variable in an LME which includes treatment and cohort as fixed factors, the square root of the baseline value as a covariate, country/region within cohort as a random effect, and with different residual errors specified for each treatment. Denominator degrees of freedom was calculated using the Kenward and Roger's approximation. The p-value for the absolute difference is reported as the test result. The results were back-transformed as follows; from the LME, estimated least square means on the square root transformed scale were output along with associated covariance matrix. For the adjusted means and absolute difference, the SE was approximated by using the first order Delta method (first order Taylor approximation), and from this the 95% CI was calculated. For the relative difference, Fieller's theorem was first used to calculate the 95% CI, and then this was back-transformed by applying a monotone transformation.

Rhinitis Daily Medication Score (DMS)

The nonparametric analysis of the average rhinitis DMS for the FAS population during the last 8 weeks of treatment is presented in the table below.

Table 12. Analysis of Average Rhinitis DMS During the Primary Efficacy Period, Observed Case (FAS), Study MT-12

Treatment	N_{FAS}	n_{obs}	Adjusted Mean (SE)	Estimate [95% CI]	p-value
Placebo	731	706	1.9 (0.2)	--	--
12 SQ-HDM	727	693	1.4 (0.2)	--	--
12 SQ-HDM - Placebo	--	--	--	-0.5 [-0.8, -0.2]	0.0016
(12 SQ-HDM - Placebo-)/Placebo (%)	--	--	--	-25.3 [-38.3, -10.5]	

Source: Applicant Response to FDA IR dated 10/24/2024, pg. 23. Table 21
Abbreviations: FAS=full analysis set, SE=standard error, CI=confidence interval, N_{FAS}=number of participants in FAS, n_{obs}=number of participants with observations contributing to the analysis, DMS=daily medication score
Notes: The endpoint was square root transformed and analyzed as the response variable in an LME which includes treatment and cohort as fixed factors, the square root of the baseline value as a covariate, country/region within cohort as a random effect, and with different residual errors specified for each treatment. Denominator degrees of freedom was calculated using the Kenward and Roger's approximation. The p-value for the absolute difference is reported as the test result. The results were back-transformed as follows; from the LME, estimated least square means on the square root transformed scale were output along with associated covariance matrix. For the adjusted means and absolute difference, the SE was approximated by using the first order Delta method (first order Taylor approximation), and from this the 95% CI was calculated. For the relative difference, Fieller's theorem was first used to calculate the 95% CI, and then this was back-transformed by applying a monotone transformation.

Total Combined Rhinoconjunctivitis Score (TCS)

The nonparametric analysis of the average TCS for the FAS population during the last 8 weeks of treatment is summarized in the table below.

Table 13. Analysis of Average Daily TCS During the Primary Efficacy Period, Observed Case (FAS), Study MT-12

Treatment	N_{FAS}	n_{obs}	Adjusted Mean (SE)	Estimate [95% CI]	p-value
Placebo	731	706	5.2 (0.4)	--	--
12 SQ-HDM	727	693	4.0 (0.4)	--	--
12 SQ-HDM - Placebo	--	--	--	-1.1 [-1.7, -0.6]	<.0001
(12 SQ-HDM - Placebo)/Placebo (%)	--	--	--	-22.2 [-31.5, -12.0]	

Source: Applicant Response to FDA IR dated 10/24/2024, pg. 28, Table 27
Abbreviations: FAS=full analysis set, SE=standard error, CI=confidence interval, N_{FAS}=number of participants in FAS, n_{obs}=number of participants with observations contributing to the analysis, TCS=total combined score
Notes: The endpoint was square root transformed and analyzed as the response variable in an LME which includes treatment and cohort as fixed factors, the square root of the baseline value as a covariate, country/region within cohort as a random effect, and with different residual errors specified for each treatment. Denominator degrees of freedom was calculated using the Kenward and Roger's approximation. The p-value for the absolute difference is reported as the test result. The results were back-transformed as follows; from the LME, estimated least square means on the square root transformed scale were output along with associated covariance matrix. For the adjusted means and absolute difference, the SE was approximated by using the first order Delta method (first order Taylor approximation), and from this the 95% CI was calculated. For the relative difference, Fieller's theorem was first used to calculate the 95% CI, and then this was back-transformed by applying a monotone transformation.

Clinical Reviewer Comment: The secondary endpoint analyses demonstrate a decrease in both medication use as well as symptoms of allergic rhinitis/rhinoconjunctivitis and provide additional supportive data for the clinical benefit of Odactra in this age group.

6.1.11.3 Subpopulation Analyses

Subgroup analysis based on the observed case analysis of the average TCRS during the last 8 weeks of treatment included asthma status, pollen sensitization, allergen sensitivity (mono vs. polysensitization), sex, race, and geographic location. The tables below present data specific to asthma status, pollen sensitization, allergen sensitivity, sex, race, and geographic location.

Table 14. Analysis of Average Daily TCRS During the Primary Efficacy Period by Asthma Status, Pollen Sensitization, and Baseline Sensitization, Observed Case, FAS, Study MT-12

Status	N_{FAS}	n_{obs}	Adjusted mean (SE)	Estimate [95% CI]	p-value
Asthma history: No[a]	--	--	--	--	--
Placebo	441	426	4.1 (0.4)	--	--
12 SQ-HDM	460	442	3.3 (0.3)	--	--
12 SQ-HDM - Placebo	--	--	--	-0.8 [-1.4, -0.2]	0.0090
(12 SQ-HDM - Placebo)/Placebo (%)	--	--	--	-18.9 [-30.9, -5.1]	--
Asthma history: Yes[a]	--	--	--	--	--
Placebo	290	280	4.9 (0.4)	--	--
12 SQ-HDM	267	251	3.6 (0.4)	--	--
12 SQ-HDM - Placebo	--	--	--	-1.3 [-2.1, -0.5]	0.0020
(12 SQ-HDM - Placebo)/Placebo (%)	--	--	--	-25.7 [-38.8, -10.3]	--
Pollen sensitized: No[b]	--	--	--	--	--
Placebo	484	468	4.3 (0.4)	--	--
12 SQ-HDM	460	441	3.4 (0.3)	--	--
12 SQ-HDM - Placebo	--	--	--	-0.9 [-1.4, -0.3]	0.0034
(12 SQ-HDM - Placebo)/Placebo (%)	--	--	--	-20.2 [-31.6, -7.2]	--
Pollen sensitized: Yes[b]	--	--	--	--	--
Placebo	247	238	4.7 (0.4)	--	--
12 SQ-HDM	267	252	3.5 (0.4)	--	--
12 SQ-HDM - Placebo	--	--	--	-1.2 [-2.0, -0.4]	0.0039

Status	N_{FAS}	n_{obs}	Adjusted mean (SE)	Estimate [95% CI]	p-value
(12 SQ-HDM - Placebo)/Placebo (%)	--	--	--	-25.5 [-39.3, -9.0]	--
HDM only[c]	--	--	--	--	--
Placebo	360	346	4.3 (0.4)	--	--
12 SQ-HDM	337	327	3.5 (0.3)	--	--
12 SQ-HDM - Placebo-	--	--	--	-0.8 [-1.5, -0.2]	0.0157
(12 SQ-HDM - Placebo)/Placebo (%)	--	--	--	-19.3 [-32.5, -4.0]	--
HDM and others[c]	--	--	--	--	--
Placebo	371	360	4.5 (0.4)	--	--
12 SQ-HDM	390	366	3.4 (0.3)	--	--
12 SQ-HDM - Placebo	--	--	--	-1.1 [, -1.8, -0.4]	0.0010
(12 SQ-HDM - Placebo)/Placebo (%)	--	--	--	-24.4 [-36.3, -10.7]	--

Source: Applicant Responses to FDA IRs dated 10/24/2024, pg. 7, Table 7, and 11/20/2024, pgs. 7 and 11, Tables 3 and 7
Abbreviations: FAS=full analysis set, SE=standard error, CI=confidence interval, N_{FAS}=number of participants in FAS, n_{obs} = number of participants with observations contributing to the analysis, TCRS=total combined rhinitis score.
Notes:
a. Asthma status: The p-value for the interaction effect between subgroup and treatment is p=0.4040.
b. Pollen sensitization: The p-value for the interaction effect between subgroup and treatment is p=0.5539. Pollen sensitized refers to whether the participant had a positive SPT test to either grass, birch, oak or ragweed.
c. Baseline sensitization: The p-value for the interaction effect between subgroup and treatment is p=0.5865. Baseline sensitizations are based on skin prick test. HDM refers to "HDM*, Dermatophagoides pteronyssinus*, and HDM, *Dermatophagoides farinae*". Others refer to "Cat (*Felis domesticus*), Grass (*Phleum pratense*), Dog (*Canis familiaris*), Birch (*Betula verrucosa*), *Ambrosia artemisiifolia*, Mold (*Alternaria alternata*), *Cladosporium*, and *Quercus alba*."
The endpoint was square root transformed and analyzed as the response variable in an LME which included treatment, cohort, asthma history, and treatment by asthma history interaction as fixed factors, pollen sensitization, and treatment by pollen sensitization interaction as fixed factors, the square root of the baseline value as a covariate, country/region within cohort as a random effect, and with different residual errors specified for each treatment.
Denominator degrees of freedom was calculated using the Kenward and Roger's approximation. The p-value for the absolute difference is reported. The results were back-transformed as follows: from the LME, estimated least square means on the square root transformed scale were output along with associated covariance matrix. For the absolute difference the SE was approximated by using the first order Delta method (first order Taylor approximation), and from this the 95% CI was calculated. For the relative difference, Fieller's theorem was first used to calculate the 95% CI, and then this was back-transformed by applying a monotone transformation.

Table 15. Analysis of Average Daily TCRS During the Primary Efficacy Period by Sex, Age Group, Race, and Geographic Region - Observed Case (FAS)

Demographic Characteristic	Effect	N_{FAS}	n_{obs}	Adjusted Mean (SE)	Estimate [95% CI]	p-value
Sex[a]	--	--	--	--	--	--
Female	Placebo	254	248	4.40 (0.42)	-	-
Female	12 SQ-HDM	241	230	3.12 (0.36)	-	-
Female	Placebo - 12 SQ-HDM	-	-	-	1.28 [0.48; 2.07]	0.0015
Female	(Placebo - 12 SQ-HDM)/Placebo(%)	-	-	-	29.1 [12.3; 43.1]	-
Male	Placebo	477	458	4.42 (0.36)	-	-
Male	12 SQ-HDM	486	463	3.61 (0.33)	-	-
Male	Placebo - 12 SQ-HDM	-	-	-	0.81 [0.22; 1.40]	0.0066
Male	(Placebo - 12 SQ-HDM)/Placebo(%)	-	-	-	18.4 [5.5; 29.7]	-
Age[b]	--	--	--	--	--	--
4 to 7 years	Placebo	286	279	4.85 (0.43)	-	-
4 to 7 years	12 SQ-HDM	291	280	3.90 (0.38)		

Demographic Characteristic	Effect	N_{FAS}	n_{obs}	Adjusted Mean (SE)	Estimate [95% CI]	p-value
4 to 7 years	Placebo - 12 SQ-HDM	-	-	-	0.95 [0.16; 1.74]	0.0177
4 to 7 years	(Placebo - 12 SQ-HDM)/Placebo(%)	-	-	-	19.6 [3.7; 33.0]	-
8 to 11 years	Placebo	445	427	4.14 (0.36)	-	-
8 to 11 years	12 SQ-HDM	436	413	3.15 (0.32)	-	-
8 to 11 years	Placebo - 12 SQ-HDM	-	-	-	0.99 [0.40; 1.58]	0.0009
8 to 11 years	(Placebo - 12 SQ-HDM)/Placebo(%)	-	-	-	23.9 [10.6; 35.6]	-
Race[c]	--	--	--	--	--	--
White	Placebo	714	690	4.31 (0.34)	-	-
White	12 SQ-HDM	722	689	3.40 (0.30)	-	-
White	Placebo - 12 SQ-HDM	-	-	-	0.91 [0.44; 1.38]	0.0001
White	(Placebo - 12 SQ-HDM)/Placebo(%)	-	-	-	21.1 [10.9; 30.4]	-
Non-White	Placebo	17	16	7.09 (1.58)	-	-
Non-White	12 SQ-HDM	5	4	3.45 (2.15)	-	-
Non-White	Placebo - 12 SQ-HDM	-	-	-	3.64 [-1.45; 8.73]	0.2055
Non-White	(Placebo - 12 SQ-HDM)/Placebo(%)	-	-	-	51.3 [-40.0; 92.7]	-
Geographic Region[d]	--	--	--	--	--	--
Europe	Placebo	692	671	4.32 (0.36)	-	-
Europe	12 SQ-HDM	688	659	3.41 (0.32)	-	-
Europe	Placebo - 12 SQ-HDM	-	-	-	0.91 [0.43; 1.40]	0.0002
Europe	(Placebo - 12 SQ-HDM)/Placebo(%)	-	-	-	21.2 [10.7; 30.7]	-
North America	Placebo	39	35	5.36 (1.09)	-	-
North America	12 SQ-HDM	39	34	3.34 (0.87)	-	-
North America	Placebo - 12 SQ-HDM	-	-	-	2.02 [-0.23; 4.27]	0.0754
North America	(Placebo - 12 SQ-HDM)/Placebo(%)	-	-	-	37.6 [-4.9; 64.8]	-

Source: Applicant Response to FDA IR, dated 10/24/2024, STN 125592/218
Abbreviations: NFAS=number of participants in FAS; nobs=number of observed values
Notes:
a. For sex, the p-value for the interaction of the subgroup and treatment is p=0.3197
b. For age, the p-value for the interaction of the subgroup and treatment is p=0.7891. Two participants were analyzed as 4 years old at randomization due to recording of partial dates.
c. For race, the p-value for the interaction of the subgroup and treatment is p=0.369
d. For geographic region, the p-value for the interaction of the subgroup and treatment is p=0.3656
The endpoint was square root transformed and analyzed as the response variable in an LME which included treatment, cohort, sex, sex by treatment interaction, age group, age group by treatment interaction, race, race by treatment interaction, region, and region by treatment interaction as fixed factors, the square root of the baseline value as a covariate, country/region within cohort as a random effect, and with different residual errors specified for each treatment.
Denominator degrees of freedom was calculated using the Kenward and Roger's approximation. The p-value for the absolute difference is reported.
The results were back-transformed as follows: from the LME, estimated least square means on the square root transformed scale were output along with associated covariance matrix. For the absolute difference the SE was approximated by using the first order Delta method (first order Taylor approximation), and from this the 95% CI was calculated.

