BLA Clinical Review Memorandum

Application Type	Supplemental Biologics License Application (Safety)
STN	125592/157
CBER Received Date	12/22/2021
PDUFA Goal Date	1/20/2023 (non-PDUFA product)
Division / Office	DVRPA/ OVRR
Priority Review (Yes/No)	No
Reviewer Name	Anubha Tripathi, MD
Review Completion Date/ Stamped Date	01/20/2023
Supervisory Concurrence	Kathleen Hise, MD Maria Allende, MD
Applicant	ALK Abello A/S
Proper (Established) Name	House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract
Trade Name	Odactra
Pharmacologic Class	Allergenic Extract
Formulation, including Adjuvants, etc.	Extract
Dosage Form, Route 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 and Intended Population	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 12 through 65 years of age. [Licensed Indication (February 7, 2017): Immunotherapy for house dust mite-induced allergic rhinitis with or without conjunctivitis, confirmed by in vitro testing for IgE antibodies to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* house dust mites, or skin testing to licensed house dust mite allergen extracts. The intended population is adults 18 through 65 years of age.]
Orphan Designated (Yes/No)	No

TABLE OF CONTENTS

GLOSSARY

AE	adverse event
AESI	adverse event of special interest
ADR	adverse drug reaction
AIT	allergen immunotherapy
AR/C	allergic rhinitis with or without conjunctivitis
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research (U.S. FDA)
CI	confidence interval
CMC	Chemistry, Manufacturing, and Controls (DBPAP/ OVRR/ CBER)
CRF	case report form
CSR	clinical study report
DB	Division of Biostatistics (OBPV/ CBER)
DMS	daily medication score
DPV	Division of Pharmacovigilance (OBPV/ CBER)
DSS	daily symptom score
eCRF	electronic case report form
EoE	eosinophilic esophagitis
GCP	Good Clinical Practice
DVRPA	Division of Vaccines and Related Products Applications (OVRR/ CBER)
FDA	U.S. Food and Drug Administration
FEV1	forced expiratory volume in 1 second
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
ISS	integrated summary of safety
MedDRA	Medical Dictionary for Regulatory Activities
MG	Medication Guide
non-TEAE	non-treatment-emergent adverse event
OBPV	Office of Biostatistics and Pharmacovigilance (CBER)
OVRR	Office of Vaccines Research and Review (CBER)
PDUFA	Prescription Drug User Fee Act
PeRC	Pediatric Review Committee
PI	Prescribing Information
PMR	post-marketing requirement
PREA	Pediatric Research Equity Act
PSP	pediatric study plan
PT	Preferred Term (terms per MedDRA)
PVP	pharmacovigilance plan
SAE	serious adverse event
SCS	summary of clinical safety
sBLA	supplemental Biologics License Application
SCIT	subcutaneous (allergen) immunotherapy
SLIT	sublingual (allergen) immunotherapy
SMQ	standardized MedDRA query

SQ-HDM	standardized quality-house dust mite
SOC	System Organ Class (terms per MedDRA)
SPT	skin prick test
TCRS	total combined rhinitis score
TEAE	treatment-emergent adverse event
TEB	Therapeutics Evaluation Branch (DB/ OBPV/ CBER)

1. EXECUTIVE SUMMARY

On December 22, 2021, ALK-Abello A/S (the Applicant) submitted a biologics license application (BLA) supplement (STN 125592/ Amendment 157) to support licensure of House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract (licensed product name: Odactra®) for use in adolescents 12 through 17 years of age. The proprietary name for this product, Odactra, will be used in this document. Odactra was approved for licensure on February 7, 2017 (the original BLA for Odactra was submitted under STN 125592/ Amendment 0), for the treatment of house dust mite (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* and *Dermatophagoides pteronyssinus* house dust mites or by skin testing to licensed house dust mite allergen extracts, in adults 18 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 12 through 65 years of age."

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), the Applicant was required to conduct studies to evaluate Odactra in children 5 through 11 years of age and adolescents 12 through 17 years of age. The pediatric study plan for Odactra initially included two studies in pediatric subjects 5 through 17 years of age [the first study was to evaluate both safety and efficacy and the second study was to evaluate safety in this age group; see Section 2.5 for details of the proposed pediatric study plan (PSP)]. At the time of the approval of this product in adults 18 through 65 years of age, studies in children 5 through 11 years of age had not yet been completed (and are currently ongoing); however, efficacy evaluation of Odactra in the adolescent age group had been completed in the Phase 3 efficacy and safety study, Study P001 (which supported licensure of Odactra in adults 18 through 65 years of age but also included efficacy and safety evaluation of Odactra in adolescents 12 through 17 years of age). A post-hoc sub-population efficacy analysis of the primary efficacy endpoint from Study P001 revealed a treatment difference of -22.4 (95% CI: -42.6, -8.1) in the adolescent age subgroup versus a treatment difference of -16.0 (95% CI: -23.2, -5.3) in the adult age subgroup. As results between age subgroups were comparable, the efficacy data in adolescents from Study P001 were deemed adequate to support licensure of the product in adolescents. However, the sample size of the adolescent age group exposed to the product was not large enough (n=94 adolescent subjects on active treatment in Study P001) to meet requirements of an adequate safety database in this age subgroup. Therefore, supplemental safety data in adolescents were required to support an indication for adolescents (see Section 2.5). Study MT-18 was conducted to supplement the safety database for the adolescent population to support the extension of the indication of Odactra to the adolescent age group.

This sBLA submission (STN 125592/157) included safety data from Study MT-18 (a Phase 3, 28-day, open-label, single-arm safety study; the safety data from Study MT-18 are the focus of this clinical review, see Section 6.1 Study MT-18) as well as efficacy and safety data from Study TO-203-3-2 (a Phase 2/3, randomized, double-blinded, placebo-controlled study conducted in Japan; the safety data from this study are considered supportive of the safety data from Study MT-18 and are briefly summarized in this

review, see Section 6.2 Study TO-203-3-2). In addition, key safety data in the adolescent population from Study P001 (a Phase 3, randomized, double-blind, placebo-controlled study in adults and adolescents 12 through 85 years of age) are summarized in this review (see Section 8, Integrated Overview of Safety); efficacy and safety data in the adult and adolescent populations from Study P001 were reviewed together under the original BLA submission.

Study MT-18 was a Phase 3, single-arm, open-label, multi-national, multi-site clinical study that evaluated the safety and tolerability of daily treatment with the investigational product (IP), Odactra (12 SQ-HDM, sublingual), over 28 days in 253 adolescents (12 through 17 years of age) with HDM-induced allergic rhinitis with or without conjunctivitis or asthma. This study was conducted in Europe in countries in which the HDM sublingual immunotherapy (SLIT) tablet is approved for use in the adolescent age group (Czech Republic, Slovakia, and Germany) so that all subjects had the opportunity to continue treatment after study completion. This study was conducted throughout the year, irrespective of coinciding pollen seasons, provided the 28-day treatment period did not overlap with the relevant season for an allergen to which the individual subject was allergic. The study consisted of three periods: a screening period, a 28-day open-label treatment period, and a 5-7-day follow-up period. The first dose of Odactra was administered under medical supervision in a healthcare setting equipped to treat systemic allergic reactions, and subsequent doses were self-administered at home. During the 28-day period, 15 pre-specified adverse reactions were solicited/ collected from subjects via a side effect report card/ diary. Unsolicited adverse events were collected for the duration of the study (which was 28 days in the case of Study MT-18).

As expected, adverse reactions occurred in the treatment group more often than in the placebo group in Study MT-18. The most common solicited adverse reactions occurring in ≥10% of adolescent subjects taking Odactra were throat irritation/tickle, itching in the mouth, itching in the ear, tongue pain, stomach pain, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat swelling, nausea, tongue ulcer/sore on the tongue, and mouth ulcer/sore in the mouth, and diarrhea. The majority of these events were assessed as mild to moderate in severity, occurred very early in treatment, and resolved without complication. Similar common solicited adverse reactions occurred in adults 18 through 65 years of age in Study P001. In addition, throat irritation, oral pruritus, ear pruritus, and lip swelling have also been reported as the most common adverse reactions for licensed SLIT products. Discontinuation from treatment and subsequent withdrawal from Study MT-18 occurred in 0.8% of subjects due to two IP-related, solicited treatment-emergent adverse events (TEAEs), abdominal pain (duration of 6 days) and mouth ulceration (duration of 3 days), both of moderate severity and both of which resolved after discontinuation of Odactra. In terms of adverse events of special interest (AESIs), one subject was assessed as having had a possible treatment-emergent systemic allergic reaction and no subjects were assessed as having TEAEs of severe local swelling/edema of the mouth and/or throat, TEAEs treated with epinephrine, or TEAEs of eosinophilic esophagitis (EoE).

A brief integrated review of the safety data from Study P001 and Study TO-203-3-2 found safety data from these studies to be comparable to that of Study MT-18 (with the exception that Study P001 identified one case of EoE in an adolescent subject). This brief integrated review did not identify any new safety signals that would require additional evaluation in this age group and found the overall safety profile of Odactra in the adolescent population to be acceptable.

Overall, the safety data from Studies P001, MT-18, and TO-203-3-2, and the efficacy data from Study P001 support a favorable risk-benefit assessment of Odactra 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 by skin testing to licensed HDM allergen extracts in adolescents 12 through 17 years of age.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

A total of 25 study sites in 3 countries enrolled and randomized at least 1 participant (listed by number of sites per country): Czech Republic (8), Slovakia (12), and Germany (5). Review of demographic data (gender, age, race) for subjects in Study MT-18 (Section 6.1.10, Table 5) revealed the following: the mean age of study subjects was 14 years with a range of 12−17 years, subjects had HDM-induced AR/C for a mean of 5.9 years, the study population was 60% male, nearly all of subjects were white (99.6%), 44% of the subjects were sensitized to HDM only while the remaining subjects in the study were sensitized to at least one allergen in addition to HDM at baseline, the mean skin prick test (SPT) wheal size was 8.1 mm for *Dermatophagoides pteronyssinus* and 7.3 mm for *Dermatophagoides farinae*, and 43% of the subjects had asthma. Among the study subjects with asthma, individuals had asthma for a mean of 6.7 years, the mean forced expiratory volume in 1 second (FEV1) (% predicted) was 96%, and 29% of subjects reported the use of low/medium dose of inhaled corticosteroid (ICS) with or without long-acting beta agonists.

> *Reviewer Comment:*
> *The population size of non-Caucasian subjects in Study MT-18 was small; therefore, subgroup analyses by race were not performed for this study since interpretation of any treatment differences in the non-Caucasian populations is limited by small population size. Of note, however, as Study TO-203-3-2 (of which the safety data in adolescents are reviewed here) exclusively enrolled Asian subjects (as the study was conducted in Japan), safety data for Odactra in an adequately sized Asian subpopulation were available for the adolescent population. As noted later in this review (see Section 6.2 Discussion of Individual Studies/ Study TO-203-3-2), the supplemental safety data from Study TO-203-3-2 support safety of Odactra in the adolescent population.*
>
> *The larger male study population in Study MT-18 is consistent with the greater prevalence of AR/C among males in childhood.*

1.2 Patient Experience Data

Patient experience data were not submitted as part of this application.

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 developed nations (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 the age of 6 years, and

80% of all individuals with AR/C develop symptoms before 20 years of age (Meltzer et al. 2009). Among adolescents 13 to 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 to 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 to 19 years of age) and 28% in the general population (6 to 59 years of age) based on the NHANES survey, with age identified as a predictor of HDM sensitization (Arbes et al. 2005), and HDM sensitization rates across 7 inner city metropolitan areas in the U.S. showed an average of 62% of inner-city children with 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)

Currently available pharmacologically unrelated interventions for the proposed indication (treatment of HDM-induced AR/C) include avoidance measures for physical exposure to HDM allergen in indoor environments. These include minimizing carpeting and upholstered furniture, keeping indoor humidity levels below 45% relative humidity, vacuuming weekly using a vacuum cleaner with a double thickness bag and HEPA filter, washing bedding regularly at 130 degrees Fahrenheit, and covering mattresses and pillows with impermeable covers (Adkinson et al. 2014).

However, since avoidance measures for this allergen are hard to achieve and sustain and may not minimize presence of the allergen entirely, clinical management typically relies on combined pharmacologic therapy regimens. Currently available pharmacologically unrelated treatments for the proposed indication (treatment of HDM-induced allergic rhinitis, with or without conjunctivitis) include oral antihistamines, intranasal antihistamines, intranasal anticholinergics, and intranasal steroids. These medications treat symptoms but do not modify the course of the disease.

2.3 Safety and Efficacy of Pharmacologically Related Products

Currently available pharmacologically related products for the proposed indication (treatment of HDM-induced AR/C) are classified as allergen-specific immunotherapy. Unlike avoidance and symptomatic therapy, allergen-specific immunotherapy offers the potential to reduce allergic symptoms and decrease the need for symptomatic treatment by increasing an individual's tolerability to a specific allergen. It is the only known treatment that modifies the immune response and treats the cause rather than the symptoms. Allergen immunotherapy (AIT) involves the administration of gradually increasing doses of the allergen over a period of time to desensitize the patient to the allergen. In the United States (U.S.), the licensed routes of administration of HDM extract-containing allergen immunotherapy are subcutaneous allergen immunotherapy (SCIT) and SLIT.

Studies evaluating subcutaneously administered AIT have generated data showing that this approach may modify the disease course and decrease medication use (Cox et al. 2011). Effectiveness of SCIT extracts is based on a 1985 publication by the Panel on Review of Allergenic Extracts, an advisory committee to the U.S. FDA (Implementation of Efficacy Review, Allergenic Extracts, Federal Register 1985) (Panel on Review of Allergenic Extracts 1985). There is no defined dose or regimen (i.e., standard versus accelerated) for SCIT, which is tailored to an individual patient and varies from one allergist-immunologist to another. In poly-sensitized individuals, SCIT prescriptions may be one or two different mixtures of multiple allergens. SCIT is contraindicated in persons with severe, unstable, or uncontrolled asthma. Despite the documented benefits of SCIT, only 5% of the U.S. population with allergic rhinitis, asthma, or both receive SCIT due to: the level of discomfort associated with SCIT; the inconvenience of the frequency of administration of the injections; the inconvenience of delivery of SCIT, which is required to occur in a monitored healthcare setting due to the risk of systemic allergic reactions associated with SCIT; and the risks of occurrence of local and systemic allergic reactions associated with SCIT. The most common adverse reactions occurring in over

26 to 82% of all patients who receive SCIT are local adverse reactions at the injection site (e.g., erythema, itching, swelling, tenderness, pain). Systemic adverse reactions, occurring in ≤ 7% of patients, include generalized skin erythema, urticaria, pruritus, angioedema, rhinitis, wheezing, laryngeal edema, and hypotension.

SLIT products approved for licensure in the U.S. to date are listed in Table 1.

Table 1. Sublingual Allergen Immunotherapy Products Currently Approved for Licensure in the United States

Proper Name (Dose, Schedule)	**Indication**	**Approval Date/ Age Range (Trade Name)**
Timothy Grass Pollen Allergen Extract (2,800 BAU, 1 tablet daily)	Treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens in persons 5 through 65 years of age	2014/ persons 5 through 65 years of age (Grastek)[1]
Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract (300 IR, 1 tablet daily in persons 18 through 65 years of age; 100 IR, 1 tablet daily in persons 5 through 17 years of age)	Treatment of confirmed grass pollen-induced allergic rhinitis with or without conjunctivitis for any of the five grass pollens contained in the product in persons 5 through 65 years of age	2014/ persons 10 through 65 years of age (Oralair) 2018/ persons 5 through 9 years of age (Oralair)
Short Ragweed Pollen Allergen Extract (12 Amb a 1-U, 1 tablet daily)	Treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for short ragweed pollen in persons 18 through 65 years of age	2014/ persons 18 through 65 years of age (Ragwitek)[2]
House Dust Mite Pollen Allergen Extract (12 SQ-HDM, 1 tablet daily)	Treatment of 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 persons 18 through 65 years of age	2017/ persons 18 through 65 years of age (Odactra)

Source: FDA-generated table.
Abbreviations: BAU=Bioequivalent Allergen Units, IR=Index of Reactivity, Amb a 1-U=Units of *Ambrosia artemisiifolia* major allergen 1, SQ-HDM=the dose unit for Odactra (SQ is a method of standardization of biological potency, major allergen content, and complexity of the allergen extract; HDM=house dust mite.
[1] Approved in the European Union under the trade name Grazax®

[2] Approved in Canada under the trade name Ragwitek® in 2014 and approved in 9 European countries (Austria, Czech Republic, France, Hungary, Italy, Romania, Slovakia, Slovenia, and Germany) and Russia under the trade name of Ragwizax® in 2017

Though the mechanism of SLIT is complex and not fully characterized, administration and absorption of allergens through the oral and gingival mucosa via the sublingual route can decrease the allergic response through desensitization to the allergen, at least temporarily and potentially permanently (i.e., tolerance).

A Cochrane review suggested that SLIT is a viable alternative to SCIT with a lower risk profile and little difference in overall efficacy (Radulovic et al. 2010). Notably, the lower incidence of severe or serious adverse events associated with SLIT allows SLIT to be self-administered at home while safe use of SCIT requires administration in a clinic staffed by medical professionals that are trained to treat systemic allergic reactions. However, as with SCIT products, SLIT is contraindicated in persons with severe, unstable, or uncontrolled asthma. Unlike most SCIT products, SLIT products are used according to defined dosing regimens.

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

Odactra was licensed in the U.S. in 2017 for the treatment of HDM-induced allergic rhinitis with or without conjunctivitis in adults 18 to 65 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 adults for the treatment of HDM-induced AR/C in Canada, Europe, Japan, and Australia, and for the treatment of HDM-induced allergic asthma (AA) in adults in Europe and Australia. Additionally, it is approved in Europe and Japan for treatment of HDM-induced AR/C in adolescents (12 through 17 years of age).

U.S. Experience

Data from 8 clinical studies were submitted in support of licensure of Odactra for treatment of HDM-induced allergic rhinitis/ rhinoconjunctivitis in adults 18 through 65 years of age. The 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). Subjects 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 skin prick test 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 subjects 18 years of age and older with mild to moderate asthma and AR/C.

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 subjects 12 years of age and older (N=1482) with HDM-induced AR/C with or without asthma. Subjects 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 total combined rhinitis score (TCRS), daily symptom scores (DSS), and daily medication scores (DMS) for rhinoconjunctivitis were calculated. 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 subjects daily on a scale of 0 (none) to 3 (severe) and then summed. Subjects 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% confidence interval (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 to 65 years with HDM-induced AR/C with or without asthma. 992 subjects 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 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 environmental exposure chamber (EEC) in subjects with HDM-induced AR/C with or without asthma. The study enrolled 124 subjects 18 years of age and older. The study was conducted at a single center located in Austria. Subjects were randomized 1:1:1 to receive either Odactra 12 SQ-HDM (n=42), Odactra 6 SQ-HDM (n=41), or placebo (n=41). Subjects received daily dosing with Odactra for 24 weeks prior to a 6-hour challenge in an EEC. In the EEC, subjects 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, subjects 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 subjects were provided medical treatment if warranted. While in the EEC, subjects 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 subjects who received at least 1 dose of study drug. Of these 1482 subjects, 640 subjects 18 through 65 years of age received at least 1 dose of Odactra and 631 subjects received placebo. The median treatment duration for subjects who received Odactra was 267 days (range 1 to 368 days). Study subjects 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 subjects 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 adverse events were reported more frequently with Odactra than with placebo and occurred in ≥1% of subjects 18 through 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 subjects who dropped out of the study was higher in the Odactra group (24.2%) compared to the placebo group (17.3%). The rates of serious adverse events (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 subjects 18 through 65 years of age were treated with at least one dose of Odactra of whom 1104 (86%) completed at least 4 months of therapy. The placebo group had 1277 subjects. The percentages of subjects 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 subjects who received Odactra were throat irritation (1.5%), oral pruritus (1.3%), ear pruritus (1.1%), and mouth swelling (1.0%). Serious adverse events rates were 16/1279 (1.3%) among Odactra recipients and 23/1277 (1.8%) among placebo recipients. A causal relationship between these serious adverse events and Odactra was not established. No deaths occurred.

Of 1279 subjects who received Odactra, 34 (2.7%) reported dyspepsia compared to 0/1277 (0%) of subjects who received placebo. Twenty subjects who received Odactra

(1.6%) reported symptoms of gastroesophageal reflux disease compared to 3/1277 (0.2%) of subjects who received placebo.

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

Across 8 clinical studies submitted to the BLA (MT-01/P011, P008, MT-03/P013, P003, MT-02/P012, P001, MT-06/P015, MT-04/P014), 1458 subjects 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%) subjects who received Odactra compared to 0/1636 (0%) subjects who received placebo.