For the relative difference, Fieller's theorem was first used to calculate the 95% CI, and then this was back-transformed by applying a monotone transformation.

Clinical Reviewer Comment: The percent treatment difference relative to placebo follows a consistent trend towards symptomatic improvement in all subgroups listed above. Allergic rhinitis patients are usually polysensitized and observation of a treatment benefit in the subgroup of polysensitized participants with treatment to only one of the aeroallergens to which they are sensitized further supports the clinical benefit of this product in this age group.

Analyses of the average rhinitis DSS, rhinitis DMS, and TCS during the last 8 weeks of treatment by asthma status is shown in the tables below.

Table 16. Analysis of Average Rhinitis DSS During the Primary Efficacy Period by Asthma Status, Observed Case, FAS, Study MT-12

Status	N_{FAS}	n_{obs}	Adjusted mean (SE)	Estimate [95% CI]	p-value
Asthma history: No	--	--	--	--	--
Placebo	441	426	1.9 (0.2)	--	--
12 SQ-HDM	460	442	1.5 (0.1)	--	--
12 SQ-HDM - Placebo	--	--	--	-0.4 [-0.7, -0.2]	0.0012
(12 SQ-HDM - Placebo)/Placebo (%)	--	--	--	-21.2 [-32.0, -9.0]	--
Asthma history: Yes	--	--	--	--	--
Placebo	290	280	1.9 (0.2)	--	--
12 SQ-HDM	267	251	1.5 (0.2)	--	--
12 SQ-HDM - Placebo	--	--	--	-0.5 [-0.8, -0.1]	0.0039
(12 SQ-HDM - Placebo)/Placebo (%)	--	--	--	-23.9 [-37.1, -8.4]	--

Source: 1.11.3 Applicant response to FDA IR dated 11/20/2024, pg. 8, Table 4
Abbreviations: DSS=daily symptom score, FAS=full analysis set, SE=standard error, CI=confidence interval, N_{FAS}=number of participants in FAS, n_{obs}=number of participants with observations contributing to the analysis
Notes: The p-value for the interaction effect between subgroup and treatment is p=0.7774
The endpoint was square root transformed and analyzed as the response variable in an LME which included treatment, cohort, asthma history, and treatment by asthma history interaction as fixed factors, the square root of the baseline value as a covariate, country/region within cohort as a random effect, and with different residual errors specified for each treatment.
Denominator degrees of freedom was calculated using the Kenward and Roger's approximation. The p-value for the absolute difference is reported. The results were back-transformed as follows: from the LME, estimated least square means on the square root transformed scale were output along with associated covariance matrix. For the absolute difference the SE was approximated by using the first order Delta method (first order Taylor approximation), and from this the 95% CI was calculated. For the relative difference, Fieller's theorem was first used to calculate the 95% CI, and then this was back-transformed by applying a monotone transformation.

Table 17. Analysis of Average Rhinitis DMS During the Primary Efficacy Period by Asthma Status, Observed Case, FAS, Study MT-12

Status	N_{FAS}	n_{obs}	Adjusted mean (SE)	Estimate [95% CI]	p-value
Asthma history: No	--	--	--	--	--
Placebo	441	426	1.7 (0.2)	--	--
12 SQ-HDM	460	442	1.3 (0.2)	--	--
12 SQ-HDM - Placebo	--	--	--	-0.3 [-0.7, 0.0]	0.0678
(12 SQ-HDM - Placebo)/Placebo (%)	--	--	--	-20.3 [-38.0, 1.7]	
Asthma history: Yes	--	--	--	--	--
Placebo	290	280	2.4 (0.3)	--	--
12 SQ-HDM	267	251	1.7 (0.2)	--	--
12 SQ-HDM - Placebo	--	--	--	-0.7 [-1.3, -0.2]	0.0091
(12 SQ-HDM - Placebo)/Placebo (%)	--	--	--	-30.2 [-47.5, -8.5]	--

Source: 1.11.3 Applicant response to FDA IR dated 11/20/2024, pg. 9, Table 5
Abbreviations: DMS=daily medication score, FAS=full analysis set, SE=standard error, CI=confidence interval, N_{FAS}=number of participants in FAS, n_{obs}=number of participants with observations contributing to the analysis
Notes: The p-value for the interaction effect between subgroup and treatment is p=0.3510
The endpoint was square root transformed and analyzed as the response variable in an LME which included treatment, cohort, asthma history, and treatment by asthma history interaction as fixed factors, the square root of the baseline value as a covariate, country/region within cohort as a random effect, and with different residual errors specified for each treatment.
Denominator degrees of freedom was calculated using the Kenward and Roger's approximation. The p-value for the absolute difference is reported. The results were back-transformed as follows: from the LME, estimated least square means on the square root transformed scale were output along with associated covariance matrix. For the absolute difference the SE was approximated by using the first order Delta method (first order Taylor approximation), and from this the 95% CI was calculated. For the relative difference, Fieller's theorem was first used to calculate the 95% CI, and then this was back-transformed by applying a monotone transformation.

Table 18. Analysis of Average Daily TCS During the Primary Efficacy Period by Asthma Status, Observed Case, FAS, Study MT-12

Status	N_{FAS}	n_{obs}	Adjusted mean (SE)	Estimate [95% CI]	p-value
Asthma history: No	--	--	--	--	--
Placebo	441	426	4.8 (0.4)	--	--
12 SQ-HDM	460	442	3.9 (0.4)	--	--
12 SQ-HDM - Placebo	--	--	--	-0.9 [-1.6, -0.2]	0.0106
(12 SQ-HDM - Placebo)/Placebo (%)	--	--	--	-18.9 [-31.2, -4.8]	
Asthma history: Yes	--	--	--	--	--
Placebo	290	280	5.8 (0.5)	--	--
12 SQ-HDM	267	251	4.3 (0.4)	--	--
12 SQ-HDM - Placebo	--	--	--	-1.5 [-2.5, -0.6]	0.0020
(12 SQ-HDM - Placebo)/Placebo (%)	--	--	--	-26.1 [-39.5, -10.5]	

Source: 1.11.3 Applicant response to FDA IR dated 11/20/2024, pg. 10, Table 6
Abbreviations: TCS=total combined score, DSS=daily symptom score, FAS=full analysis set, SE=standard error, CI=confidence interval, N_{FAS}=number of participants in FAS, n_{obs}=number of participants with observations contributing to the analysis
Notes: The p-value for the interaction effect between subgroup and treatment is p=0.3860
The endpoint was square root transformed and analyzed as the response variable in an LME which included treatment, cohort, asthma history, and treatment by asthma history interaction as fixed factors, the square root of the baseline value as a covariate, country/region within cohort as a random effect, and with different residual errors specified for each treatment.
Denominator degrees of freedom was calculated using the Kenward and Roger's approximation. The p-value for the absolute difference is reported. The results were back-transformed as follows: from the LME, estimated least square means on the square root transformed scale were output along with associated covariance matrix. For the absolute difference the SE was approximated by using the first order Delta method (first order Taylor approximation), and from this the 95% CI was calculated. For the relative difference, Fieller's theorem was first used to calculate the 95% CI, and then this was back-transformed by applying a monotone transformation.

Clinical Reviewer Comment: The subgroup analyses by asthma history did not show a clinically meaningful difference in treatment effect between the subgroups. These results demonstrate a

consistent treatment effect in participants with allergic rhinitis/rhinoconjunctivitis independent of baseline asthma status.

6.1.11.4 Dropouts and/or Discontinuations

Section 6.1.10.1.3 provides a table detailing dropouts and discontinuations for Study MT-12. The number of discontinuations was higher in the Odactra group (36/727 [5.0%]) than the placebo group (24/731 [3.3%]). Of those who discontinued study treatment, more Odactra recipients discontinued due to AEs (14 [1.9%]) than placebo recipients (6 [0.4%]). Of the 36 participants who discontinued Odactra, a total of 4 (0.6%) reported severe AEs, all of which were assessed as unlikely related to Odactra. Four SAEs resulted in discontinuation of Odactra (attention deficit hyperactivity disorder, hallucinations, immune system disorder, and pseudomonas bronchitis). These SAEs are discussed in more detail in Section 6.1.12.4. All of these events were assessed as unlikely related to treatment.

Clinical Reviewer Comment: The number of dropouts and discontinuations for Study MT-12 was low and as a result, they are unlikely to affect interpretation of the efficacy data given the small number. The Applicant performed additional sensitivity analyses to evaluate the impact of this missing data using different estimand approaches which showed a similar treatment effect as the primary analysis.

6.1.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.1.12 Safety Analyses

6.1.12.1 Methods

A total of 1458 participants (727 Odactra; 731 placebo) were included in the safety analyses. The median duration of treatment was 367 days in the safety population. The range was 1 to 436 days.

AEs were assessed throughout the 52-57 weeks of the trial, beginning with the run-in period, randomization period, through telephone contact during the trial and 2 weeks after the last study visit, during the treatment phase, efficacy assessment period, and final study visit. AEs were recorded in the electronic case report form by the investigator. An eDiary was completed by participants for the first 28 days of treatment and filled out within the first 60 minutes of study drug intake. AEs were assessed by their intensity, severity, and relation to the study treatment. Unsolicited AEs, SAEs, adverse events of special interest (AESIs), and deaths were monitored throughout the study.

6.1.12.2 Overview of Adverse Events

The two tables below summarize all AEs in the safety population, including solicited (captured by eDiary) and unsolicited AEs.

Table 19. Summary of Safety Profile, Safety Analysis Set (SAS), Study MT-12

Participants Experiencing	Placebo (N=731) n (%n)	Odactra (N=727) n (%n)
TEAE	585 (80.0%)	632 (86.9%)
IMP-related TEAE	391 (53.5%)	548 (75.4%)

Participants Experiencing	Placebo (N=731) n (%n)	Odactra (N=727) n (%n)
IMP-related severe TEAE	2 (0.3%)	4 (0.6%)
IMP-related treatment-emergent SAE	0 (0.0%)	0 (0.0%)
IMP-related TEAE leading to discontinuation of IMP[a]	7 (1.0%)	13 (1.8%)
Solicited TEAE	411 (56.2%)	555 (76.3%)
IMP-related solicited TEAE	367 (50.2%)	543 (74.7%)
IMP-related treatment-emergent systemic allergic reaction including anaphylaxis	1 (0.1%)	2 (0.3%)
IMP-related TEAE treated with adrenaline/epinephrine	0 (0.0%)	0 (0.0%)
IMP-related treatment-emergent severe local swelling or edema of the mouth and/or throat	0 (0.0%)	2 (0.3%)
IMP-related TEAE of eosinophilic esophagitis	0 (0.0%)	0 (0.0%)

Source: Adapted from Applicant CSR, Study MT-12, Table 37, pg. 87
Abbreviations: SAS=Safety set, N=Number of participants in SAS; n=Number of participants with events, %n=Percent participants with events of SAS; TEAE=treatment-emergent adverse event; IMP=investigational medicinal product
Notes:
a. Taken from the AE form 'Changes to IMP due to AE' action 'Drug withdrawn'.