The number of adolescents 12 through 17 years of age (N=94) and 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 either of these age groups at the time of original BLA submission.

Foreign Experience

The HDM SLIT tablet was approved by the European Medicines Agency decentralized procedure comprising 11 EU countries (Austria, Czech Republic, Denmark, Finland, France, Germany, Italy, Norway, Poland, Slovakia, and Sweden) on August 30, 2015 and marketed in those 11 European Union 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 ICS and associated with mild to severe HDM-induced allergic rhinitis in adults 18 through 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. Subjects were initially treated for 7-12 months with one of two doses of Acarizax (6 or 12 SQ-HDM) or placebo. Inhaled corticosteroids were reduced and withdrawn over a 6-month period. Efficacy was assessed as the time to first moderate or severe asthma exacerbation in subjects 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 subjects 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). Subjects 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. Subjects taking 6 SQ-HDM experienced a relative mean ICS reduction from baseline of 42% versus 15% for the placebo group.

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

Pre-submission Regulatory Activity

On 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 through 65 years of age.

Odactra is not currently licensed for the treatment of HDM-induced AR/C in adolescents in the U.S. because the number of adolescent subjects 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 subjects 12 through 17 years of age on active treatment randomized in Study P001).

The deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act as outlined in the March 1, 2017 Approval Letter were as follows:

1. Deferred pediatric study (Study 1) under PREA to evaluate safety and efficacy of Odactra in pediatric subjects 5 through 17 years of age with HDM-induced allergic rhinitis/rhinoconjunctivitis with or without asthma.
2. Deferred pediatric study (Study 2) under PREA to evaluate the safety of Odactra in pediatric subjects 5 through 17 years of age with HDM-induced allergic rhinitis/rhinoconjunctivitis with or without asthma.

In response, the Applicant submitted two phase 3 protocols in 2017 (MT-12 and MT-14) to the IND to evaluate the safety and efficacy of Odactra in pediatric subjects 5 through 17 years of age for the treatment of allergic rhinitis. MT-12 was planned as a 1-year efficacy study and MT-14 was proposed as a 28-day supplementary safety study. However, in July 2018 (July 30, 2018 Type C Meeting Briefing Package), the Applicant proposed a revised pediatric plan (for full detail see CBER Written Responses Only document dated 9/19/2018, CRMTS #11361, IND 15015).

Based on CBER's responses to the Applicant's July 2018 proposal, the Applicant submitted a revised proposal. In evaluation of the revised proposal, the clinical team reassessed the need for additional efficacy data in adolescents 12 through 17 years of age. It was concluded that CBER will not require additional efficacy data for a sBLA submission in adolescents 12 through 17 years of age because supportive adolescent efficacy data was already submitted to the original BLA (STN 125592/0) and because it was not expected that adolescents would differ biologically in treatment response to Odactra given the treatment response in a post-hoc subpopulation analysis of the primary efficacy endpoint data in the age subgroups for Study P001 were comparable [adolescents 12 through 17 years of age: -22.4 (-42.6, -8.1); adults 18 through 65 years of age: -16.0 (-23.2, -5.3)]. Therefore, it was determined that only safety data in adolescents to supplement those obtained in adolescents in Study P001 would be required to support a sBLA in adolescents. In addition, the clinical team noted that an institutional review board may raise objections to the study under 21CFR 50 subpart D, as adolescents would be exposed to a greater than minimal risk in a previously

proposed EEC study that may not be scientifically necessary (the risk is more than minimal in an environmental exposure chamber because exposure to large quantities of dust mite may induce an asthmatic response in sensitive subjects). These decisions were conveyed to the Applicant, and the Applicant elected to pursue other study designs.

The Applicant then submitted a Type C Meeting briefing package on September 11, 2019 to continue discussion of their plans to obtain efficacy data in children 5-11 years of age and safety data in children 5-17 years of age. From this Type C Meeting interaction, CBER determined that an open-label, 28-day safety study would be sufficient support the adolescent safety database. [This decision was based on regulatory precedent with the grass allergen SLIT product Oralair (which is indicated as immunotherapy for the treatment of grass pollen-induced AR/C); a 30-day open label study in 307 subjects 5 through 9 years of age in Europe was supportive of the licensure of Oralair in children of 5 years of age and above.] CBER also determined that the Applicant could proceed to study efficacy and safety in pediatric subjects 5 through 11 years of age in Study MT-12.

Following discussions between the Applicant and CBER regarding the deferred pediatric studies, CBER agreed that for the age group 12 through 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 concurred with a revised, staged development approach which included two separate studies for the two age groups, children 5 through 11 years of age and adolescents 12 through 17 years of age as follows:

1. Study MT-18: an open-label 28-day safety study to evaluate safety and tolerability of Odactra in adolescents 12 through 17 years of age with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma over 28 days of treatment.
2. Study MT-12: a Phase 3, double-blind, parallel-group, placebo-controlled study to evaluate safety, tolerability, and efficacy of Odactra in children 5 through 11 years of age with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma.

The design and conduct of the supplemental safety study, Study MT-18, was based on CBER's responses to the Applicant's September 11, 2019 Type C Meeting briefing package as discussed above. CBER agreed with a proposed open-label 28-day study design for adolescents 12-17 years of age to supplement the existing safety database in this age group. CBER also agreed that Study MT-18 could be conducted in Europe and that a sample size of 250 adolescents with HDM-induced AR/C with or without asthma was acceptable.

On July 9, 2020, the Applicant submitted a Type C Meeting Request and Briefing Package to obtain the Agency's concurrence on the proposed data package [Study MT-18 results as well as existing clinical data from completed studies involving adolescent subjects 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)] to support the sBLA submission to extend the current indication to include the adolescent population 12 through 17 years of age.

- The Applicant requested input on whether the MT-18 data package as described in the submission was sufficient to support the planned supplemental BLA (sBLA) submission. (CBER agreed that the data package, as described, would be

sufficient to support the submission of the sBLA, further requesting that the annotated case report form (CRF) with SDTM domains/ variables be submitted to the IND for CBER review/ concurrence.)

- The Applicant requested input on their proposal to include studies not previously submitted to the FDA (i.e., Studies TO-203-3-2, MT-18) in the data package with the sBLA submission. (CBER agreed with the Applicant's proposal to submit clinical study reports (CSRs) and dataset packages for Study MT-18 and Study TO-203-3-2 and requested that the Applicant submit the clinical safety and efficacy summaries for all adolescents 12 through 17 years of age who have received the 12 SQ-HDM dose of Odactra (including the corresponding placebo comparators) with the sBLA.)
- The Applicant requested input on whether the Study TO-203-3-2 data package in the format described in the briefing package was sufficient to support the planned sBLA submission. (CBER agreed that the safety and efficacy data from Study TO-203-3-2 should be included in the sBLA submission and further requested that the tabulation datasets (Legacy) be included to ensure traceability.)

Post-submission Regulatory Activity

- Major Amendment Activity:
  Upon review of the datasets submitted to the sBLA by the Data Standards and Validation Committee, various discrepancies were identified in several datasets. An initial information request (IR) was sent on February 23, 2022 to the Applicant requesting clarification and correction of various discrepancies identified. Upon receipt of response from the Applicant, ongoing discrepancies were re-identified by the Data Validation and Review Committee another IR was sent on April 14, 2022. The resulting response from the Applicant to these IRs was received on May 31st, 2022 and was considered a major amendment by the Division due to the extent of revisions required of the results reported in the Study MT-18 CSR and Integrated Summary of Safety (the review clock was therefore extended by 3 months, moving the Action Due Date for the BLA from 10/21/2022 to 1/20/2023).

- Pediatric Review Committee (PeRC) Activity:
  The CSRs of Study MT-18 and Study TO-203-3-2 were submitted under sBLA 125592/157 on December 22, 2021. After review of the data, the Division concluded that the safety data from Study MT-18, the safety data from Study T0-202-3-2, and the efficacy and safety data from Study P001 (previously reviewed under STN 125592/0) support approval of Odactra in adolescents 12 through 17 years of age.

  The following language was proposed for Section 8.4 (Pediatric Use) of Section 8 (Use in Specific Populations) of the Prescribing Information (PI): The safety and effectiveness of Odactra have been established in adolescents 12 through 17 years of age. The safety and effectiveness have not been established in persons below 12 years of age.

  On December 13, 2022, a meeting with PeRC was held 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):

1. Release of the Applicant from PMR#1 and PMR#2 (listed in the March 1, 2017 Approval Letter).
2. 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 through 11 years of age with HDM-induced allergic rhinitis/rhinoconjunctivitis with or without asthma).

   Reviewer Comment:
   Please see the reviewer comment in Section 9.1.3 for further information on the discussion with CBER's PeRC during the review of this sBLA.

2.6 Other Relevant Background Information

Not applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The application was, in general, organized to accommodate the conduct of a complete clinical review.

3.2 Compliance with Good Clinical Practices and Submission Integrity

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

- Clinical Study Report for Study MT-18: "The trial was conducted in accordance with the Declaration of Helsinki (1964, and its subsequent amendments and clarifications) (World Medical Association 2013) and ICH GCP (ICH 1996)."
- Clinical Study Report for Study TO-203-3-2: "This study is to be conducted in compliance with the ethical principles of the Declaration of Helsinki, Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law, and Ordinance on Good Clinical Practice (MHW Ordinance No. 28 dated March 27, 1997) and applicable notifications. Study-related documents and materials are appropriately archived by responsible divisions. (b) (4) Development Division, Torii Pharmaceutical Co., Ltd."

3.3 Financial Disclosures

Covered clinical study (name and/or number): Study MT-18
Was a list of clinical investigators provided? Yes
Total number of investigators identified: 49 (including sub-investigators; 5 persons were investigators/ sub-investigators at 2 study sites)
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0
Number of investigators with certification of due diligence (Form FDA 3454, box 3): N/A **Is an attachment provided with the reason?** N/A

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.

Of note, allergen potency in Odactra is described by the development unit (DU). The PI states allergen potency as SQ-HDM. DU is equivalent to SQ-HDM. The potency of the tablet is determined using the (b) (4)

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Stability data determined the dating period for Odactra. This period will 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.

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 (DB)/ Therapeutics Evaluation Branch 2 (TEB2) who verified the safety data and corresponding analyses submitted to the sBLA. Please see the Biostatistical Review Memorandum for a detailed discussion of these analyses.

4.6 Pharmacovigilance

A complete review of the pharmacovigilance plan (PVP) (submitted to STN 125592/157) was conducted by Dr. Jonathan Reich, MD within CBER's Office of Biostatistics and Pharmacovigilance (OBPV)/ Division of Pharmacovigilance (DPV). Please see the pharmacovigilance review memorandum for details.

A revised PVP was submitted with this supplemental BLA. The Applicant summarized the changes from the previous PVP and the respective DPV Reviewer Comments are as follows:

1. Identified Risks: EoE has been changed from a potential risk to an identified risk.

2. Missing information: the following populations have been removed from this category:
    a. Pregnancy, lactation
    b. Use in the elderly
    c. Co-administered with other SLIT products
3. Use in severe, uncontrolled, or unstable asthma has been removed from "missing information." The Applicant's rationale for this change is that severe asthma is a contraindication to use of this product.

The final recommendations of the review with respect to the proposed PVP were as follows (please see DPV review memorandum for details):

- Item 1: DPV agreed with this change. EoE has been identified as an important and potentially serious AE, including in an adolescent in Study P001. The FAERS search identified 3 adult cases.
- Item 2:
    - Item 2a: Pregnant and lactating women have been removed from the PVP; the Applicant suggested that available information suggests no safety risk associated with use of SLIT products in these populations, and that there is now sufficient data to evaluate any unknown risks to these populations using routine surveillance. In support of this assertion, the Applicant noted that its internal safety database includes 315 reports of pregnant women who received SLIT products, and that their review of the reports reveals no relationship between therapy and adverse events. DPV disagrees that there is currently sufficient available data to fully characterize risk of use in pregnant/lactating women. However, DPV notes that the labeling adequately reflects the lack of data for these populations and, given that safety in these populations is being evaluated only through routine pharmacovigilance, DPV does not object to their removal from the Odactra PVP.
    - Item 2b: In reference to the safe use of SLIT products in the elderly, the Applicant cited three studies. A study from 2015 was a randomized, double-blinded, placebo-controlled study involving 111 60- to 75-year-old patients with allergic rhinitis and a confirmed dust mite allergy. 51 subjects received a different brand of SLIT (not Odactra) for treatment of dust mite allergy, and no safety concerns specific to use of the SLIT were noted. DPV notes that the labeling adequately reflects the lack of data for this population and, given that safety in this population is being evaluated only through routine pharmacovigilance, DPV does not object to removal of elderly from the 'Missing Information' section of the Odactra PVP.

  - Item 2c: In reference to the safety of co-administering multiple SLIT products, the Applicant notes that internal reviews and literature do not present concerns. Additionally, as noted by the Applicant, there are no enhanced pharmacovigilance activities for this safety issue over and above routine activities. DPV notes that the labeling adequately reflects the lack of data for this population. DPV does not object to removal of concomitant use with other SLIT products from the Odactra PVP.
- Item 3: Given that use in severe, uncontrolled, or unstable asthma is contraindicated, there will be no enhanced pharmacovigilance activities related to this safety issue, and it is reasonable to remove this population from the PVP.

The review concluded that review of the safety data from the submitted clinical studies done in adolescents demonstrates that Odactra has a safety profile in subjects between the ages of 12-17 years that is comparable to the safety profile in adults, that changes to the PVP, including the removal of use during pregnancy, lactation, use in the elderly, and use when co-administered with other SLIT products are acceptable. DPV concluded that the proposed PVP with agreed upon changes was adequate and that DPV will continue routine surveillance.

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

5.1 Review Strategy

Assessment of the safety of Odactra in adolescents 12 through 17 years of age was based primarily on supplemental safety data from Study MT-18 (the focus of this clinical review, see Section 6.1 Discussion of Individual Studies/ Clinical Trials; Study MT-18 was a 28-day open-label, single-arm safety study) and on safety data from Study P001 (these data were primarily reviewed under STN 125592/0; Study P001 was a Phase 3, randomized, double-blind, placebo-controlled study in adults and adolescents 12 through 85 years of age).

Safety data in adolescents from Study TO-203-3-2, a Phase 2/3, randomized, double-blinded, placebo-controlled study conducted in Japan, are considered supplemental to safety data from Studies MT-18 and P001 and are summarized in this clinical review (see Section 6.2 Discussion of Individual Studies/ Clinical Trials).

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

The following served as the basis for the clinical review of STN 125592/157:

- 125592/157/0:
  - Module 1.2 Cover Letter
  - Module 1.3.4 Certification and Disclosure of Financial Interests and Arrangements of Clinical Investigators
  - Module 1.6 Meetings
  - Module 1.14 Labeling
  - Module 2
    - Module 2.2 Introduction
    - Module 2.5 Clinical Overview
    - Module 2.7 Clinical Summary (Summary of Clinical Efficacy, Synopses of Individual Studies)

    Module 5 Clinical Study Reports (Study TO-203-3-2)

- 125592/157/6, Major Amendment:
  - Module 2
    - Module 2.5 Clinical Overview
    - Module 2.7 Clinical Summary (Summary of Clinical Safety)
  - Module 5 Clinical Study Reports (Study MT-18)

- 125592/157/9, 10, 12, 14, 15: Labeling [PI and Medication Guide (MG)] Review FDA IRs with Applicant Responses

- 125592/157/16: Applicant Response to FDA IR

5.3 Table of Studies/Clinical Trials

Table 2. Table of Studies/ Clinical Trials

Study ID **Study Dates** (month/year) **Study Design**	**Study Arms** **Treatment Duration**	**Study Endpoints**	**Sample Size**	**Study Population** (Age in years) Key Inclusion Criteria	**Countries** (# of study sites*)
P001 1/24/2013-4/27/2015 Phase 3, R, DB, PC	HDM SLIT tablet (12 SQ-HDM) or placebo sublingual daily 52 weeks	<u>Efficacy:</u> Difference in average TCRS between active and placebo arms during the last 8 weeks of treatment <u>Safety:</u> Proportion of subjects reporting: pre-specified AESIs; SAEs; discontinuations due to AE.	N=1482 (12 through 85 years of age) (Active: n=741, Placebo: n=741) *Adolescents 12-17 years of age:* Efficacy (FA Set) Active n=76; Placebo n=84 Safety (Safety Set): Active n=94; Placebo n=95	12 through 85 HDM-induced AR/C (with or without asthma) diagnosed by clinical history of AR/C when exposed to HDM of at least 1 year duration despite Rx with meds; positive SPT to HDM: average of 2 species: 5mm > negative control; positive specific IgE >0.7 IU/ml	North America (182)

Study ID **Study Dates** (month/year) **Study Design**	**Study Arms** **Treatment Duration**	**Study Endpoints**	**Sample Size**	**Study Population** (Age in years) Key Inclusion Criteria	**Countries** (# of study sites*)
MT-18 9/23/2020-4/24/2021 Phase 3, Single-arm, Open-Label	HDM SLIT tablet (12 SQ-HDM) sublingual daily 28 days	<u>Safety</u> *Primary:* ≥ 1 TEAE *Secondary:* proportion of subjects with ≥ 1: solicited TEAE; IP-related AE; treatment-emergent SAE *Other:* - Daily duration of recurrent TEAEs - Proportion of subjects with ≥ 1 treatment-emergent AESI: systemic allergic reaction including anaphylaxis; AE treated with epinephrine; severe edema of mouth/ throat -a TEAE of EoE -a TEAE leading to discontinuation.	N=253 (251 completed: 248 completed the 28-day treatment period, 2 discontinued)	12 through 17 HDM-induced AR/C (with or without asthma) diagnosed by clinical history of AR/C when exposed to HDM of at least 1 year duration despite Rx with meds, positive SPT to HDM ≥ 3mm	Czech Republic (8) Slovakia (12) Germany (5)

Study ID **Study Dates** (month/year) **Study Design**	**Study Arms** **Treatment Duration**	**Study Endpoints**	**Sample Size**	**Study Population** (Age in years) Key Inclusion Criteria	**Countries** (# of study sites*)
TO-203-3-2 6/07/2012-12/27/2013 Phase 2/3, R (1:1:1:), DB, PC	HDM SLIT tablet (6 or 12 SQ-HDM) or placebo sublingual daily 52 weeks	Efficacy - Symptom score, medication score - Japanese Allergic Rhinitis Standard QOL Questionnaire Safety - Symptoms and signs - Physiological examinations (blood pressure and pulse rate) - Laboratory tests (hematology and blood chemistry)	Active: 627 (Adolescents, 12 SQ HDM dose, n=107) (79 adolescents completed 52 weeks of treatment) Placebo: 319 (Adolescents n=99)	12 through 64 HDM-induced AR/C diagnosed by clinical history of AR/C when exposed to HDM of at least 1 year duration despite Rx with allergy pharmaco-therapy, positive SPT to HDM ≥ 3 mm	Japan (multi-center)

Source: Adapted from BLA 125592/157/0: Tabular Listing of All Clinical Studies; Clinical Overview.
Abbreviations: R=randomized; DB=double-blind; PC=placebo-controlled; HDM=House dust mite; SQ-HDM=Standardized Quality- House Dust Mite (unitage); N=Number of subjects (includes all subjects who were randomized and received at least one dose of treatment; AR/C=Allergic rhinitis with or without conjunctivitis; TCRS=Total Combined Rhinitis Score; SPT=skin prick test; AE=Adverse Event; TEAE=Treatment-Emergent Adverse Event; SAE=Serious Adverse Event; AESI=adverse event of special interest; QOL=Quality of Life; EoE=eosinophilic esophagitis.
* Number of study sites which enrolled and randomized at least 1 study subject.

5.4 Consultations

5.4.1 Advisory Committee Meeting

Not applicable.

5.4.2 External Consults/Collaborations

Not applicable.

5.5 Literature Reviewed

Adkinson, N. Franklin, Bruce S. Bochner, A. Wesley Burks, W. W. Busse, S. T. Holgate, Robert F. Lemanske, Robyn E. O'Hehir, and Elliott Middleton. Middleton's Allergy: Principles and Practice. 8th ed. 2014 Philadelphia: Elsevier/Saunders, PA. Print.

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study MT-18

Study Title:
“A 28-day, single-armed, open-label trial to evaluate safety of the house dust mite (HDM) sublingual allergy immunotherapy (SLIT) tablet in adolescent subjects (12-17 years of age) with HDM allergic rhinitis/rhinoconjunctivitis (AR/C) with or without asthma”

6.1.1 Objectives (Primary, Secondary, etc.)

The objective of the study was to evaluate safety and tolerability of the HDM SLIT tablet (12 SQ-HDM) in adolescents (12 through 17 years of age) with HDM-induced allergic rhinitis with or without conjunctivitis over 28 days of treatment.