Table 20. Summary of IMP-Related TEAEs, Safety Analysis Set (SAS), Study MT-12

TEAEs	Placebo (N=731) n (%n)	Placebo (N=731) e (%e)	Odactra (N=727) n (%n)	Odactra (N=727) e (%e)
All events	391 (53.5%)	2183 (100%)	548 (75.4%)	5220 (100%)
Severity	--	--	--	--
Mild	379 (51.8%)	2068 (94.7%)	542 (74.6%)	4894 (93.8%)
Moderate	47 (6.4%)	113 (5.18%)	96 (13.2%)	314 (6.02%)
Severe	2 (0.3%)	2 (0.09%)	4 (0.6%)	12 (0.23%)
Serious Outcome	--	--	--	--
Recovered / resolved	391 (53.5%)	2182 (100%)	548 (75.4%)	5216 (99.9%)
Not recovered / not resolved	--	--	3 (0.4%)	3 (0.06%)
Unknown	1 (0.1%)	1 (0.05%)	1 (0.1%)	1 (0.02%)
Changes to IMP due to AE	--	--	--	--
None	381 (52.1%)	2143 (98.2%)	545 (75.0%)	5109 (97.9%)
Drug interrupted	23 (3.1%)	32 (1.47%)	36 (5.0%)	82 (1.57%)
Drug withdrawn	7 (1.0%)	8 (0.37%)	13 (1.8%)	29 (0.56%)

Source: Adapted from Applicant CSR MT-12, pg. 91, Table 39
Abbreviations: N=number of participants in SAS; n=Number of participants with events; %n=percent participants with events of SAS; e=number of events; %e=percent events; TEAEs=treatment-emergent adverse events; AE=adverse event, IMP=investigational medicinal product

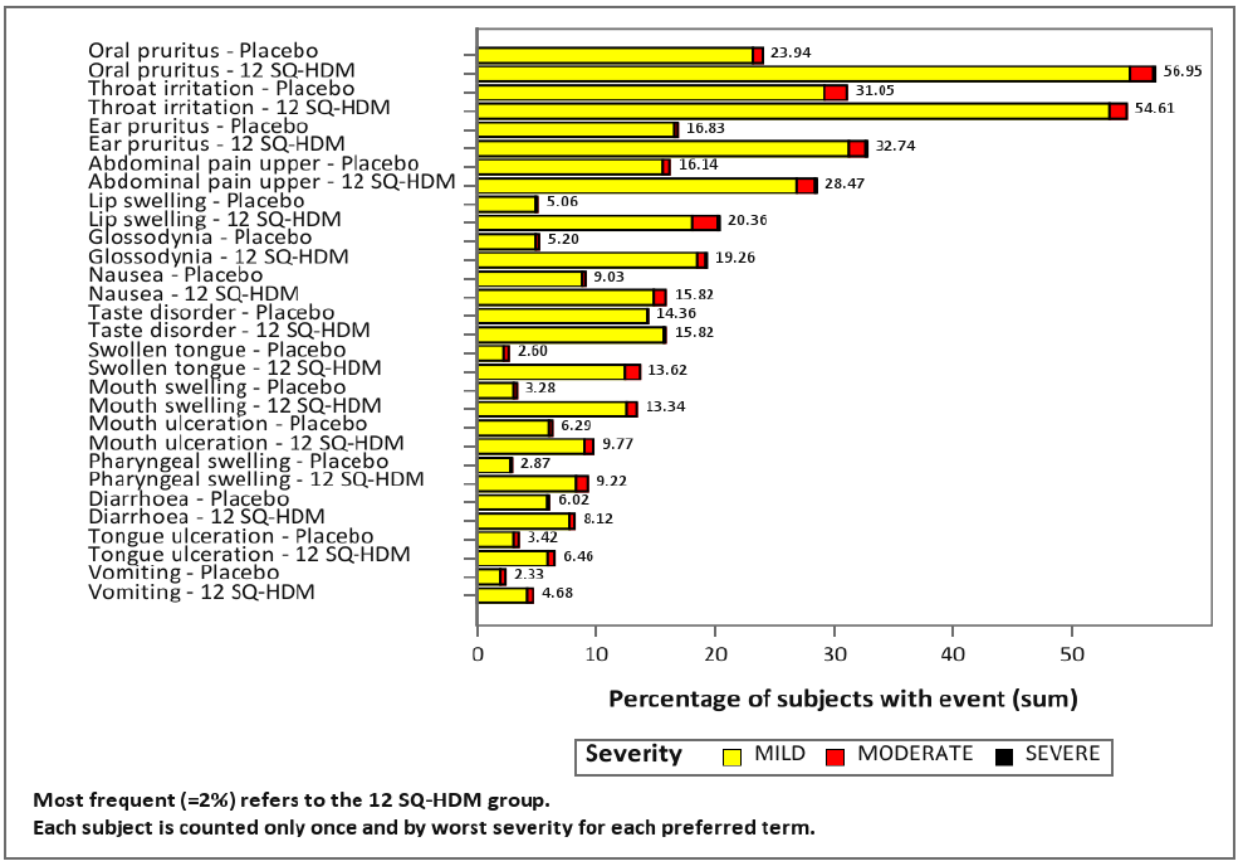
Notes: IMP-related AEs are TEAEs reported as 'possibly related' by the investigator.

A total of 9912 AEs were reported by 1217 (83.5%) of the 1458 participants in the safety population. A total of 86.9% participants in the 12-SQ-HDM group reported AEs (6489 events) and 80.0% of the participants in the placebo group reported AEs (3423 events). The most commonly reported AEs occurred under the System Organ Classes (SOCs) of Gastrointestinal disorders (50.5%) and Respiratory, thoracic, and mediastinal disorders (19.7%). The most frequently reported AEs were oral pruritus (15.9%), throat irritation (15.9%), ear pruritus (8.5%), upper abdominal pain (8.4%), nausea (3.9%), and glossodynia (3.7%).

A total of 64.4% of participants in the study (939/1458) reported AEs that were considered by the investigator as possibly or probably related to study treatment, including 75.4% pf

participants in the 12 SQ-HDM group and 53.5% of participants in the placebo group; these events included throat irritation, oral pruritus, upper abdominal pain, and ear pruritus, all of which have been observed in previous SLIT trials. A plot of treatment-related AEs reported in ≥2% of participants is shown in Figure 2.

Figure 2. Plot of Most Frequent (≥2%) IMP-Related TEAEs by System Organ Class, Preferred Term, and Severity, Safety Analysis Set (SAS), Study MT-12



Source: Applicant CSR, MT-12, Figure 15.3.1.14, page 314
Abbreviations: TEAEs=treatment-emergent adverse events; IMP=investigational medicinal product

The percentage of participants who discontinued the study because of an adverse reaction while exposed to ODACTRA or placebo was 1.8% and 1.0%, respectively. The most common adverse reactions that led to study discontinuation in participants who were exposed to ODACTRA were nausea (0.6%), lip swelling (0.4%) and throat irritation (0.4%).

The median time to onset of each adverse reaction following initiation of treatment with Odactra varied from 1.5 and 14.5 days. Adverse reactions that occurred on the first day of treatment initiation had a median duration of 1-2 days. Recurrent adverse reactions were defined as events that re-occurred daily. The median total duration for recurrent reactions ranged between 2 to 5 days. The median daily duration ranged between 5-30 minutes.

Severe adverse reactions occurred in <1% of participants taking Odactra. Of the 6 participants in the SAS with severe ARs, 4 were receiving Odactra. Three of these participants had drug-related local application site reactions. The severe local application reactions included oral pruritus (1 participant with 3 separate events), ear pruritus (1 participant with 3 separate events), and glossodynia (1 participant with 2 separate events). Other severe adverse reactions

included lip swelling (1 participant with 2 events and 1 participant with 1 event) and abdominal pain upper (1 participant with 1 event). No participants discontinued from the trial due to severe local application site reactions, none were considered SAEs and all resolved. None of the participants with severe local ARs were treated with epinephrine.

Adverse reactions were solicited through an eDiary during the first 28 days of treatment in which the parent/caregiver along with the participant recorded whether they experienced any of the 15 pre-specified symptoms/signs identified as local side effects of SLIT. A notably higher proportion of Odactra recipients reported solicited adverse reactions and a higher number of events per participant compared to placebo recipients. The majority of adverse reactions in the Odactra recipients were mild, had an outcome of resolved/recovered, and did not lead to an interruption in treatment or discontinuation of treatment. See Table 21 and Table 22 below for solicited adverse reactions.

Table 21. Summary of IMP-Related Solicited TEAEs, Safety Analysis Set (SAS), Study MT-12

TEAEs	Placebo (N=731) n (%n)	Placebo (N=731) e (%e)	Odactra (N=727) n (%n)	Odactra (N=727) e (%e)
All events	367 (50.2%)	2083 (100%)	543 (74.7%)	4980 (100%)
Severity	--	--	--	--
Mild	360 (49.2%)	1985 (95.3%)	536 (73.7%)	4680 (94.0%)
Moderate	36 (4.9%)	98 (4.70%)	82 (11.3%)	288 (5.78%)
Severe	--	--	4 (0.6%)	12 (0.24%)
Serious Outcome	--	--	--	--
Recovered/ resolved	367 (50.2%)	2083 (100%)	543 (74.7%)	4979 (100%)
Not recovered/ not resolved	--	--	1 (0.1%)	1 (0.02%)
Changes to IMP due to AE	--	--	--	--
None	366 (50.1%)	2070 (99.4%)	541 (74.4%)	4891 (98.2%)
Drug interrupted	7 (1.0%)	12 (0.58%)	30 (4.1%)	70 (1.41%)
Drug withdrawn	1 (0.1%)	1 (0.05%)	8 (1.1%)	19 (0.38%)

Source: Adapted from Applicant CSR MT-12, pg. 96, Table 43
Abbreviations: N=number of participants in SAS; n=Number of participants with events; %n=percent participants with events of SAS; e=number of events; %e=percent events; TEAEs=treatment-emergent adverse events; AE=adverse event, IMP=investigational medicinal product
Notes: IMP-related adverse events are treatment-emergent adverse events reported as 'possibly related' by the investigator.

Table 22. Solicited Adverse Reactions* Occurring Within 28 Days After Initiation of Treatment with Odactra or Placebo (Study 6, Safety Analysis Set) in Participants 5 through 11 Years of Age

Adverse Reaction	Any Intensity Odactra (N=727)	Placebo (N=731)	Severe† Odactra (N=727)	Severe† Placebo (N=731)
Ear and labyrinth disorders	--	--	--	--
Itching in the ear	32.7%	17.0%	0.1%	-
Gastrointestinal disorders	--	--	--	--
Itching in the mouth	57.1%	23.9%	0.1%	-
Stomach pain	28.2%	15.7%	0.1%	-
Swelling of the lips	20.5%	4.9%	0.3%	-
Tongue pain	19.4%	5.2%	0.1%	-
Nausea (feel like throwing up)	15.7%	9.0%	-	-
Swelling in the back of the mouth	13.5%	3.3%	-	-
Swelling of the tongue	13.5%	2.6%	-	-
Mouth ulcer	10.0%	6.4%	-	-
Diarrhea	8.0%	5.9%	-	-
Tongue ulcer	6.3%	3.4%	-	-

Adverse Reaction	Any Intensity Odactra (N=727)	Placebo (N=731)	Severe† Odactra (N=727)	Severe† Placebo (N=731)
Vomiting	4.5%	2.2%	-	-
Nervous system disorders	--	--	--	--
Food tastes different	16.0%	14.5%	-	-
Respiratory, thoracic and mediastinal disorders	--	--	--	--
Throat irritation/tickle	55.2%	31.5%	-	-
Throat swelling	9.2%	2.9%	-	-

Source: Odactra USPI, updated 2/2025 (initial approval: 2017), pg. 10, Table 4
Notes: The dashes in the table represent no participants.
*Solicited adverse reactions (modified from World Allergy Organization [WAO] list of local side effects of sublingual immunotherapy [SLIT]) were those reported by participants within the first 28 days after treatment initiation and determined by the investigator to be possibly related to the study treatment.
†Severe adverse reactions were those assessed by the investigator as severe in intensity, which is defined as incapacitating with inability to work or do usual activity.

Clinical Reviewer Comment: The most frequently reported solicited adverse reactions in children with HDM SLIT were consistent with those reactions frequently reported in children with treatment with seasonal pollen extracts (Grastek, Oralair, and Ragwitek).

The percentage of Odactra recipients reporting unsolicited ARs was greater than placebo recipients (15.5% vs. 10.3% respectively). Most of the unsolicited ARs in the Odactra group were mild or moderate and had an outcome of recovered/resolved (98.5% with 1.1% not recovered/not resolved and 0.4% unknown). See table below for unsolicited adverse reactions occurring during the entire trial.

Table 23. Unsolicited Adverse Reactions Occurring During the Entire Trial After Initiation of Treatment with Odactra or Placebo (Study 6, Safety Analysis Set) Reported in ≥1% of Participants 5 through 11 Years of Age

Adverse Reaction	Odactra (N=727)	Placebo (N=731)
Ear and labyrinth disorders	--	--
Ear pruritus	1.5%	0.4%
Gastrointestinal disorders	--	--
Oral pruritus	5.4%	1.1%
Abdominal pain upper	1.5%	0.7%
Nausea	1.1%	0.3%
Respiratory, thoracic and mediastinal disorders	--	--
Throat irritation	3.4%	1.4%

Source: Odactra USPI, updated 2/2025 (initial approval: 2017), pg. 11, Table 5
Notes: In Table 5, the events are presented by SOC and PT.

Participants with asthma

The majority of AEs in participants with asthma were mild or moderate in severity, and none met the criteria for an SAE. The most common treatment-related solicited events (occurring in ≥10% of Odactra recipients) were itching in the mouth, throat irritation/tickle, stomach pain, itching in the ear, swelling of the lips, tongue pain, nausea (feel like throwing up), food tastes different, swelling of the tongue, swelling in the back of the mouth, mouth ulcer, throat swelling, and diarrhea. None of the Odactra recipients had a TEAE of acute worsening of asthma symptoms (asthma exacerbation) assessed as related to the study drug. The most common treated-related unsolicited events (occurring in ≥2% of participants) were oral pruritus, throat irritation, ear pruritus, and nausea.