6.1.2 Design Overview

Study MT-18 was a Phase III, single-arm, open-label, multi-national, multi-site clinical study conducted in Europe. The study investigated safety and tolerability of the HDM SLIT tablet over 28 days in adolescents (12 through 17 years of age) with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma. This study was conducted throughout the year irrespective of coinciding pollen seasons, provided the 28-day treatment period did not overlap with the relevant season for an allergen to which the individual subject was allergic.

The purpose of this study was to collect safety data in adolescents with HDM-induced AR/C with or without asthma to supplement existing safety data (from Study P001) in this age group. The study was conducted in countries in which the HDM SLIT tablet is approved for use in the adolescent age group, thereby giving all subjects the opportunity to continue treatment after study completion. To ensure an unbiased selection of subjects and reporting of AEs, subjects had to be naive to treatment with the HDM SLIT tablet.

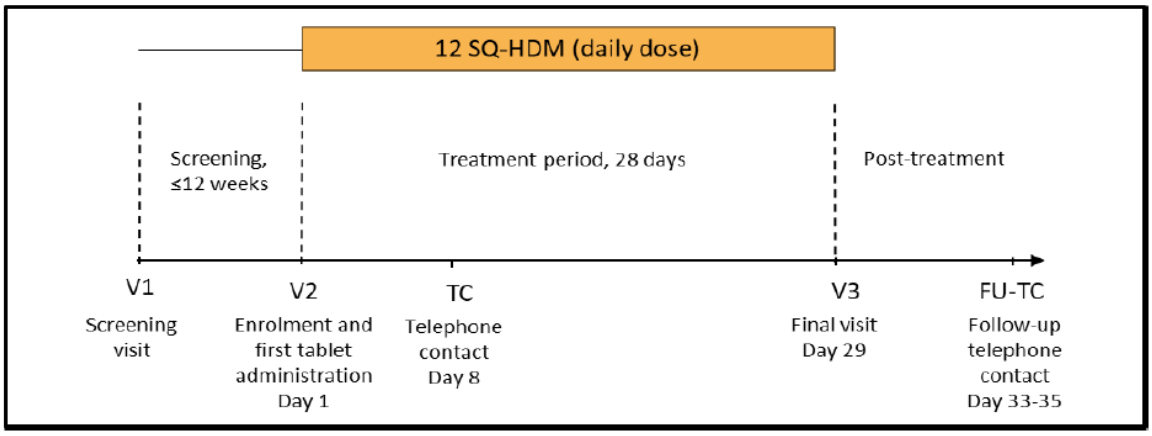
A total of 253 subjects were enrolled to receive daily treatment with the HDM SLIT-tablet (12 SQ-HDM). The study consisted of three study periods: a screening period, a 28-day open-label treatment period and a 5-7-day follow-up period (see Figure 1**).**

Each subject participated in three in-clinic visits: screening (Visit 1), enrollment and first tablet administration (Visit 2), and a final visit (Visit 3). In addition, subjects were contacted by telephone 7-9 days after V2 and 5-7 days after intake of the last IP dose. Unscheduled visits could take place in case of technical issues with lab samples and/or need for safety follow-up.

A subject was considered to have completed the study if he/she completed the treatment period (V3). The overall end of the study was defined as the date of last contact (FU-TC) for the last subject in the study globally.

The overall study design is shown in Figure 1.

Figure 1. Study Design



Source: BLA 125592/157/6, Study MT-18, Section 9.1, Figure 1, p. 22.

Reviewer Comment:
Per the Applicant, the open-label study design was chosen to reduce the time of study conduct, since recruitment of the relevant study population, adolescents (12-17 years of age) with HDM-induced AR/C, was likely to be less challenging if all subjects were offered active treatment, and to eliminate the ethical considerations of placebo treatment since the efficacy of the active treatment has been previously established. A treatment period of 28 days was chosen based on previous experience with the onset of AEs in the HDM SLIT tablet development program. In addition, the proposed treatment duration of 28 days allowed for solicitation of pre-specified AEs of SLIT tablets, as conducted in Study P001.

6.1.3 Population

The study enrolled 253 adolescents 12 through 17 years of age with HDM-induced AR/C at 25 study sites [Czech Republic (8 sites), Slovakia (12 sites), and Germany (5 sites)].

Inclusion Criteria:

- Written informed consent obtained from subjects' legal representatives before any study related procedures were performed
- Male or female subjects aged ≥12 to ≤17 years on the screening day (Visit 1) and at the follow-up telephone call
- A clinical history of allergic rhinitis/rhinoconjunctivitis when exposed to HDM (diagnosed by a physician) of 1-year duration or more (with or without asthma) and with AR/C symptoms despite having received allergy pharmacotherapy during the previous year prior to screening visit (Visit 1)
- Positive SPT to *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae* at screening (wheal size of ≥3 mm)
- Lung function measured by FEV1 ≥ 70% of predicted value or according to local requirements while on subject's usual asthma medication
- Willingness and ability to comply with study protocol and adhere to IP treatment

Exclusion Criteria:

- A clinically relevant history of symptomatic perennial allergic rhinitis/ rhinoconjunctivitis caused by a perennial allergen source, such as animal hair

and dander and/or mold to which the subject was exposed during the 28-day treatment period

- A clinically relevant history of symptomatic seasonal allergic rhinitis/ rhinoconjunctivitis caused by an allergen to which the subject is exposed, and which could potentially overlap with the 28-day treatment period
- A subject who had previously been included in studies with the HDM SLIT tablet, or otherwise being treated with the marketed HDM SLIT tablet (e.g., Acarizax, Odactra)
- Any SLIT or SCIT treatment with *D. pteronyssinus* or *D. farinae* reaching the maintenance dose within the last 5 years. In addition, any SLIT or SCIT treatment with *D. pteronyssinus* or *D. farinae* within the previous 12 months prior to Visit 1
- Ongoing treatment with any allergen immunotherapy product at screening
- Severe chronic oral inflammation
- A diagnosis or history of EoE
- Systemic immunosuppressive treatment within 3 months prior to screening
- Any clinical deterioration of asthma that resulted in emergency treatment, hospitalization, or treatment with systemic corticosteroids within 3 months prior to first tablet administration (Visit 2)
- Any clinically relevant chronic disease, including malignancy, that, in the opinion of the investigator, would interfere with the study evaluations or the safety of the subject
- A history of chronic urticaria (> 6 weeks) and/or chronic angioedema (> 6 weeks) within the last 2 years prior to screening visit that, in the opinion of the investigator, may constitute an increased safety concern
- 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
- Active or poorly controlled autoimmune diseases, immune defects, immunodeficiencies, immunosuppression or malignant neoplastic diseases with current disease relevance
- Treatment with an investigational drug within 30 days or 5 half-lives of the drug (whichever is the longest) prior to screening visit
- Known history of allergy, hypersensitivity, or intolerance to any of the excipients or active substances of the IP (except for *D. pteronyssinus* and/or *D. farinae*)
- Female with positive urine pregnancy test, breastfeeding, pregnant or planning to become pregnant within the projected duration of the study
- Sexually active female of childbearing potential without medically accepted contraceptive method
- A business or personal relationship with study staff or Applicant who is directly involved with the conduct of the study
- Previous enrollment into this study, participated in this study at another investigational site, or participated or planned to participate in any other clinical study during the duration of this study
- A history or current evidence of any condition, treatment, laboratory values out of range or other circumstance that in the opinion of the investigator were clinically relevant and might expose the subject to risk by participating in the study, confound the results of the study, or interfered with the subject's participation for the full duration of the study

- Presence of a condition or required treatment that may increase the risk of the subject developing severe adverse reactions after adrenaline/epinephrine administration
- Treatment with restricted and prohibited concomitant and previous medications

Reviewer Comment:
Subjects in both Studies P001 and MT-18 had to have a clinical history of AR/C when exposed to HDM (diagnosed by a physician) of 1-year duration or more (with or without asthma) despite having received allergy pharmacotherapy during the previous year prior to screening visit.

However, the inclusion criteria for HDM-induced AR/C for subjects in Study P001 were more specific than those of Study MT-18, thereby conferring greater specificity of subjects in Study P001 for HDM-induced AR/C. Key inclusion criteria for Study P001 differed from those of Study MT-18 by the following:

- *subjects in Study P001 had to have a positive skin prick test response (average wheal diameter of 2 tests must be at least 5 mm larger than the saline control after 15 to 20 minutes) to D. pteronyssinus* (b) (4) *and/or D. farinae* (b) (4) (b) (4) *at the Screening Visit [In contrast, in Study MT-18 subjects had to have a positive SPT To either or both of the HDM species at a wheal size of ≥3 mm]*
- *subjects in Study P001 had to have a specific IgE against D. pteronyssinus and/or D. farinae at the Screening Visit of at least IgE Class 2 (0.7 kU/L) [in contrast, specific IgE level to the HDM species was not an inclusion criterion for subjects in Study MT-18]*
- *subjects in Study P001 had to have a rhinitis DSS of at least 6, or a score of at least 5 with 1 symptom being severe, on 5 of 7 consecutive calendar days before randomization [this was not an inclusion criterion in for subjects in Study MT-18]*

While Study P001 inclusion criteria were appropriately specific given the objectives of the study (investigation of efficacy and safety of Odactra in adults for 1 year of treatment), the inclusion criteria of Study MT-18 more closely mimic diagnosis of HDM-induced AR/C in the clinical setting, in which subjects are typically diagnosed by 1) presence of a clinical history of AR/C when exposed to HDM and 2) positive SPT (wheal size of ≥3 mm) or elevated specific IgE to the HDM species (>0.35 kUA/L). In addition, the proposed indication for Odactra in adolescents is for treatment of subjects diagnosed with HDM-induced AR/C based on positivity of either SPT(s) or specific IgE level(s). Therefore, the inclusion criteria for Study MT-18, though less stringent that those of Study P001, were acceptable for basic comparison purposes.

In terms of the asthma inclusion criterion, Study P001's asthma population was better controlled as subjects in Study P001 had to have a FEV1 of at least 80% of predicted value at the Screening, Run-in, and Randomization Visits (following at least a 6-hour washout of short-acting beta2 agonists and 12-hour washout of long-acting beta2 agonists) [in

contrast, subjects in Study MT-18 had to have an FEV1 ≥ 70% of predicted value or according to local requirements while on their usual asthma medication]. An FEV1 of at least 80% ensures that asthmatic individuals had good lung function prior to enrollment. However, the asthma inclusion criteria for both studies limit generalizability of safety data to persons with severe or unstable asthma.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The IP provided in the study was the HDM SLIT tablet (see Table 3). The IP was manufactured and provided by the Applicant. There was no placebo treatment in this study.