Clinical Reviewer Comment: *Odactra recipients with asthma reported more solicited and unsolicited AEs than those without asthma. The most common AEs in asthmatic participants were similar to the most common AEs in all participants and the overall safety profile of Odactra in asthmatics was comparable to that of non-asthmatics.*

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 18 SAEs were reported in 16 Odactra recipients (2.2%) versus 6 in 6 placebo recipients (0.8%). These events are listed below. None of the SAEs were considered related to the study treatment as assessed by study investigators. Some participants experienced more than one SAE, grouped together below:

Odactra group

1. Nausea and vomiting
2. Attention deficit hyperactivity disorder
3. Hallucinations, mixed
4. Laryngitis
5. Tonsillitis
6. Campylobacter gastroenteritis and gastroenteritis norovirus
7. Angioedema
8. Contusion
9. Gastroenteritis norovirus
10. Fracture
11. Influenza
12. Non-cardiac chest pain
13. COVID-19
14. Pneumonia
15. Immune system disorder (Severe multisystem inflammatory syndrome, suspected COVID-19 infection)
16. Pseudomonas bronchitis

Placebo group

1. Pneumonia
2. Appendicitis
3. Nasopharyngitis
4. Carbon monoxide poisoning
5. Testicular torsion
6. Pneumonia

Clinical Reviewer Comment: This reviewer agrees with the assessment that the SAEs listed above are unrelated to the study treatment. Eleven SAEs had a clear alternative infectious or traumatic etiology (laryngitis, tonsillitis, campylobacter gastroenteritis and gastroenteritis norovirus, contusion, gastroenteritis norovirus, fracture, influenza, COVID-19, pneumonia, severe multisystemic inflammatory syndrome and suspected COVID-19), and pseudomonas bronchitis). Two SAEs did not have a biologically plausible relationship (attention deficit hyperactivity disorder and hallucinations, mixed). Two SAEs did not have a temporal

relationship to Odactra (nausea and vomiting and angioedema). The Odactra participant who experienced nausea and vomiting developed symptoms on Day 259 after first intake of Odactra and symptoms persisted for 2 days. Odactra was interrupted for 2 days due to the nature of the symptoms and symptoms did not recur when Odactra was restarted. The Odactra participant who experienced angioedema developed symptoms 12 hours after the last intake of Odactra. This delay in onset of symptoms does not fit an immediate IgE-mediated allergic reaction which would typically occur within 2 hours of intake thus making the symptoms to be unlikely due to Odactra. Furthermore, symptoms did not recur when Odactra was restarted in this participant 1 day later. The Odactra participant who experienced non-cardiac chest pain developed symptoms on Day 73 which persisted for 5 days. The symptom may have been due to a viral infection (sore throat, rhinorrhea, and wet cough also present) vs. mild gastroesophageal reflux (a 24-hours pH-metry performed at the time of symptoms confirmed mild gastroesophageal reflux).

There were no drug-related serious systemic allergic reactions, including anaphylactic reactions. Please see Section 6.1.12.5 for a discussion of systemic allergic reactions.

6.1.12.5 Adverse Events of Special Interest (AESIs)

AESIs were defined as treatment-emergent events that were pre-specified and considered critical for the evaluation of the product's safety profile and for which additional data were collected. The AESIs in the study were: systemic allergic reactions including anaphylaxis, events treated with adrenaline/epinephrine, severe local swelling/edema of the mouth and/or throat, and EoE.

Systemic allergic reactions including anaphylaxis

A total of 5 participants reported 5 systemic allergic reactions, including 3 participants in the 12 SQ-HDM group and 2 participants in the placebo group, each of whom experienced 1 mild or moderate, non-serious systemic allergic reaction/anaphylactic reaction. Two of the 3 events in the 12 SQ-HDM group were assessed as possibly related to the study drug. No events were captured by the standardized MedDRA query (SMQ) 'Anaphylactic reaction' search.

Events related to study drug:

- One 6-year-old participant experienced mild urticaria on the chest and abdomen 30 minutes after intake of Odactra on Day 184. Urticaria persisted for 30 minutes. This pattern was repeated for 66 days. The initial event was treated with loratadine on Day 184 and as needed thereafter. The participant recovered after 66 days. The reaction was assessed as mild. No action was taken on dosing of Odactra. The participant completed treatment.
- One 11-year-old participant experienced epigastric pain and malaise 6 minutes after intake of Odactra on Day 1. The participant was treated with a single dose of loratadine and recovered the same day. The reaction was assessed as moderate. Odactra was discontinued.

Events unrelated to study drug:

- One 5-year-old participant developed moderate swelling of the face 12 hours after intake of Odactra on Day 51. The participant was hospitalized and treated with IM steroids, IM chloropyramine, inhaled budesonide, inhaled ipratropium, and oral cetirizine, and recovered after one day. The reaction was assessed as moderate. Odactra temporarily interrupted. 17 days after event, the participant withdrew trial consent.

- One 5-year-old participant taking placebo had an anaphylactic reaction with symptoms of facial swelling and erythema after eating nuts to which he was allergic. The participant was treated with desloratadine and recovered after 6 days. The reaction was assessed as mild.
- One 6-year-old participant developed acute urticaria on the trunk 10 days after first intake of placebo. The participant was treated with desloratadine and recovered after 6 days. The reaction was assessed as mild.

Clinical Reviewer Comment: In the Odactra group, the events reported as systemic allergic reactions did not meet the criteria for anaphylaxis according to consensus guidelines. Each participant met only one of the required criteria (skin-mucosal tissue involvement after exposure to a likely allergen and persistent gastrointestinal symptoms, respectively), not two or more which would include the following: skin-mucosal tissue involvement, respiratory compromise, reduced blood pressure, or persistent gastrointestinal symptoms (Golden et al., 2024). Therefore, while this reviewer does not consider these events to represent anaphylaxis, these two events are considered systemic allergic events related to Odactra administration.

TEAEs treated with epinephrine

No TEAEs requiring treatment with epinephrine were reported in Study MT-12.

Treatment-emergent severe local swelling or edema of the mouth and/or throat

Two participants in the 12 SQ-HDM group reported severe, non-serious TEAEs of 'local swelling or edema of the mouth and/or throat.' Both events were assessed as possibly related to the study drug.

- One 7-year-old participant experienced severe lip swelling 5 minutes after intake of Odactra on Day 11. No treatment was administered and participant recovered in approximately 1 hour. Odactra was temporarily interrupted for 8 days. On Day 30, the participant developed severe lip swelling 5 minutes after intake of Odactra. The participant received desloratadine and recovered within 1 hour. Odactra was discontinued.
- One 9-year-old participant experienced severe lip swelling 15 minutes after intake of Odactra on Day 3. The participant was treated with desloratadine and recovered on the same day. The study drug was temporarily interrupted for 7 days due to the event. The participant completed treatment.

Clinical Reviewer Comment: Because of the frequency with which it can occur, swelling of the lips is listed as one of the most common solicited adverse reactions to Odactra in the USPI.

Eosinophilic esophagitis (EoE)

No events of EoE were reported in Study MT-12.

Adverse events of special interest (AESIs) are summarized by subpopulation in the table below.

Table 24. Treatment-Emergent Adverse Events of Special Interest by Subpopulation, Safety Set, Study MT-12

Events of Special Interest	Placebo N	Placebo n	Placebo e	Odactra N	Odactra n	Odactra e
All events	--	--	--	--	--	--
Race	--	--	--	--	--	--
American Indian or Alaska native	-	-	-	1	0	0

Events of Special Interest	Placebo N	Placebo n	Placebo e	Odactra N	Odactra n	Odactra e
Asian	3	0	0	1	0	0
Black or African American	4	0	0	1	0	0
White	714	2	2	722	3	3
Multiple	3	0	0	1	0	0
Other	7	0	0	1	0	0
Sex	--	--	--	--	--	--
Female	254	0	0	241	0	0
Male	477	2	2	486	3	3
Age	--	--	--	--	--	--
4-7 years	286	2	2	291	1	1
8-11 years	445	0	0	436	2	2
Geographic region	--	--	--	--	--	--
Europe	692	2	2	688	3	3
North America	39	0	0	39	0	0
Anaphylactic reactions, anaphylaxis, and/or systemic allergic reactions	--	--	--	--	--	--
Race	--	--	--	--	--	--
American Indian or Alaska native	-	-	-	1	0	0
Asian	3	0	0	1	0	0
Black or African American	4	0	0	1	0	0
White	714	2	2	722	3	3
Multiple	3	0	0	1	0	0
Other	7	0	0	1	0	0
Sex	--	--	--	--	--	--
Female	254	0	0	241	0	0
Male	477	2	2	486	3	3
Age	--	--	--	--	--	--
4-7 years	286	2	2	291	1	1
8-11 years	445	0	0	436	2	2
Geographic region	--	--	--	--	--	--
Europe	692	2	2	688	3	3
North America	39	0	0	39	0	0
Events treated with epinephrine	--	--	--	--	--	--
Race	--	--	--	--	--	--
American Indian or Alaska native	-	-	-	1	0	0
Asian	3	0	0	1	0	0
Black or African American	4	0	0	1	0	0
White	714	0	0	722	0	0
Multiple	3	0	0	1	0	0
Other	7	0	0	1	0	0
Sex	--	--	--	--	--	--
Female	254	0	0	241	0	0
Male	477	0	0	486	0	0
Age	--	--	--	--	--	--
4-7 years	286	0	0	291	0	0
8-11 years	445	0	0	436	0	0
Geographic region	--	--	--	--	--	--
Europe	692	0	0	688	0	0
North America	39	0	0	39	0	0
Severe local swelling or edema of the mouth and/or throat[a]	--	--	--	--	--	--

Events of Special Interest	Placebo N	Placebo n	Placebo e	Odactra N	Odactra n	Odactra e
Race	--	--	--	--	--	--
American Indian or Alaska Native	-	-	-	1	0	0
Asian	3	0	0	1	0	0
Black or African American	4	0	0	1	0	0
White	714	0	0	722	0	0
Multiple	3	0	0	1	0	0
Other	7	0	0	1	0	0
Sex	--	--	--	--	--	--
Female	254	0	0	241	0	0
Male	477	0	0	486	0	0
Age	--	--	--	--	--	--
4-7 years	286	0	0	291	0	0
8-11 years	445	0	0	436	0	0
Geographic region	--	--	--	--	--	--
Europe	692	0	0	688	0	0
North America	39	0	0	39	0	0
Eosinophilic esophagitis	--	--	--	--	--	--
Race	--	--	--	--	--	--
American Indian or Alaska Native	-	-	-	1	0	0
Asian	3	0	0	1	0	0
Black or African American	4	0	0	1	0	0
White	714	0	0	722	0	0
Multiple	3	0	0	1	0	0
Other	7	0	0	1	0	0
Sex	--	--	--	--	--	--
Female	254	0	0	241	0	0
Male	477	0	0	486	0	0
Age	--	--	--	--	--	--
4-7 years	286	0	0	291	0	0
8-11 years	445	0	0	436	0	0
Geographic region	--	--	--	--	--	--
Europe	692	0	0	688	0	0
North America	39	0	0	39	0	0

Source: Applicant Response to FDA Clinical IR, 1.11.3, Dated 2/19/25
Abbreviations: MedDRA=Medical Dictionary of Regulatory Activities; N=number of participants in subgroup; n=number of participants with events; e=number of events
a Identified by the following MedDRA preferred terms: Acquired C1 inhibitor deficiency, Allergic pharyngitis, Allergic stomatitis, Allergy to dental material, Angioedema, Aphonia, Choking, Choking sensation, Contact stomatitis, Dysphonia, Epiglottic oedema, Gingival oedema, Gingival swelling, Idiopathic angioedema, Laryngeal obstruction, Laryngeal oedema, Laryngotracheal oedema, Mouth swelling, Oedema mouth, Oropharyngeal oedema, Oropharyngeal swelling, Palatal oedema, Palatal swelling, Pharyngeal oedema, Pharyngeal swelling, Sensation of foreign body, Stertor, Stridor, Suffocation feeling, Swollen tongue, Throat tightness, Tongue oedema, Tracheal oedema, and Upper airway obstruction

Clinical Reviewer Comment: AESIs were balanced across race, sex, age group, and geographic region and do not seem to disproportionately affect a specific subpopulation.

6.1.12.6 Clinical Test Results

Exploratory clinical laboratory testing followed the change from Visit 1 (baseline) to Visit 7 (end of trial) for total IgE and specific IgE and IgG4 against *D. farinae* and *D. pteronyssinus*. Post-treatment, there was an increase in all immunological parameters in the Odactra group, with a

marked quantitative increase in HDM-specific IgG4. There was no noticeable post-treatment change in the means of the immunological parameters in the placebo group.

The proportion of participants reporting shifts from 'normal' values or shifts between 'high' and 'low' values from the start to end of trial in regard to complete blood count, blood chemistry and urinalysis was low and similar between the treatment groups. Minor differences between treatment groups were observed; however, these were not considered to be clinically relevant. There were no drug-related treatment-emergent SAEs related to hematology, blood chemistry or urinalysis.

Clinical Reviewer Comment: The trends in specific IgE and IgG4 are consistent with well-documented trends in these biomarkers during allergen immunotherapy. These trends were also seen in study P001, which evaluated treatment with Odactra in adolescents and adult participants in the original BLA review. However, none of these biomarkers has yet to be validated to predict clinical efficacy.

6.1.12.7 Dropouts and/or Discontinuations

A total of 24 (1.6%) participants had AEs resulting in discontinuation of the study drug. Of these participants, 18 had at least 1 AE assessed with maximum intensity of mild or moderate. The most frequently reported AEs leading to discontinuation of Odactra were nausea (4 participants), lip swelling (3 participants), throat irritation (3 participants), upper abdominal pain (2 participants), tongue swelling (2 participants), vomiting (2 participants), and pharyngeal swelling (2 participants).

Clinical Reviewer Comment: The percentage of participants who discontinued treatment due to an AE in the Odactra group was significantly higher in adults than in adolescents and children 5 through 11 years of age. This difference in discontinuation rate may be due to the increased plasticity of the immune system in children and adolescents. The high rate of discontinuations due to AEs in adults is reflected in the product labeling.