The HDM SLIT tablet belongs to a class of AIT products characterized by their content of an unmodified natural allergen extract in a fast-dissolving freeze-dried formulation developed for sublingual administration. The HDM SLIT tablet contains allergen extract from the 2 HDM species *D. farinae* and *D. pteronyssinus* in a 1:1:1:1 potency ratio of *D. farinae* group 1 allergen, *D. farinae* group 2 allergen, *D. pteronyssinus* group 1 allergen, and *D. pteronyssinus* group 2 allergen. The dose of each HDM SLIT tablet is 12 SQ-HDM.

The proposed dose for adolescent use (12 SQ-HDM) is the same as the marketed dose in adults, which is in accordance with the general practice for AIT (Cox et al. 2011).

Table 3. Investigational Product (IP)

IP Name	HDM SLIT Tablet
Active ingredients	Allergen extract of *D. pteronyssinus* and *D. farinae*
Pharmaceutical form	Oral lyophilizate (SLIT tablet)
Excipients	Gelatin (fish source), mannitol, sodium hydroxide
Route of administration	Sublingual
Dose/strength	12 SQ-HDM

Source: BLA 125592/157/6, Study MT-18 CSR, Section 9.4.1, Table 2, p. 27.
Abbreviations: *D.=Dermatophagoides*, HDM=house dust mite, SQ=SQ is a method for standardization on biological potency, major allergen content and complexity of the allergen extract; SQ-HDM is the dose unit for the HDM SLIT tablet, SLIT=sublingual immunotherapy.

6.1.5 Directions for Use

The treatment started at Visit 2 (enrollment and first tablet administration). Prior to first IP intake, an oropharyngeal examination had to be performed. The first intake of IP had to be done at the clinic under medical supervision, with a subsequent observation period of at least 30 minutes. The IP had to be taken with dry fingers from the blister unit immediately after opening the blister and placed under the tongue, where it disperses. Swallowing had to be avoided for approximately 1 minute. Food and beverages should not have been taken for the following 5 minutes after intake of IP. The daily dose of IP was 1 HDM SLIT tablet, which should have preferably been taken in the morning. Treatment could be interrupted for up to 7 days due to any of the following reasons:

- In case of oral surgery including dental extraction, and shedding of a tooth, to allow healing of the oral cavity
- Inflammatory conditions in the oral cavity

- Upper airway viral infection in an asthmatic subject
- Other reasons if deemed necessary by the investigator

Interruptions were to be kept to a minimum. If IP was interrupted for more than 7 consecutive days, the subject should have been discontinued. The goal with this was to reduce the risk of confounding safety evaluation due to limited observation time.

6.1.6 Sites and Centers

A total of 28 sites [Czech Republic (8 sites), Slovakia (12 sites), Germany (8 sites)] were approved by ethics review boards and activated as study sites; however, only 5 of the 8 sites approved in Germany screened and enrolled subjects. Thus, the study was conducted at a total of 25 study sites that screened and enrolled subjects in 3 countries (number of sites is listed in parentheses): Czech Republic (8), Slovakia (12), and Germany (5).

6.1.7 Surveillance/Monitoring

The surveillance/ monitoring procedures for Study MT-18 are described in Table 4.

Table 4. Study MT-18: Surveillance and Monitoring Procedures

Procedure	Visit 1 Screening, Max. 12 Weeks Prior to Day 1	Visit 2 Treatment Day 1*	Telephone Call Treatment Day 8, +/- 1 day	Visit 3[1] Treatment Day 29, +3 days[4]	Telephone Call[2]* Follow-Up Post-Treatment After 5-7 days	Unscheduled Visit[3]
Informed consent/assent	X	--	--	--	--	--
Demography	X	--	--	--	--	--
Smoking habits	X	--	--	--	--	--
Medical history	X	--	--	--	--	--
Previous[5] and concomitant medication	X	X	X	X	X	X
Height and weight	X	X	--	--	--	--
Vital signs	X	X	--	X	--	(X)
FEV_1[6]	X	X	--	X	--	(X)
Physical examination	X	--	--	--	--	(X)
Oropharyngeal examination	--	X[7]	--	X	--	(X)
Assess symptoms of eosinophilic esophagitis	X	X	X	X	X	(X)
Urine pregnancy test, if applicable[8]	X	X	--	X	--	(X)
SPT[9]	X	(X)	--	--	--	--
Blood and urine sampling for safety analyses	X	--	--	--	--	(X)

Procedure	Visit 1 Screening, Max. 12 Weeks Prior to Day 1	Visit 2 Treatment Day 1*	Telephone Call Treatment Day 8, +/- 1 day	Visit 3[1] Treatment Day 29, +3 days[4]	Telephone Call[2]* Follow-Up Post-Treatment After 5-7 days	Unscheduled Visit[3]
Assess compliance with inclusion/exclusion criteria	X	X	--	--	--	--
Assess AEs since last visit/TC	X[10]	X[11]	X	X	X[12]	X
Provide the subject with a subject card	X	--	--	--	--	--
Provide the *Local and systemic allergic reaction emergency plan* and instruct	--	X	--	--	--	--
Dispense IP and instruct in the use of IP	--	X	(X)[13]	--	--	(X)[14]
Intake of IP at clinic	--	X[14]	--	--	--	
Provide and instruct in the use of the diary	--	X	(X)[15]	--	--	(X)[15]
Collect and evaluate diary	--	--	--	X	--	--
Collect IP, perform compliance check and drug accountability[16]	--	--	--	X	--	--

Source: BLA 125592/157/6, Study MT-18 CSR, Section 9.5.1, Table 6, p. 33.
Abbreviations: AE=adverse event, IP=investigational product
*Visit 2 Treatment=Enrolment & Administration of First Tablet
[1] If a subject discontinues prior to completing the 28-day treatment period, the assessments of V3 should be performed 5-7 days after last IP intake
[2] Post-study treatment with HDM SLIT-tablets must not be initiated before FU-TC has been performed
[3] Assessments at unscheduled visit(s) marked (X) are performed as applicable; Scheduling window is up to 3 days post treatment, Day 28+ (1 to 3) days

[4] Conducted on Day 29 to allow for diary completion for last day of treatment (Day 28)
[5] Previous medications to be assessed only at V1 and covering at least 1 year
[6] Measure forced expiratory volume in 1 second (FEV1) and calculate the % of predicted FEV1
[7] Oropharyngeal examinations will be done before IP administration at V2
[8] For female subjects of childbearing potential. Additional urine pregnancy tests should be performed during the study, at an unscheduled visit, if a menstrual period is missed
[9] If medication that could interfere with the skin prick test has not been washed out at visit 1, the skin prick test must be performed after the interfering medication has been washed out and before tablet administration
[10] Any AE occurring during the visit from the time the informed consent/assent was signed
[11] This includes AEs related to first IP dose: Staff must record time of onset for any event occurring or worsening 0-30 minutes post dosing
[12] If an AE was ongoing at the previous visit or if a new AE is identified at the telephone contact the subject could be asked to return to the study site or have an additional telephone contact for follow-up
[13] Re-instruct in use of IP, as applicable
[14] For subjects with severe oral inflammation (e.g., oral lichen planus, mouth ulcers or thrush), oral wounds or following oral surgery, including dental extraction, or following tooth loss, initiation of IP treatment should be postponed until the oral cavity has healed
[15] Re-instruct in use of the diary, as applicable
[16] Collect unused, partly used, and empty blister packages

Overall, AEs reported during the study were categorized as TEAEs or non-treatment emergent (non-TEAEs). The severity of AEs was assessed by the investigator using the following definitions:

- Mild: Transient symptoms, no interference with the subject's daily activities
- Moderate: Marked symptoms, moderate interference with the subject's daily activities
- Severe: Considerable interference with the subject's daily activities, unacceptable

Additionally, AE relationship to the IP was assessed by the investigators during AE reporting. The causal relationship between an AE and the IP was assessed by the investigator using the following definitions:

- Possible: A reasonable possibility of a causal relationship between the event and the IP
- Unlikely: The event is most likely had a different etiology than the IP

Adverse reactions, as reported in this review, are defined as treatment-emergent adverse events that are assessed as possibly related to treatment with the IP.

A side effect report card/diary was completed by subjects for approximately 28 days after first treatment; the report card/diary prompted subjects to record 'Yes' or 'No' on a checklist as to whether they experienced any of 15 pre-specified symptoms/signs after administration of SLIT. The 15 pre-specified solicited terms for both studies were: diarrhea, food tastes different, itching in the ear, itching of the mouth, mouth ulcer/sore in the mouth, nausea (feel like throwing up), stomach pain, swelling of the lips, swelling of the tongue, swelling of the uvula/back of the mouth, throat irritation/tickle, throat swelling, tongue pain, tongue ulcer/sore on the tongue, and vomiting. In Study MT-18, the report card/diary prompted subjects to record 'Yes' or 'No' as to whether they experienced any of the 15 pre-specified symptoms/signs of SLIT after taking study drug (no specific time limit for reporting was specified in Study MT-18).

The report card/diary served as a memory tool to help the subjects remember dates and details of the experienced symptoms, for subsequent discussion with the investigator at the next visit to the clinical site. The investigator was to discuss all symptoms/signs with the subject and based on the investigator's medical evaluation and discretion, AEs were reported on the electronic case report form (eCRF). The AE descriptions on the eCRF were subsequently coded to specific Preferred Terms (PTs) through the Applicant's standard AE coding procedure.

Solicited symptoms (Table 9) included all symptoms the investigators reported in the eCRF and the signs/symptoms subjects reported in the diary (whether or not they were reported in the eCRF by the investigators) under 1 subject-specific record per solicited term. The subset of the solicited symptoms that were not reported in the eCRF have a sign/symptom category (solicited term) that is based on the subject's own evaluation (study subjects were provided side effect report cards in which they recorded the occurrence of specific solicited adverse reactions daily for the first 28 days following treatment initiation with Odactra); this subset therefore includes some symptoms with unknown severity or outcome.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint in this study was occurrence of at least 1 TEAE.

Secondary endpoints in the study were:

- At least 1 solicited TEAE
- At least 1 IP-related AE
- At least 1 treatment-emergent SAE

Other endpoints in the study were:

- At least 1 treatment-emergent systemic allergic reaction including anaphylaxis (Sampson et al. 2006)
- At least 1 TEAE treated with adrenaline/epinephrine
- At least 1 treatment-emergent severe local swelling or edema of the mouth and/or throat
- A TEAE of EoE
- A TEAE leading to discontinuation
- Daily duration of recurrent TEAEs

6.1.9 Statistical Considerations & Statistical Analysis Plan

A sample size of 250 subjects for MT-18 was based on the total required safety database so that, at the time of submission of this sBLA, approximately 500 adolescent subjects will have been exposed to the HDM SLIT tablet (12 SQ-HOM dose) in clinical studies. This rationale was based on the ability to exclude a 1% or higher proportion of subjects experiencing an AE for rare events (e.g., severe systemic allergic reaction including anaphylaxis, or severe local swelling/edema of the mouth and/or throat), when the observed proportion was 0.2%.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The following analysis sets were defined in the protocol:

- Total Analysis Set: all subjects who entered the study including screening failures. The total population was used for listing reasons for screening failures and AEs before enrolment.
- Safety Analysis Set: all subjects who received at least one dose of IP. This analysis set was used for all safety analyses.

6.1.10.1.1 Demographics

The mean age of study subjects was 14 years with a range of 12−17 years. Sixty percent of the subjects were male and the majority of subjects were white (99.6%) and 2.4% were Hispanic or Latino. Overall, 44% of the subjects at baseline were sensitized to HDM alone, while the remaining subjects in the study were sensitized to at least one allergen in addition to HDM. The mean skin prick test wheal size was 8.1 mm for *Dermatophagoides pteronyssinus* and 7.3 mm for *Dermatophagoides farinae*. 43% of the subjects had asthma, and 29% of subjects reported the use of low/ medium dose of ICS with or without long-acting beta agonists. On average, subjects had a medical history of HDM-induced AR/C for 5.9 years and asthma for 6.7 years. The mean FEV1 (% predicted) was 96%.

Subject demographic and baseline characteristics are summarized in Table 5.

Table 5. Study MT-18: Demographic and Baseline Characteristics (Safety Analysis Set)

Characteristic	12 SQ-HDM (N=253)
Age (years)	--
Mean (SD)	14.1 (1.7)
Median	14.0
Min - Max	12 - 17
Sex, n (%)	--
Female	101 (39.9%)
Male	152 (60.1%)
Race, n (%)	--
Native Hawaiian or Other Pacific Islander	1 (0.4%)
White	252 (99.6%)
Ethnic origin, n (%)	--
Hispanic or Latino	6 (2.4%)
Not Hispanic or Latino	229 (90.5%)
Not Reported	18 (7.1%)
Country, n (%)	--
Czech Republic	87 (34.4%)
Germany	29 (11.5%)
Slovakia	137 (54.2%)

Source: BLA 125592/157/6, Study MT-18, Section 10.4, Table 15, p. 56.
Abbreviations: N=number of subjects in safety set, n=number of subjects with observations, SD=standard deviation, Country=country of the study site.

Reviewer Comment:
A total of 25 study sites in 3 countries randomized at least 1 participant (listed by number of sites and percentage of subjects randomized per country): Czech Republic (8), Slovakia (12), and Germany (5). The majority of subjects were male (60.1%), which is consistent with the greater prevalence of AR/C among males in childhood. Ninety-nine percent of the study subjects were Caucasian in this study (in comparison, demographics for the combined age group population in Study P001 in which Odactra was studied were 76.3% Caucasian, 10.5% African American, 5.7% multi-racial, 0.7% American Indian or Alaskan Native, and 6.7% Asian).

Incidence of AR/C in specific racial groups is not readily available in the published literature on this topic, but literature does suggest that AR/C occurs in persons of all races, with varied prevalence among different populations and cultures (possibly due to various factors including genetic differences, geographic factors, environmental differences, or other population-based factors) (Wegienka et al. 2013). Therefore, the cause for the racial demographic imbalance in this study is not clear although it may possibly be due to enrollment of subjects at study sites outside of the U.S. that may be less diverse than the U.S. in terms of ethnicity. While clinical presentation of AR/C is not known to differ among races, interpretation of any treatment differences with Odactra in the non-Caucasian

populations in Study P001 and Study MT-18 was limited by the small number of non-Caucasian subjects.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Key baseline disease characteristics of study subjects are summarized in Table 6.

In line with the inclusion criteria, all subjects reported allergy to HDM with symptoms of AR/C. In addition, 24 subjects (9.5%) had a medical history of atopic dermatitis, 9 subjects (3.6%) had food allergy, 108 subjects (42.7%) reported that they had allergic asthma to HDM, and 3 (1.2%) subjects had allergic asthma to grass pollen. 40 subjects (15.8%) reported a medical history other than allergy, asthma, or dermatitis. There were no apparent issues of medical concern.

Table 6. Study MT-18: Baseline Characteristics (Safety Analysis Set)

Characteristic	12 SQ-HDM (N=253)
FEV_1 (% predicted) [a]	--
Mean (SD)	96.10 (12.84)
Median	94.89
Min - Max	71.8 - 155.8
Baseline sensitisations, n (%) [b]	--
HDM only	112 (44.3%)
HDM and others	141 (55.7%)
Duration of HDM allergic rhinitis/rhinoconjunctivitis (years)[c]	--
Mean (SD)	5.9 (3.5)
Median	5.0
Min - Max	1 - 15
Asthma status, n (%)	--
No	144 (56.9%)
Yes	109 (43.1%)
Inhaled corticosteroids, n (%) [d]	--
No	180 (71.1%)
Yes	73 (28.9%)
Duration of asthma (years)[c]	--
n	109
Mean (SD)	6.7 (3.9)
Median	7.0
Min - Max	0 - 15
Smoking history, n (%)	--
Current	3 (1.2%)
Never	250 (98.8%)

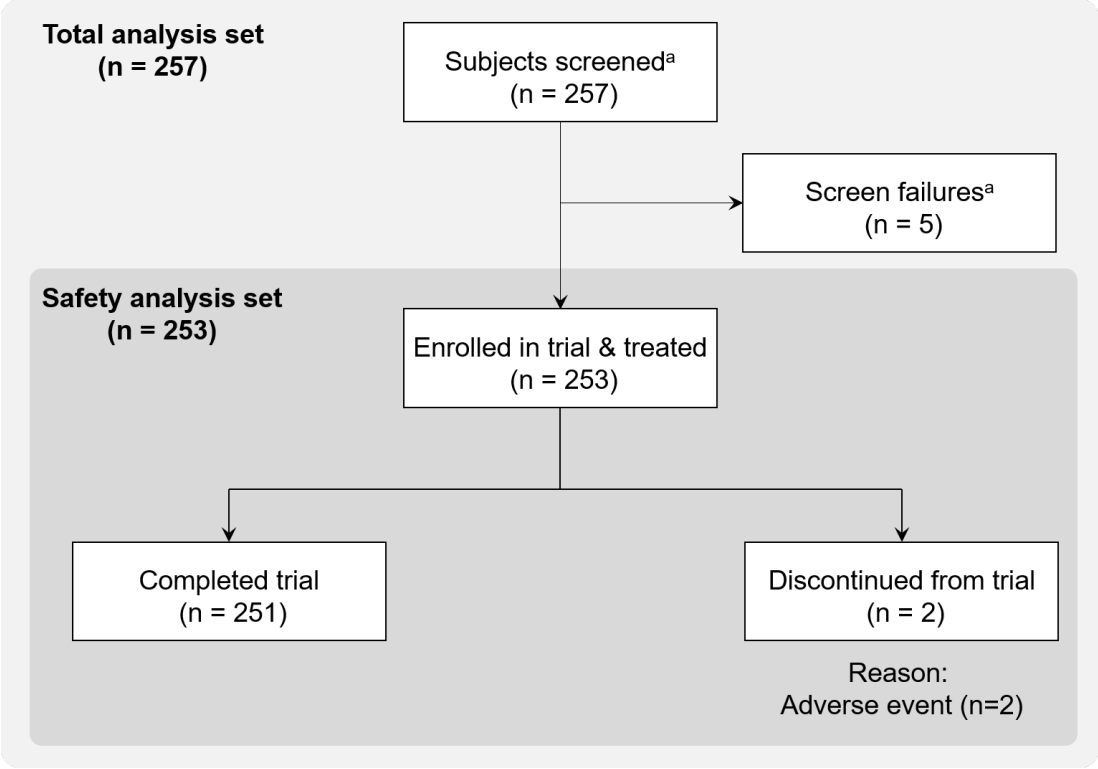
Source: BLA 125592/157/6, Study MT-18 CSR, Section 10.4.2, Table 16, p. 57.
Abbreviations: N=number of subjects in safety set, n=number of subjects with observations, SD=standard deviation, FEV_1=forced expiratory volume in 1 second, HDM=house dust mite.
[a] FEV_1 measurements are defined as last measurement before or on the date of first IP treatment.
[b] Baseline sensitisations are based on skin prick test.
[c] Duration of asthma and duration of HDM allergic rhinitis/rhinoconjunctivitis are based on medical history and calculated at date of first dose.
[d] Inhaled corticosteroid status is based on concomitant medication at screening.

In line with the inclusion criteria, almost all subjects in the safety set (with 2 exceptions) had positive SPTs (mean wheal diameter ≥3 mm) against both HDM species. 1 subject tested negative for *D. pteronyssinus*, and another tested negative for *D. farinae*. All subjects had positive SPT results for the positive control (histamine) and negative SPT results for the negative control (saline). The mean SPT wheal size for *D. pteronyssinus* was 8.1 mm and for *D. farinae* it was 7.3 mm.

> *Reviewer Comment:*
> *All treated subjects reported a mean duration of 6.7 years of HDM-induced AR/C (in Study P001, all treated subjects reported a mean duration of 18.6 years; of note Study P001 enrolled adults making a longer mean duration of asthma history reasonable). A similar percentage of subjects (55.7%) were polysensitized (HDM allergen and other allergens) compared to those (44.3%) that were mono-sensitized (HDM allergen only) (in Study P001, 24% were mono-sensitized to HDM).*
>
> *In terms of asthma, 43.1% of subjects reported current history of asthma with a median duration of 7 years (which was similar to the 31% of subjects who had asthma in Study P001). 28.9% of those with asthma reported use of ICS. Median FEV1 was reported as 95% predicted. 99% reported a negative smoking history.*

6.1.10.1.3 Subject Disposition
Subjects were recruited from October 5, 2020 to March 9, 2021. 257 subjects were screened, of which 5 were screen failures (1 of these was later re-screened). 253 subjects were allocated to treatment, and 251 (99.2%) subjects completed Study MT-18. Subject disposition and the data sets used for the analyses are summarized in Figure 2.