6.1.13 Study Summary and Conclusions

Study MT-12 was a double-blind, randomized, placebo-controlled multicenter Phase 3 trial that evaluated the efficacy and safety of daily HDM sublingual immunotherapy for one year in the treatment of HDM-induced allergic rhinitis/rhinoconjunctivitis with or without asthma in children 5-11 years of age. Participants were enrolled from 174 sites in the U.S., Canada, and Europe with 70 sites in the U.S.

In Study MT-12, 1460 participants 5-11 years of age were randomized 1:1 to Odactra or placebo. The study enrolled similar numbers of male and female participants across treatment and placebo groups. There were more males than females in the study overall. Of the 1460 participants randomized, 1398 (691 Odactra recipients and 707 placebo recipients) completed the study.

The primary efficacy endpoint was the percent treatment difference relative to placebo of the average TCRS during the last 8 weeks of treatment in the FAS population. The relative treatment difference between the groups was -22.0% (95% CI: -31.1%, -12.0%). The point estimate met the prespecified success criterion of -15%.

The most frequently reported solicited adverse reactions were consistent with the adverse reactions reported in adolescent and adult participants in Study P001, reviewed in the original

BLA for Odactra, as well as those reported following other licensed aeroallergen sublingual immunotherapy products. The majority of these reactions occurred within 7 days of the first dose and resolved. No participants had allergic reactions that required the use of epinephrine. No participants had anaphylaxis. No participants had EoE. No deaths related to the study drug occurred during the trial.

Clinical Reviewer Comment Study MT-12 met its primary efficacy endpoint thus we expect Odactra to benefit children (5-11 years of age) with allergic rhinitis/rhinoconjunctivitis secondary to dust mites. Most of the adverse reactions to Odactra are allergic in nature and easily treatable. The safety and efficacy data from MT-12 included in the USPI for Odactra reflect the relevant findings of this study. Allergic rhinitis is the most common chronic disorder in the pediatric population. It can negatively affect sleep and cause daytime sleepiness, with school absenteeism, "presenteeism" or inattention, mood disturbances and psychosocial problems. These factors can in turn reduce school performance. First generation antihistamines can actually worsen the situation. However, proper treatment of allergic rhinitis has been shown to reduce this impact and improve school performance (Jáuregui et al., 2009).

6.2 Study MT-11

Study title: "A phase 3 trial evaluating the efficacy and safety of the house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet in children and adolescents (5-17 years of age) with HDM allergic asthma"

6.2.1 Objectives and Endpoints

Primary Objective

To demonstrate efficacy of the HDM SLIT-tablet versus placebo as add-on treatment in children and adolescents (5-17 years of age) with HDM allergic asthma based on clinically relevant asthma exacerbations after at least 4 months of treatment.

A clinically relevant asthma exacerbation was defined as meeting at least 1 of the following criteria:

- Doubling of ICS dose compared to background treatment
- Systemic corticosteroids for treatment of asthma symptoms for at least 3 days
- Emergency room visit due to asthma, requiring systemic corticosteroids
- Hospitalization for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids

Key Secondary Objective

To demonstrate efficacy of the HDM SLIT-tablet versus placebo after at least 4 months as add-on treatment in children and adolescents with HDM allergic asthma with respect to:

- Nocturnal awakening due to asthma which require SABA rescue medication
- Rescue medication (SABA) use
- Lung function (FEV1)

Secondary Objective: To evaluate the HDM SLIT-tablet versus placebo for treatment of HDM allergic asthma with respect to:

- Asthma symptoms
- Asthma control
- Severe asthma exacerbations
- Treatment of HDM allergic rhinitis

- Treatment of HDM allergic rhinoconjunctivitis
- Changes in immunological parameters
- Safety and tolerability

A severe asthma exacerbation was defined as at least 1 of the following criteria:

- Systemic corticosteroids for treatment of asthma symptoms for at least 3 days
- Emergency room visit due to asthma, requiring systemic corticosteroids
- Hospitalization for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids

Primary Endpoint:

Annualized rate of clinically relevant asthma exacerbations calculated as the number of exacerbations per year per participant during the efficacy evaluation period (period 4). The result of the primary efficacy analysis was considered successful if the p-value was below 0.05.

Key Secondary Endpoints:

1. Proportion of days with nocturnal awakenings due to asthma requiring SABA rescue medication during the 14 days eDiary recording every 4 months after randomization
2. Proportions of days with SABA use during the 14 days eDiary recording every 4 months after randomization
3. Percentage predicted FEV1 assessed every 4 months after randomization

Multiple additional secondary endpoints were assessed in Study MT-11; however, these endpoints are not relevant to the proposed indication and are not reviewed further as a result.

6.2.2 Study Design

MT-11 was a randomized, parallel-group, double-blind, placebo-controlled multi-center phase 3 study conducted at 64 sites in 9 countries (Bulgaria, France, Germany, Hungary, Poland, Russia, Spain, U.K., U.S.). The trial population included children and adolescents (5-17 years of age) with HDM allergic asthma on low dose ICS plus long-acting β2-agonist (LABA) or medium/high dose ICS with or without LABA, with a documented medical history of asthma exacerbations occurring over the past 1-3 years and with HDM allergic rhinitis. The purpose of the trial was to investigate whether add-on treatment with HDM SLIT-tablet had an acceptable safety profile and a relevant treatment benefit, measured as a reduced number of asthma exacerbations in the trial population. Participants 5-17 years of age with HDM allergic asthma and HDM allergic rhinitis (n=533) were randomized (1:1) to Odactra 12DU or placebo for 24-30 months. Demographics were balanced between the treatment groups and comparable to the demographics in MT-12; most participants were male, White, from Europe, and 60.1% were in the younger age strata of 5-11 years of age. The mean duration of history of HDM allergic asthma was 4.4 years and the mean duration of history of HDM allergic rhinitis was 3.9 years. The majority of participants (66.6%) were polysensitized.

The study was initiated prior to the COVID-19 pandemic. During the pandemic, this study was impacted by an overall decrease in asthma exacerbation rates. The decrease in asthma exacerbation rates led to difficulty in the recruitment of participants and therefore the trial was ended after randomizing 533 participants instead of the planned 600 participants.

(b) (4)

(b) (4)

Clinical Reviewer Comment: (b) (4)

Hurst et al. 2021 found a >70% reduction in asthma exacerbations requiring treatment with systemic steroids in children and adolescents 5-17 years of age during the first 12 months of the pandemic regardless of race/ethnicity. (b) (4)

The outcome of this trial does not have a bearing on the proposed indication of Odactra in this age group however since this trial studied a different indication. This study was included in the review of this supplement as a supportive safety evaluation for Odactra in the 5 through 11-year-old age group.

Safety findings from this study will be discussed in Section 8: Integrated Overview of Safety. Of note, in Study MT-11, the median time to onset of the 4 most frequently reported adverse reactions following initiation of treatment with Odactra varied from 1 to 6 days. The median duration of these adverse reactions that occurred on the first day of treatment initiation varied from 1-2 days.

7. INTEGRATED OVERVIEW OF EFFICACY

An integrated overview of efficacy is not applicable to this review as only one study (Study MT-12) contributed efficacy data for the pediatric population of participants 5-11 years of age. Please see Section 6.1.11 for efficacy results from the study.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety evaluations included solicited adverse reactions, unsolicited AEs, SAEs, and deaths. In Study MT-03, all AEs were assessed for 28 days. In Study MT-11, solicited adverse reactions were assessed for 28 days and unsolicited AEs, SAEs, and deaths were assessed for 24-30 months. In Study MT-12, solicited adverse reactions were assessed for 28 days and unsolicited AEs, SAEs, and deaths were assessed for 12 months. All summaries of AEs were based on the safety population defined as randomized participants who received at least one dose of the study treatment.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety of Odactra was evaluated in 3 clinical studies submitted to the sBLA. These studies were conducted in both North America and Europe. Please see Section 5.3 for a summary of these studies. Two of the studies summarized in this section are Phase 3 studies (MT-12, MT-11) that evaluated the final dose and formulation, Odactra 12DU, that included children 5-11 years of age for which the Applicant seeks licensure. The third study included in the safety evaluation is a Phase 1 study (MT-03) that evaluated 6 different doses (0.5, 1, 3, 6, 9, and 12DU) that included children 5-11 years of age.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The overall pediatric (5-11 years of age) exposure to Odactra 12 SQ-HDM across all completed studies in the clinical development program is shown in Table 25. A total of 895 participants were exposed to a least one dose of 12 SQ-HDM, and of these, 878 participants received treatment for at least 4 weeks (28 days).

Table 25. Extent of Exposure to Odactra by Duration and Study in Children 5-11 Years of Age at Randomization, Safety Set

Duration of Exposure	MT-03 Placebo	MT-03 Odactra	MT-11 Placebo	MT-11 Odactra	MT-12 Placebo	MT-12 Odactra	Overall Placebo	Overall Odactra
≥1 day	15	6	156	163	729	726	900	895
≥2 weeks	15	6	156	162	724	719	895	887
≥4 weeks	14	6	156	160	722	712	892	878
≥3 months (91 days)	-	-	156	157	714	702	870	859
≥6 months (182 days)	-	-	153	156	710	697	863	853
≥9 months (273 days)	-	-	153	155	708	690	861	845
≥12 months (365 days)	-	-	151	155	612	594	763	749
≥18 months (547 days)	-	-	148	153	-	-	148	153
≥24 months (730 days)	-	-	145	148	-	-	145	148

Source: 5.3.5.3 ISS Addendum, Children Indication Table 1.2.1-1, pg. 14, submitted by Applicant

Study MT-03 was a phase 1, randomized, multiple-dose, dose-escalation (0.5, 1, 3, 6, 9, and 12DU), double-blind, placebo-controlled study evaluating the safety of HDM SLIT-tablet in children (5-14 years of age) with HDM-induced mild-to-moderate allergic asthma (with or without rhinitis). Participants were treated for 28 days and dose groups received treatment in a staggered manner at intervals of approximately 14 days. Safety (AEs, clinical safety laboratory tests, vital signs, weight, oral examinations, spirometry, peak expiratory flow and physical examinations) and immunological (*D. farinae* and *D. pteronyssinus* allergen-specific IgE antibodies) parameters were assessed in this trial. In Study MT-03, a total of 6 participants (4 males) received 12DU of Odactra. In the 12DU treatment group, 100% were White. By ethnicity, 0% were Hispanic or Latino. In the placebo group, 100% were White. By ethnicity, 17% were Hispanic or Latino.

In Study MT-11, a total of 106 (65.0%) males versus 57 (35.0%) females received 12DU Odactra. The mean age was 8.2 years in the Odactra group and 8.3 years in the placebo group. In the 12DU Odactra group, 96.9% were White, 2.5% Black, and 0.6% Other. By ethnicity, 6.1% were Hispanic or Latino. In the placebo group, 95.5% were White, 2.6% Black, and 1.9% Other. By ethnicity, 9.6% were Hispanic or Latino.

In Study MT-12, a total of 486 (66.9%) males versus 241 (33.1%) females received 12DU Odactra. The mean age was 8.1 years in the treatment and placebo groups. In the 12DU treatment group, 99.3% were White, <0.1% Black, <0.1% Asian, <0.1% American Indian or Alaskan Native, <0.1% multi-racial, and <0.1% Other. By ethnicity, 3.6% were Hispanic or Latino. In the placebo group, 97.7% were White, 0.5% Black, 0.4% Asian, 0.4% multi-racial, and 1.0% Other. By ethnicity, 2.6% were Hispanic or Latino.

8.2.3 Categorization of Adverse Events

See Section 8.1.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Pooled safety data should be interpreted with caution. Study MT-12 and Study MT-11 both used an eDiary to solicit adverse events for the first 28 days. Study MT-03 utilized a daily diary to record AEs for the first 28 days. Unsolicited events were recorded for the entire study period in each study (28 days in Study MT-03, 24-30 months in Study MT-11, and 12 months in Study MT-12).

Clinical Reviewer Comment: There were differences in data collection methods and duration of data collection periods (as above) among the 3 studies. Studies MT-11 and MT-12 queried 15 pre-specified symptoms/signs (solicited AEs) identified as potential local side effects of sublingual immunotherapy whereas Study MT-03 did not query any specific symptoms/signs. However, only 6 participants 5 through 11 years of age received active treatment in Study MT-03. Since this number is small relative to total number of pooled participants 5 through 11 years of age who received active treatment (895 participants) among the 3 studies, the differences in data collection should not affect overall safety conclusions.

8.4 Safety Results

A table summarizing AEs including solicited events, severe AEs, and SAEs in participants who received Odactra 12DU compared with placebo is below.

Table 26. Summary of TEAEs in Children 5-11 Years of Age, Pool of MT-03, MT-11 and MT-12, Safety Set

TEAEs	Placebo n	Placebo %n	Odactra n	Odactra %n
Participants in population	900	100%	895	100%
With one or more adverse events	757	84%	804	90%
Intensity	-	-	-	-
Mild	716	80%	783	87%
Moderate	304	34%	322	36%
Severe	15	1.7%	21	2.3%
Unknown	100	11%	149	17%
With drug-related adverse event	484	54%	685	77%
With serious adverse event	15	1.7%	27	3.0%
With serious drug-related adverse event	0	0.0%	1	0.1%
Discontinued due to an adverse event[a]	8	0.9%	21	2.3%
Discontinued due to a drug-related adverse event[a]	8	0.9%	16	1.8%
Discontinued due to a serious adverse event[a]	0	0.0%	5	0.6%
Discontinued due to a serious drug-related adverse event[a]	0	0.0%	1	0.1%
Deaths	0	0.0%	0	0.0%

Source: Applicant response to IR dated 11/27/24, pg. 5, Table 1
Abbreviations: TEAEs=treatment-emergent adverse events, n=number of participants fulfilling criterion, %n=percent participants of safety set fulfilling criterion.
Notes:
a. Discontinuation from IMP, defined by action taken with IMP set to drug withdrawn.

8.4.1 Deaths

No deaths were reported in any of the studies.

8.4.2 Nonfatal Serious Adverse Events

Overall, 30 Odactra recipients (12DU) reported a SAE compared with 18 of placebo recipients. Fourteen of these Odactra recipients (12DU) and 12 of these placebo recipients were in Study MT-11 and 16 of these Odactra recipients and 6 of these placebo recipients were in Study MT-12. All SAEs were assessed to be unrelated to the IP with one exception as listed below.

SAEs considered by the investigator to be related to the study treatment

One participant taking Odactra 12DU in Study MT-11 experienced 5 episodes of nausea and vomiting over a period of 3 weeks beginning on Day 6. On Day 31, the participant's vomiting recurred and the participant was hospitalized 3 days later. Upper endoscopy with biopsy from the supracardial esophagus during hospitalization was diagnostic of EoE (50 eosinophils per high power field). A 24-hour pH esophageal manometry did not show any evidence of gastroesophageal reflux disease. The participant was treated with omeprazole 40 mg once daily x 14 days, then 20 mg once daily x 3 months and his diet was adjusted to age. The participant was discharged from the hospital after 6 days. Odactra was stopped after Day 30. His EoE was reported as recovered on Day 479 based upon results of a repeat upper endoscopy.

Clinical Reviewer Comment: This reviewer agrees with the assessment of this SAE of EoE as related and does not consider the other reported SAEs to be related to the study treatment. This event was considered an SAE because it resulted in hospitalization of the participant. The participant recovered after withdrawal of Odactra and treatment with omeprazole. EoE is a known rare, but important potential side effect of SLIT, including Odactra. Patients who develop EoE as a consequence of SLIT typically have a good prognosis with usual improvement of clinical and histological manifestations following removal of the inciting factor (SLIT treatment). EoE is included under 'Warnings and Precautions' in the Odactra USPI because healthcare providers should be aware that it is a rare but important potential side effect. A diagnosis of EoE should be considered in patients who experience severe or persistent gastroesophageal symptoms including dysphagia or chest pain. The overall incidence of EoE as a result of SLIT is low and does not have a significant impact on Odactra's benefit-risk assessment as a result. The incidence can further be mitigated by awareness (EoE is included in both the USPI and patient medication guide) and resolved by withdrawing the medication when concerning symptoms occur.

8.4.3 Study Dropouts/Discontinuations

Of the Odactra recipients, 5.4% discontinued the study, 2.5% discontinued the study due to an AE (most common reason for discontinuation) and 1.9% discontinued due to a drug-related AE. In placebo recipients, 3.6% discontinued the study, 0.8% discontinued the study due to an AE and 0.8% discontinued due to a drug-related AE. The most common reason for discontinuation among placebo recipients was withdrawal by participant/withdrawal of consent (1.7%).

8.4.4 Common Adverse Events

A table summarizing all TEAEs by Medical Dictionary of Regulatory Activities (MedDRA) SOC and Preferred Term is below.

Clinical Reviewer Comment: The table below does not contain AEs from the 6 participants in Study MT-03 as the small number of participants did not contribute to the overall risk

assessment of Odactra. However, the AEs reported in MT-03 were similar to those reported in MT-11 and MT-12.

Table 27. All TEAEs (Including Solicited TEAEs) in ≥2% in Either Treatment Group by SOC and PT in Children 5-11 Years of Age, Pool of MT-11 and MT-12, Safety Set

System Organ Class Preferred Term	Placebo N=885 n	Placebo N=885 %n	Placebo N=885 e	Odactra N=889 n	Odactra N=889 %n	Odactra N=889 e
All events	709	80%	2905	782	88%	4684
Ear and labyrinth disorders	--	--	--	--	--	--
All	179	20%	183	313	35%	326
Ear pruritus	179	20%	183	313	35%	326
Eye disorders	--	--	--	--	--	--
All	13	1%	13	20	2%	27
Conjunctivitis allergic	13	1%	13	20	2%	27
Gastrointestinal disorders	--	--	--	--	--	--
All	490	55%	1180	686	77%	2480
Oral pruritus	236	27%	245	540	61%	618
Abdominal pain upper	240	27%	248	339	38%	360
Nausea	124	14%	126	216	24%	234
Lip swelling	51	6%	51	197	22%	203
Glossodynia	58	7%	58	196	22%	202
Mouth swelling	40	5%	40	157	18%	158
Mouth ulceration	94	11%	100	155	17%	163
Diarrhea	110	12%	115	141	16%	146
Swollen tongue	27	3%	27	140	16%	146
Vomiting	50	6%	56	88	10%	95
Tongue ulceration	53	6%	53	82	9%	85
Tooth loss	35	4%	61	43	5%	70
General disorders and administration site conditions	--	--	--	--	--	--
All	19	2%	22	20	2%	22
Pyrexia	19	2%	22	20	2%	22
Infections and infestations	--	--	--	--	--	--
All	399	45%	675	397	45%	713
Nasopharyngitis	208	24%	282	228	26%	333
Pharyngitis	47	5%	63	59	7%	72
Bronchitis	60	7%	75	49	6%	60
COVID-19	42	5%	42	41	5%	41
Upper respiratory tract infection	53	6%	73	41	5%	57
Influenza	33	4%	35	33	4%	36
Respiratory tract infection viral	25	3%	27	31	3%	41
Tonsillitis	32	4%	35	26	3%	28
Gastroenteritis	22	2%	24	20	2%	25
Respiratory tract infection	15	2%	19	18	2%	20
Nervous system disorders	--	--	--	--	--	--
All	167	19%	174	200	22%	212

System Organ Class Preferred Term	Placebo N=885 n	Placebo N=885 %n	Placebo N=885 e	Odactra N=889 n	Odactra N=889 %n	Odactra N=889 e
Dysgeusia	158	18%	159	182	20%	186
Headache	13	1%	15	24	3%	26
Respiratory, thoracic and mediastinal disorders	--	--	--	--	--	--
All	407	46%	631	564	63%	882
Throat irritation	319	36%	333	527	59%	565
Pharyngeal swelling	36	4%	36	115	13%	121
Asthma	107	12%	175	76	9%	145
Rhinitis allergic	31	4%	56	20	2%	27
Cough	26	3%	31	18	2%	24
Skin and subcutaneous tissue disorders	--	--	--	--	--	--
All	21	2%	27	15	2%	22
Dermatitis atopic	21	2%	27	15	2%	22

Source: Applicant Response to FDA IR dated 11/27/24, pg. 6, Table 2
Abbreviations: TEAEs=treatment-emergent adverse events, MedDRA=Medical Dictionary of Regulatory Activities; SOC=system organ class, PT=preferred term, N=number of participants in safety set, n=Number of participants with events, %n=percent participants with events of safety set, e=number of events
Notes: An adverse event (AE) is considered treatment-emergent if AE start date is on or after the time of first IMP administration and no later than 7 days after last IMP administration. System organ class and preferred term coded in MedDRA 24.0 Includes data from MT-11, MT-12

Solicited Adverse Reactions

In Study MT-12, the most common solicited adverse reactions reported in ≥10% of Odactra recipients were itching in the mouth, throat irritation/tickle, itching in the ear, stomach pain, swelling of the lips, tongue pain, food tastes different, nausea, swelling in the back of the mouth, swelling of the tongue, and mouth ulcer. Severe solicited adverse reactions were reported in 4 (0.6%) of Odactra recipients and no placebo recipients in this study. In Study MT-11, those reported in ≥10% of Odactra recipients were itching in the mouth, throat irritation, itching in the ear, stomach pain, tongue pain, swelling of the lips, nausea, swelling of the mouth, swelling in the back of the mouth, swelling of the tongue, food tastes different, and diarrhea. Severe solicited adverse reactions were reported in 4 (1.5%) of Odactra recipients and 1 (0.4%) of placebo recipients in this study. These events were frequently reported across safety data from Phase 2 and 3 studies and were more common in the Odactra recipients. In placebo recipients, the most common adverse reactions were throat irritation/tickle, itching in the mouth, itching in the ear, stomach pain, and food tasting different.

Clinical Reviewer Comment: Overall, the pattern of the most frequently reported solicited adverse reactions, both with regards to type of reported events and the frequency by which they were reported, was similar between the two studies. The safety data results of Study MT-11 support those of MT-12 and support labeling only Study MT-12 in the USPI.

A table summarizing solicited AEs is below.

Table 28. Solicited Symptoms in Either Treatment Group by Solicited Term in Children 5-11 Years of Age, Pool of MT-11 and MT-12, Safety Set

Solicited	Placebo N=885 n	Placebo N=885 %n	Placebo N=885 e	Odactra N=889 n	Odactra N=889 %n	Odactra N=889 e
All events	555	63%	1734	715	80%	3338
Solicited term	--	--	--	--	--	--
Itching in the mouth	234	26%	234	538	61%	538
Throat irritation/tickle	317	36%	317	526	59%	526
Stomach pain	231	26%	231	336	38%	336
Itching in the ear	179	20%	179	313	35%	313
Nausea (feel like throwing up)	123	14%	123	212	24%	212
Tongue pain	58	7%	58	196	22%	196
Swelling of the lips	50	6%	50	195	22%	195
Food tastes different	158	18%	158	182	20%	182
Mouth ulcer	91	10%	91	152	17%	152
Swelling in the back of the mouth	39	4%	39	152	17%	152
Swelling of the tongue	27	3%	27	138	16%	138
Diarrhea	96	11%	96	124	14%	124
Throat swelling	36	4%	36	114	13%	114
Vomiting	42	5%	42	81	9%	81
Tongue ulcer	53	6%	53	79	9%	79

Source: Applicant Response to FDA IR dated 11/27/24, pg. 8, Table 3
Abbreviations: N=number of participants in safety set, n=Number of participants with events, %n=percent participants with events of safety set, e=number of events
Notes: A solicited symptom is defined by being recorded in the participant diary or by an adverse event coded to a preferred term considered to be synonymous with the prespecified symptom and starting no later than 28 days after first treatment. Includes data from MT-11, MT-12

Unsolicited Adverse Events

The overall proportion of participants in reporting unsolicited TEAEs was similar in both the 12 SQ-HDM group (56%) and the placebo group (55%). A table summarizing unsolicited TEAEs is below.

Table 29. Unsolicited TEAEs in ≥2% in Either Treatment Group by SOC and PT in Children 5-11 Years of Age, Pool of MT-11 and MT-12, Safety Set

System Organ Class Preferred Term	Placebo N=885 n	Placebo N=885 %n	Placebo N=885 e	Odactra N=889 n	Odactra N=889 %n	Odactra N=889 e
All events	489	55%	1138	496	56%	1241
Eye disorders	--	--	--	--	--	--
All	13	1%	13	20	2%	27
Conjunctivitis allergic	13	1%	13	20	2%	27
Gastrointestinal disorders	--	--	--	--	--	--
All	69	8%	108	119	13%	196
Oral pruritus	10	1%	11	52	6%	80
Tooth loss	35	4%	61	43	5%	70
Abdominal pain upper	16	2%	17	20	2%	24
Diarrhea	18	2%	19	20	2%	22
General disorders and administration site conditions	--	--	--	--	--	--
All	19	2%	22	20	2%	22
Pyrexia	19	2%	22	20	2%	22
Infections and infestations	--	--	--	--	--	--

System Organ Class Preferred Term	Placebo N=885 n	Placebo N=885 %n	Placebo N=885 e	Odactra N=889 n	Odactra N=889 %n	Odactra N=889 e
All	399	45%	675	397	45%	713
Nasopharyngitis	208	24%	282	228	26%	333
Pharyngitis	47	5%	63	59	7%	72
Bronchitis	60	7%	75	49	6%	60
COVID-19	42	5%	42	41	5%	41
Upper respiratory tract infection	53	6%	73	41	5%	57
Influenza	33	4%	35	33	4%	36
Respiratory tract infection viral	25	3%	27	31	3%	41
Tonsillitis	32	4%	35	26	3%	28
Gastroenteritis	22	2%	24	20	2%	25
Respiratory tract infection	15	2%	19	18	2%	20
Nervous system disorders						
All	13	1%	15	24	3%	26
Headache	13	1%	15	24	3%	26
Respiratory, thoracic and mediastinal disorders	--	--	--	--	--	--
All	142	16%	278	130	15%	235
Asthma	107	12%	175	76	9%	145
Throat irritation	15	2%	16	34	4%	39
Rhinitis allergic	31	4%	56	20	2%	27
Cough	26	3%	31	18	2%	24
Skin and subcutaneous tissue disorders	--	--	--	--	--	--
All	21	2%	27	15	2%	22
Dermatitis atopic	21	2%	27	15	2%	22

Source: Applicant Response to FDA IR dated 11/27/24, pg. 9, Table 4
Abbreviations: TEAEs=treatment-emergent adverse events, MedDRA=Medical Dictionary of Regulatory Activities; SOC=system organ class, PT=preferred term, N=number of participants in safety set, n=Number of participants with events, %n=percent participants with events of safety set, e=number of events
Notes: An adverse event (AE) is considered treatment-emergent if AE start date is on or after the time of first IMP administration and no later than 7 days after last IMP administration. System organ class and preferred term coded in MedDRA 24.0 Includes data from MT-11, MT-12

Clinical Reviewer Comment: In contrast to studies in adolescents and adults, significantly fewer children 5 through 11 years of age reported unsolicited TEAEs. Overall, the pattern of the most frequently reported unsolicited TEAEs with regards to type of reported events was similar across age groups with one exception. Significantly more children in Study MT-11 reported an unsolicited TEAE of asthma (12 SQ-HDM vs placebo): 30.0% vs. 37.3% compared with children in Study MT-12 and adolescents and adults in earlier studies. MT-11 was primarily an asthma-focused study and we would expect more asthma events in a study population in which all participants had asthma. It is also reassuring that more placebo participants than Odactra participants had unsolicited TEAEs of asthma thus making it unlikely that these events were caused by Odactra. These results skew the above pooled safety results for asthma events as in Study MT-12, unsolicited TEAEs of asthma occurred in 1.9% of Odactra recipient and 5.2% of placebo recipients. Overall, the safety profile in children is favorable and children may tolerate Odactra better than adolescents and adults.

8.4.5 Clinical Test Results

Minor differences between treatment groups in both Study MT-11 and Study MT-12 were observed for hematology, blood chemistry, and urinalysis; however, no differences were considered clinically relevant. There were no drug related treatment-emergent SAEs related to hematology, blood chemistry analysis, or urinalysis.

Immunological parameters were assessed only in Study MT-12. There was an increase in all immunologic parameters (total IgE, specific IgE and IgG_4 against *D. farinae* and *D. pteronyssinus*) measured in this study for the Odactra group only. There was no noticeable post-treatment change in the means of the immunological parameters in the placebo group.

8.4.6 Systemic Adverse Events

Across the two phase 3 trials, 4 Odactra recipients and 2 placebo recipients reported systemic allergic reactions. Three of these reactions were considered related to the study drug; however, none met the criteria for anaphylaxis These events are summarized below. No epinephrine use was reported with these episodes.

Systemic allergic reactions including anaphylaxis

Events related to study drug:

1. One 10-year-old participant in Study MT-11 taking Odactra 12DU had a systemic allergic reaction with symptoms of oral pruritus, abdominal pain, and nausea. This reaction, graded severe, occurred on Day 8 immediately after dosing. The participant was treated with desloratadine and recovered the same day. Treatment with Odactra was temporarily interrupted. The reaction was assessed as non-serious. Prior to the reported event of hypersensitivity, the participant had experienced throat irritation, upper abdominal pain, oral pruritus, and throat swelling since first intake of Odactra and recovered after 6 days. Three days after first intake of Odactra, the participant developed tongue pain lasting for 3 days. Four days after first intake, the participant developed throat and mouth swelling which resolved the same day.

2. One 11-year-old participant in Study MT-12 taking Odactra 12DU had a systemic allergic reaction with symptoms of a pruritic confluent urticarial rash on the chest and abdomen. The duration was approximately 30 minutes. The reaction, graded mild, occurred on Day 184. The event was recurrent and the participant was treated with loratadine. The participant recovered after 66 days. Treatment was continued.

3. One 11-year-old participant in Study MT-12 taking Odactra 12DU had a systemic allergic reaction with symptoms of epigastric pain and malaise. The reaction, graded as moderate, occurred on Day 1 after 6 minutes of dosing. Exam of the participant's nose, throat, mouth, chest, and skin did not reveal any changes. Vital signs were normal. The participant was treated with loratadine and recovered the same day. Treatment was discontinued.

Events unrelated to study drug:

1. One 5-year-old participant in Study MT-12 taking placebo had an anaphylactic reaction with symptoms of facial swelling and erythema after eating nuts to which he was allergic. The participant was treated with desloratadine and recovered after 6 days. The reaction was graded as mild.

2. One 5-year-old participant in Study MT-12 developed moderate swelling of the face 12 hours after intake of Odactra on Day 51. The participant was hospitalized and treated with IM steroids, IM chloropyramine, inhaled budesonide, inhaled ipratropium, and oral cetirizine, and recovered after one day. The reaction was graded as moderate. Odactra was interrupted; the participant withdrew from the study 17 days after event.

3. One 6-year-old participant in Study MT-12 developed acute urticaria on trunk 10 days after first intake of placebo. The participant was treated with desloratadine and recovered after 6 days. The reaction was graded as mild.

Clinical Reviewer Comment: This reviewer agrees with the Applicant's assessment of relatedness for those events assessed as related and unrelated to the study drug. For those three events assessed as related to the study drug, only the second listed event qualifies as a systemic allergic reaction. However, this event did not meet the criteria for anaphylaxis according to consensus guidelines. This participant met only one of the required criteria (skin-mucosal tissue involvement after exposure to a likely allergen), not two or more criteria which would include the following: skin-mucosal tissue involvement, respiratory compromise, reduced blood pressure, or persistent gastrointestinal symptoms (Golden et al., 2024). While this reviewer does not consider the remaining two events assessed as related to the study drug to be systemic allergic reactions, these two events can be considered local allergic reactions related to Odactra administration.

The second narrative under events unrelated to study drug is unlikely to be related to the Odactra given the time course of the event. An immediate IgE-mediated allergic reaction to an allergen is typically expected to occur within 2 hours of administration of a sublingual allergen. An event occurring 12 hours following administration does not fit an IgE-mediated allergic reaction and is thus unlikely related to treatment. This event was likely due to an alternative explanation such as exposure to a separate allergen just prior to onset of symptoms.

Epinephrine Use

No events of epinephrine use were reported in MT-11 or MT-12.

Clinical Reviewer Comment: The Applicant submitted a 120-day safety update report on August 26, 2024, which included postmarketing safety data for Odactra in children. Included were 4 cases of anaphylaxis from Odactra reported in children 5-11 years of age in Japan. This finding underscores the importance of prescribing auto-injectable epinephrine to patients receiving Odactra and instructing patients or their parents/guardians to recognize the signs and symptoms of a severe allergic reaction and to emergently treat such reactions with auto-injectable epinephrine.

8.4.7 Local Reactogenicity

See Section 8.4.4, as most of the common AEs were local in nature.

8.4.8 Adverse Events of Special Interest

AESIs were defined as: IP-related systemic allergic reactions including anaphylaxis (see Section 8.4.6 above), IP-related events treated with epinephrine (see Section 8.4.6 above), IP-related severe local swelling/ edema of the mouth and/or throat (see Section 8.4.6 above), as well as IP-related EoE (reported here in this section).

Eosinophilic esophagitis (EoE)

Due to the concern for the development of EoE in participants taking SLIT products, selected upper gastrointestinal tract AEs were reviewed.

One case of treatment-emergent EoE was reported in a 10-year-old taking Odactra 12 SQ-HDM in Study MT-11. This event is summarized below.

1. One 10-year-old male participant taking Odactra 12 SQ-HDM was diagnosed with EoE on Day 34 based on an upper endoscopy showing 50 eosinophils per high powered field in the supracardial esophagus. A 24-hour pH esophageal manometry was performed at that time which showed no evidence of gastroesophageal reflux disease. The participant was treated with omeprazole x 3.5 months. Odactra was discontinued 30 days after first intake. A repeat upper endoscopy performed on Day 479 reported the event as recovered. This event was considered an SAE. Please see Section 8.4.2.

In addition to the above participant, 4 participants in Study MT-11 reported potential symptoms of EoE based on specific questions posed at each visit. Two participants were in the 12 SQ-HDM group and 2 in the placebo group. None of these had a diagnosis of EoE confirmed.

1. One 7-year-old male taking Odactra 12 SQ-HDM reported dysphagia/difficulty swallowing and sensation of food lodged in throat on Day 172. He was treated with prednisone for 1 day and recovered on the same day. The AE was assessed as possibly related to treatment. The participant reported dysphagia/difficulty swallowing again on Day 474. This AE was assessed as unlikely related to treatment. No treatment was prescribed and the participant recovered after 38 days. The participant reported choking or gagging with meals on Day 582. This AE was assessed as possibly related to treatment. No treatment was prescribed and the participant recovered on the same day. Treatment with Odactra continued unchanged. The investigator felt referral to a gastroenterologist for further evaluation was not necessary. The participant completed the trial after 739 days of treatment.

2. One 9-year-old male taking Odactra 12 SQ-HDM reported persistent early satiety on Day 687. He was treated with esomeprazole for 7 days beginning on Day 758 and recovered after 85 days. The participant completed the trial after 753 days of treatment. The investigator confirmed that the participant was referred to a gastroenterologist shortly after completing the trial at which time the participant had no evidence of EoE per report. The AE was assessed as unlikely related to treatment as the investigator believed the symptom may have had an etiology other than treatment with HDM SLIT-tablet. The participant reported no recurrence of early satiety after treatment with esomeprazole in follow-up.

3. One 12-year-old male taking placebo reported dysphagia/difficulty swallowing and sensation of food lodged in throat on Day 69. No treatment was prescribed and participant recovered after 11 days. The AE was assessed as unlikely related to treatment. The participant was not referred to a gastroenterologist.

4. One 11-year-old male taking placebo reported dysphagia/difficulty swallowing on Day 721. The participant did not report this symptom at the next study visit. The participant was not referred to a gastroenterologist. The participant completed the trial after 801 days of treatment.

Clinical Reviewer Comment: One participant in Study MT-11 was diagnosed with EoE; 4 participants in the same study had unclear diagnoses because an upper endoscopy with esophageal biopsy was not performed to confirm the histopathologic component of the diagnosis of EoE. Their symptoms, especially those of narrative #2 who was taking Odactra, may have been related to concomitant EoE.

Severe asthma exacerbations and clinically relevant asthma exacerbations (included under AESIs as these events are of special interest for Study MT-11)

Study MT-12
No asthma related TEAEs were reported in this study.

Study MT-11
Three 12 SQ-HDM recipients in the younger age strata (5-11 years of age) reported any TEAEs related to asthma.

1. One 7-year-old participant experienced an asthma exacerbation on Day 3. The event was graded as moderate, nonserious, and possibly treatment related. Odactra was discontinued on Day 9 and the participant recovered by Day 32.
2. One 6-year-old participant was diagnosed with viral bronchitis and asthma on Day 475 requiring hospitalization. The event was graded as severe, assessed as serious and unrelated. Odactra was temporarily discontinued during hospitalization.
3. One 5-year-old participant was diagnosed with an asthma exacerbation on Day 427. IgM to Mycoplasma pneumoniae was positive. PCR for Influenza type A was positive. The event was graded as mild and assessed as serious and unrelated.

One placebo recipient experienced an asthma-related TEAE (pneumonia, asthma exacerbation) on Day 173. The event was graded as severe, assessed as serious and unrelated.

Clinical Reviewer Comment: Overall, there was not an increase in asthma related TEAEs in Odactra recipients compared to placebo recipients in the pooled analysis. This finding is reassuring that Odactra can be safely used in patients with well-controlled asthma. Odactra remains contraindicated in patients with severe, unstable or uncontrolled asthma.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Overdose was defined as any cumulative dose taken in one day that exceeds the dose intended, regardless of whether the dose has caused any AEs.

Overall, a total of 4 participants in the treatment group had accidental overdoses that were identified; the dosage of overdose of each of these participants was 2 tablets. No intentional overdoses were identified. One participant reported an overdose with drug-related AEs (food tastes different, itching in the ear). This AE was assessed as mild in intensity by the investigator and did not meet ICH criteria for seriousness. The remaining 3 participants with accidental overdoses were not associated with adverse effect. Overdoses were similarly reported in the treatment and placebo groups.

8.5.2 Time Dependency for Adverse Events

See individual sections for data on timing of various AEs.

8.5.3 Product-Demographic Interactions

Not applicable.

8.5.4 Product-Disease Interactions

Not applicable.

8.5.5 Product-Product Interactions

The IP was not evaluated in combination with other sublingual or subcutaneous immunotherapy investigational or licensed products.

8.5.6 Human Carcinogenicity

Not applicable.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

See Section 8.5.1 for data on overdoses. No misuse/abuse of the IP was reported in the Phase 3 studies.

8.5.8 Immunogenicity (Safety)

Not applicable.

8.5.9 Person-to-Person Transmission, Shedding

Not applicable.

8.6 Safety Conclusions

An integrated review of safety data indicates that Odactra has an acceptable safety profile. As expected, adverse reactions occurred more frequently with Odactra than with placebo. The most common solicited adverse reactions occurring in ≥10% of Odactra recipients were oral pruritus (58%), throat irritation (55%), ear pruritus (34%), upper abdominal pain (29%), lip swelling (22%), glossodynia (21%), nausea (18%), dysgeusia (16%), mouth swelling (16%), and swollen tongue (15%). Similar findings of throat irritation, oral pruritus, ear pruritus, and lip swelling have been reported in licensed SLIT products. The majority of these events were mild to moderate, occurred very early in treatment and resolved without complication.

No deaths occurred in either of the 2 clinical studies reviewed in this clinical memo. One of the reported SAEs, a diagnosis of EoE on Day 31 of Odactra, was considered to be possibly related to Odactra. Across the 2 clinical studies conducted with Odactra 12DU, EoE was reported in 1/997 (0.1%) of Odactra recipients compared to 0/994 (0%) placebo recipients. There were no serious unexpected AEs.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

The safety of the HDM SLIT-tablet during pregnancy or lactation has not been formally investigated in adequate and controlled clinical studies. Pregnant or lactating women were excluded from all studies, and appropriate methods of contraception, as well as negative pregnancy tests, were required throughout the studies for all women of childbearing potential. Per protocol, if a female participant became pregnant during the study, she was to be discontinued from treatment and followed for outcome of pregnancy (e.g., live birth, termination). No pregnancies were reported in children 5-11 years of age in Study MT-12 or Study MT-11.

9.1.2 Use During Lactation

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

9.1.3 Pediatric Use and PREA Considerations

With this submission, the Applicant has fulfilled the PMR to conduct a pediatric study evaluating the safety and efficacy of Odactra in children 5-11 years of age. A partial waiver for evaluating Odactra in children <5 years of age was granted on the basis that necessary studies are impossible or highly impracticable because the number of children <5 years of age with allergic rhinitis/rhinoconjunctivitis diagnostically due to sensitivity to the house dust mite is small (Federal Food, Drug, and Cosmetic Act (FD&C Act) Section 505B (a)(4)(B)(i)).

9.1.4 Immunocompromised Patients

The safety and effectiveness of Odactra have not been established in immunocompromised individuals.

9.1.5 Geriatric Use

Not applicable.

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

Not applicable.

10. CONCLUSIONS

The results from the Phase 3 field efficacy study (MT-12) demonstrate a reduction in TCRS during the last 8 weeks of a 52-week treatment course. The results of this Phase 3 study conducted in children 5-11 years of age in North America and Europe indicate that the point estimate difference between treatment and placebo for the difference in average TCRS (-22.0% (95% CI: -31.1%, -12.0%) exceeded the pre-specified criteria for success of -15% and the lower bound of the 95% CI of -10%. These data support the effectiveness of Odactra for the treatment of house HDM-induced allergic rhinitis, with or without conjunctivitis in persons 5-11 years of age with confirmed allergy to house dust mites.

Participants treated with Odactra 12DU had higher rates of local adverse reactions than those treated with placebo. However, these reactions were generally mild and transient in nature and primarily occurred during the first 28 days of administration. The risk of severe, systemic

adverse reactions appears to be low. The Applicant removed systemic allergic reactions including anaphylactic reactions, local allergic reactions with potential compromise of the airway, acute worsening of asthma symptoms and anaphylactic shock as an important risk from the revised PVP submitted with this sBLA as a result as these are considered to be known risks addressed by labeling and routine PVP activities. The risk of developing EoE also appears to be low, with one Odactra recipient developing confirmed EoE out of 997 children in the 2 studies. However, EoE was kept as an important identified risk in the revised PVP to keep focus on this risk during routine pharmacovigilance activities. Overall, the benefit-risk profile of Odactra is acceptable for approval for use in children down to 5 years of age.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Table 30. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Based on NHANES 2005-2006, an estimated 29% of U.S. children 6-17 years of age with current allergies are sensitized to HDM (Salo et al., 2011). HDM sensitization rates in inner city metropolitan areas in the U.S. show up to 62% of all inner-city children sensitized to HDM (Gruchalla et al. 2005). • Allergy symptoms can have a significant negative impact on quality of life (QOL). A survey of children and adolescents 4-17 years of age and their parents or caregivers indicated that allergies decreased school performance, interfered with daily activities, and disrupted sleep patterns (Meltzer et al. 2009). • The total direct medical cost of allergic rhinitis is $3-4 billion including cost of medication and medical visits.	• Sensitization to HDM-induced allergic rhinitis is prevalent in the U.S. pediatric population. • Symptoms from house dust mite allergy cause significant disruption in daily activities and function, learning and sleep.
Unmet Medical Need	• Over the counter (OTC) medications are available to treat the symptoms of allergic rhinitis/rhinoconjunctivitis. However, OTC medications have some side effects. And the cost of daily medications can be prohibitive. • Subcutaneous immunotherapy (SCIT) for treatment of house dust mite allergy is offered by some health care practitioners (HCP). However, SCIT is more invasive and must be administered in a clinical setting with appropriately trained staff to monitor for acute anaphylactic reactions. • No perennial sublingual immunotherapy (SLIT) product is licensed in the U.S. for the treatment of house dust mite induced allergic rhinitis with or without conjunctivitis (AR/C) in children 5-11 years of age.	• Sublingual immunotherapy is a non-invasive therapy. • Sublingual immunotherapy can be administered at home with proper instruction. • OTC medications treat symptoms, but not the underlying cause of rhinitis/rhinoconjunctivitis. • There is an unmet medical need for safe and effective treatments of house dust mite associated rhinitis/rhinoconjunctivitis in children.
Clinical Benefit	• Phase 3 study MT-12 was a double-blind, placebo-controlled, randomized field efficacy study that showed the relative treatment difference of the total combined rhinitis score (TCRS) compared to placebo was -22.0% (95% CI: -31.1%, -12.0%) in ages 5-11 years of age after 12 months.	• Odactra shows a therapeutic benefit over a 12-month administration period. • The duration of effectiveness on therapy beyond one year and effectiveness after discontinuation of Odactra have not been characterized.

Risk	• The most serious risks of treatment with Odactra are systemic allergic reactions such as anaphylaxis and pharyngeal edema. Pharyngeal edema occurred at a rate of 13% (pharyngeal edema) and <0.01% (severe pharyngeal edema) in the two phase 3 studies (MT-11 and MT-12). There were no reported cases of anaphylaxis in either of these two phase 3 studies however anaphylaxis has been reported in adolescents and adults and in children in postmarketing safety data. • The most common solicited adverse reactions occurring in ≥10% of participants taking Odactra were oral pruritus (58%), throat irritation (55%), ear pruritus (34%), upper abdominal pain (29%), lip swelling (22%), glossodynia (21%), nausea (18%), dysgeusia (16%), mouth swelling (16%), and swollen tongue (15%). • One participant taking Odactra 12DU developed EoE. Across 2 phase 3 clinical studies in children 5-11 years of age conducted with Odactra 12DU, EoE was reported in 1/997 (0.1%) participants who received Odactra compared to 0/994 (0%) participants who received placebo.	• The risk of systemic allergic reactions with Odactra is low. • Local reactions are common, but generally mild to moderate and self-limited. • Further studies are needed to characterize the incidence of EoE associated with SLIT products in the pediatric population. • The safety profile of Odactra in children 5-11 years of age is acceptable and is justified by the clinical benefit.
Risk Management	• The Odactra U.S. Prescribing Information (USPI) includes a boxed warning about severe allergic reactions. • Odactra should be prescribed along with a prescription for injectable intramuscular epinephrine in case of systemic reactions. • Patients should be warned about the potential risk of EoE and directly to contact a health care professional if any signs or symptoms of EoE occur.	• The rate of systemic allergic reactions is low, and the risk can be mitigated effectively with auto-injectable epinephrine. • The USPI, medication guide, and the current pharmacovigilance plan (PVP) are adequate to manage these risks.

11.2 Risk-Benefit Summary and Assessment

Allergic rhinitis is a common respiratory condition affecting 13% of children in the U.S. (Meltzer et al., 2009). This condition can affect QOL including school performance and lead to or affect other clinical disorders such as asthma, rhinosinusitis, and sleep disorders. Sublingual immunotherapy can be taken at home after the first dose with appropriate patient counseling, decreasing the burden of clinic visits for patients. Odactra is the first perennial sublingual immunotherapy product for children.

Data submitted to this sBLA demonstrate the benefit of Odactra for the treatment of house dust mite-induced AR/C in children 5-11 years of age. The duration of treatment effect after discontinuing Odactra has not been studied.

Most participants undergoing treatment with Odactra report mild to moderate adverse reactions with low risk of serious reactions. There were no severe allergic reactions or anaphylaxis reported. No TEAEs requiring treatment with epinephrine were reported either. One case of EoE was reported in a participant taking Odactra 12DU. The most common adverse reactions were oral pruritus, throat irritation, ear pruritus, upper abdominal pain, lip swelling, glossodynia, nausea, dysgeusia, mouth swelling, and swollen tongue. Based upon the submitted data, the risks of treatment with Odactra appear to be modest and adverse reactions appear to be self-limited. However, because of the small risk of systemic allergic reactions and local allergic reactions, individuals should be prescribed epinephrine. The risk of EoE can be mitigated by product labeling and patient education warning parents/caregivers to stop Odactra and contact their child's healthcare provider if their child develops heartburn, difficulty swallowing, pain with swallowing, or chest pain that does not go away or worsens.

Given the clinical benefit associated with the consistent treatment effect observed in the efficacy data and the modest risks of treatment with Odactra, the overall risk-benefit assessment is favorable.

11.3 Discussion of Regulatory Options

The decision to extend the indication of Odactra to children 5-11 years of age was based on efficacy and safety data from one field efficacy study, MT-12, as well as safety data from one supportive study, MT-11. These data are sufficient to support approval of Odactra; therefore, consideration of other regulatory options was not necessary. This reviewer continues to agree with the Applicant's rationale for a partial waiver in children <5 years of age.

11.4 Recommendations on Regulatory Actions

The data submitted to this sBLA support licensure of Odactra in children 5 through 11 years of age.

11.5 Labeling Review and Recommendations

CBER and ALK-Abelló A/S reached concurrence on the revised package insert for Odactra. The Indications and Usage section of the package insert was revised to indicate that the product is approved for use in individuals 5 through 65 years of age. Section 6 was revised to include data from Study MT-12, which supported safety in children 5-11 years of age. ALK-Abelló A/S revised Section 8 in accordance with the Pregnancy and Lactation Labeling Rule (PLLR). Section 14 was revised to include data from Study MT-12, which supported efficacy in children 5-11 years of age.

11.6 Recommendations on Postmarketing Actions

Additional postmarketing safety studies are not recommended. Routine pharmacovigilance measures are adequate.

APPENDIX 1: STUDY MT-03 (P103)

Study MT-03 was a randomized, double blind, placebo-controlled Phase 1 study conducted at 4 centers in Spain from September 13, 2007 through April 1, 2008. The objective was to identify a dose range of the ALK house dust mite tablet (Odactra) that had a safety profile allowing once-daily intake (as self-medication) by children 5-14 years of age with allergic asthma (with or without rhinitis) due to the house dust mite. Safety was evaluated based on AEs (assessed for 28 days using a daily diary), clinical safety laboratory tests, vital signs, weight, oral examinations, spirometry, peak expiratory flow and physical examinations.

Main Inclusion Criteria
Male and female participants 5-14 years of age, with a clinical history of house dust mite induced mild to moderate asthma (with or without concurrent rhinitis) for at least 1 year prior to trial entry; using appropriate medication (in accordance with the Global Initiative for Asthma [GINA] Guidelines 2002) for the control of asthma symptoms; with a positive SPT response (wheal diameter ≥3 mm) to *D. pteronyssinus* or *D. farinae* (10 histamine equivalent prick); and positive specific IgE against *D. pteronyssinus* or *D. farinae* (IgE ≥ Class 2).

Study Population Enrollment and Treatment
The study population consisted of 12 participants in 4 different dose groups each. Within each dose group, participants were randomized prior to first dosing (Day 1) to either Odactra or placebo (3:1). After study initiation, 2 additional dose groups were generated and randomized prior to first dosing (Day 1) to either Odactra or placebo (3:1).

Treatment was given once daily as tablet(s) administered sublingually. Participants received treatment for a total of 28 days, followed by a study completion visit on Day 29. All 4 centers initiated treatment at the same time and followed the same procedures.

The planned doses of the study were 0.5, 1, 3, and 6 DU, with matching placebo to maintain the blinding. After trial initiation, the Applicant decided to include doses 9 and 12 DU. The 6 dose groups were defined as 0.5, 1, 3, 6, 9 and 12 DU according to the active treatment in the respective dose group. Dose groups were treated in a staggered manner at intervals of approximately 2 weeks. A safety committee reviewed the initial safety data of the previous dose(s), and only by their approval did the trial enter the next (higher) level of dose strength.

Seventy-eight participants were screened, and 72 participants were enrolled. There were no withdrawals and data from all 72 participants were analyzed.

Demographic Information
A total of 6 participants 5 through 11 years of age (4 male, 2 female) received 12 DU of Odactra. In the 12 DU treatment group, 100% were White. By ethnicity, 0% were Hispanic or Latino. In the placebo group, 100% were White. By ethnicity, 17% were Hispanic or Latino.

Safety
The Applicant reported no serious TEAEs, deaths or systemic reactions, and no withdrawals due to AEs. A total of 921 TEAEs were reported by 68 participants (a total of 72 participated in the study), of which the 719 events (78%) were judged as IMP related and 691 of these were

reported by the treatment groups. Most participants in treatment groups 3 to 12 DU (77.8-100%) reported related AEs, whereas fewer participants (22.2-33.3%) reported related AEs in the placebo, 0.5 and 1 DU treatment groups. The number of related AEs reported per participant was distinctly higher in the 3 to 12 DU treatment groups (15.4-21.9 AEs/participant) than in the placebo, 0.5 and 1DU treatment groups (0.6-1.6 AEs/participant).

The most frequently reported related AEs were from the gastrointestinal and respiratory systems: oral pruritus, throat irritation and mouth edema. They were all mostly reported in treatment groups 3 to 12DU. No mouth edema or throat irritation was reported in the placebo group.

The majority of related AEs in the treatment groups were mild (84.7%) in severity. Only the 3 to 9 DU groups reported moderate AEs. The only severe related AE was an oral (sublingual) pruritus, reported from the 3 DU treatment group, with duration of 10 min.

No clinically relevant abnormalities were observed reviewing the clinical safety laboratory tests, vital signs, physical examinations, lung function and weight. The abnormal findings (mainly mild) at oral examinations was only observed in actively treated participants, mainly within treatment groups 3 to 12 DU. Most of the findings disappeared within 1 hour and reappeared at the next IMP intake.