Figure 2. Subject Disposition in Study MT-18



Source: BLA 125592/157/6, Study MT-18 CSR, Section 10.1, Figure 2, p. 53.
Abbreviations: n=number of subjects, Total analysis set=all subjects including screen failures, Safety analysis set=all subjects who received at least one dose of IP
[a] 1 subject was re-screened after being a screen failure at the initial screening. This subject is counted as 1 subject screened, 1 subject enrolled and 1 screen failure.

6.1.11 Efficacy Analyses:

Please see Section 2.4 Previous Human Experience of this clinical review memorandum for a summary of the Study P001 efficacy data in adolescents 12 through 17 years of age. For a more detailed review of these data and analyses, please see Clinical Review Memorandum for BLA STN 125592/0.

6.1.12 Safety Analyses

6.1.12.1 Methods

Study MT-18 was a single-arm, open label study conducted in Europe, evaluating safety and tolerability for the first 28 days of Odactra use (daily) in adolescents 12 through 17 years of age with HDM-induced AR/C and with or without asthma (60% male, 43% with asthma, 56% polysensitized to other allergens in addition to HDM; 99.6% White, 0.4% Native Hawaiian or Other Pacific Islander). All safety analyses were performed on subjects who were included in the safety analysis set (N=253). AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. The median treatment duration was 28 days (range 11 to 32 days).

6.1.12.2 Overview of Adverse Events

In total, 223 (88%) subjects experienced 1940 TEAEs during the study. Of these, 88.1% of subjects reported at least 1 TEAE (primary safety endpoint), 85.4% of subjects reported at least 1 solicited TEAE (secondary safety endpoint), and 86.2% of subjects reported at least 1 IP-related AE (secondary safety endpoint).

The majority of the TEAEs reported were assessed as ‘possibly related to IP’ and were mild or moderate in severity. One severe TEAE was reported. This was an event of a non-serious allergic conjunctivitis, which was assessed as ‘unlikely related to IP’, and the subject recovered with no changes to IP dose. The event did not lead to study discontinuation.

In terms of the most frequently reported TEAEs (i.e., reported by ≥2% of the subjects), the most frequently reported System Organ Class (SOC) was 'Gastrointestinal disorders', where 81% of subjects experienced 1149 events. Across all SOCs, the 3 most frequent TEAEs were 'Oral pruritus' (421 events), 'Throat irritation' (323 events), and 'Ear pruritus' (270 events); these were all solicited AEs, reported by 67%, 52%, and 40% of subjects, respectively. When the solicited TEAEs are excluded, the 3 most frequently reported TEAEs were 'Pharyngeal paresthesia' (7% of study subjects), 'Oral pain' (4%), and 'Tongue eruption' (2%).

With respect to time of onset after first IP intake, 76% of the most frequent TEAEs occurring on the day of first IP intake had a median onset within 30 minutes, 12% had a median onset between 30-60 minutes, and 12% had a median onset between 60-70 minutes. With respect to duration after IP intake, the most frequent TEAEs (in ≥2% of subjects) were typically short, with median durations lasting no longer than 2 days and mean durations lasting no longer than 9 days after IP intake.

There were no reports of treatment-emergent SAEs in Study MT-18.

In terms of AESIs, evaluation of other endpoints showed that 1 subject reported 1 possible treatment-emergent systemic allergic reaction. There were no reports of events treated with epinephrine, events of severe local swelling/ edema of the mouth and/or throat, or events of EoE.

Most subjects (88%) recovered by the end of the study without sequelae and in most cases, TEAEs did not lead to IP interruption or withdrawal. TEAEs lead to IP withdrawal and discontinuation from the study in 2 subjects (see Section 6.1.12.7 below).

Non-TEAEs were defined as AEs that were experienced prior to first IP intake and are usually not considered 'related to IP'. However, some of the non-TEAEs continued after treatment initiation and were reported as 'possibly related to IP' by the investigator. Any non-TEAEs that were reported as 'possibly related to IP' are included in Table 7.
A total of 26 non-TEAEs were reported, of which 14 were assessed as 'possibly related to IP'. Of these 14 non-TEAEs, 12 continued after treatment initiation. Of the 26 non-TEAEs, 15 were mild in intensity, and 11 were moderate in intensity. None were severe in intensity. None were serious.

An overview of all IP-related AEs (i.e., adverse reactions) is provided below in Table 7. A total of 1863 AEs were assessed as IP-related by the investigators. All IP-related TEAEs were mild (reported by 86% of subjects) or moderate (11% subjects) in severity. None were serious. Most subjects (86%) recovered without sequelae by the end of the study and in most cases, IP-related AEs did not lead to IP interruption or withdrawal. IP was interrupted due to AEs in 1 subject. The 2 subjects that discontinued from the study also withdrew from IP due to IP-related AEs.

Table 7. Study MT-18: Summary of IP-related AEs (Safety Analysis Set)

Category	12 SQ-HDM (N=253) n	12 SQ-HDM (N=253) %n	12 SQ-HDM (N=253) e
All events	218	86.2%	1863
Severity	--	--	--
Mild	218	86.2%	1779
Moderate	27	10.7%	84
Severe	0	0	0
Severity by worst case [a]	--	--	--
Mild	191	75.5%	0
Moderate	27	10.7%	0
Severe	0	0	0
Seriousness	--	--	--
Not serious	218	86.2%	1863
Serious	0	0	0

Category	12 SQ-HDM (N=253) n	12 SQ-HDM (N=253) %n	12 SQ-HDM (N=253) e
Outcome	--	--	--
Recovered/resolved	218	86.2%	1855
Recovered/resolved with sequelae	2	0.8%	2
Not recovered/not resolved	5	2.0%	6
Fatal	0	0	0
Unknown	0	0	0
Relationship to IP	--	--	--
Unlikely related	0	0	0
Possibly related	218	86.2%	1863
Changes to IP due to AE	--	--	--
Dose not changed	218	86.2%	1857
Drug interrupted	1	0.4%	2
Drug withdrawn	2	0.8%	3
Not applicable	1	0.4%	1
Event leading to discontinuation	--	--	--
No	218	86.2%	1860
Yes	2	0.8%	3

Source: BLA 125592/157/6, Study MT-18 CSR, Section 12.1.2, Table 20, p. 63.
Abbreviations: AE=adverse event, IP=investigational product, N=number of subjects in safety set, n=Number of subjects with events, %n=percent subjects with events of safety set, e=number of events.
[a] For 'Severity by worst-case' each subject is counted only once and by worst severity amongst their reported events. e (events) is not applicable for 'By worst-case'. IP-related adverse events are those reported as 'possibly related' by the investigator, regardless of the event start relative to treatment start.

Table 8 provides a summary of overall post-hoc safety results in Study MT-18 with regard to unsolicited TEAEs and solicited symptoms.

Overall, 224 subjects (88.5%) reported at least 1 unsolicited TEAE or solicited symptom. 218 subjects (86.2%) reported at least 1 IP-related unsolicited TEAE or solicited symptom.

Two subjects reported symptoms leading to study discontinuation. One subject was assessed as having had a possible treatment-emergent systemic allergic reaction. There were no reports of TEAEs treated with epinephrine or TEAEs of EoE. No treatment-emergent severe local swelling/edema of the mouth and/or throat were reported.

Table 8. Study MT-18: Summary of Selected Events/ Symptoms (Safety Analysis Set)

Category	12 SQ-HDM (N=253) n	12 SQ-HDM (N=253) %
At least 1 unsolicited TEAE or solicited symptom	224	88.5%
At least 1 solicited symptom	221	87.4%
At least 1 unsolicited IP-related TEAE or IP-related solicited symptom	218	86.2%
At least 1 serious TEAE	0	0.0%
At least 1 treatment-emergent systemic allergic reaction including anaphylaxis [a]	1	0.4%
At least 1 TEAE treated with epinephrine	0	0.0%
At least 1 treatment-emergent severe local edema of the mouth and/or throat	0	0.0%
A TEAE of eosinophilic esophagitis	0	0.0%
An unsolicited TEAE or solicited symptom leading to discontinuation	2	0.8%

Source: BLA 125592/157/6, Study MT-18 CSR, Section 12.3.9, Table 33.
Abbreviations: N=number of subjects in safety set, n=number of subjects with event, %=percent of subjects with events of safety set.
An AE is considered a treatment-emergent adverse event (TEAE) if AE start date is on or after the time of first IP administration and no later than 7 days after last IP administration or if it was assessed as IP-related by the investigator.
[a] 'Systemic allergic reaction including anaphylaxis' is based on a standardised MedDRA query (SMQ) and a medical evaluation. The SMQ identified 2 subjects with 2 events. Out of these, 1 subject had 1 adverse event which was medically evaluated as a possible case of systemic allergic reaction.
'Severe local swelling or edema of the mouth and/or throat' is based on a pre-specified list of events of special interest.

Solicited Adverse Events

Overall, 87.4% of the subjects in the study experienced a solicited symptom. 57 subjects (22.5%) reported 1 or more solicited symptoms in the diary that were not reported by the investigators in the eCRF, and therefore these solicited symptoms did not have a reported severity. These results are displayed in Table 9.

Of the solicited symptoms reported by the investigators in the eCRF (see Section 6.1.7 for a description on ‘solicited symptoms’), most were assessed to be mild in severity. The solicited symptoms reported by the highest proportion of subjects were 'itching of the mouth' (68.4%), 'throat irritation/tickle' (62.1%) and ‘itching in the ear’ (40.7%). The most common solicited symptoms reported in the first 28 days following treatment initiation in ≥10% of adolescent subjects treated with Odactra were: itching in 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 of the uvula/back of the mouth (21.3%), swelling of the lips (21.3%), tongue pain (19.0%), nausea (17.4%), stomach pain (16.6%), swelling of the tongue (15.4%), throat swelling (14.6%), and diarrhea (10.3%).

The majority of subjects experiencing a solicited symptom (220 out of 221) recovered by the end of the study without sequalae. Two subjects experienced 1 solicited symptom each that lead to IP withdrawal and treatment discontinuation (see Section 6.1.12.7 below). Both subjects recovered from the symptom upon treatment discontinuation.

Table 9. Study MT-18: All Solicited* Symptoms by SOC and Solicited Term (Safety Analysis Set)

SOC Solicited Symptom (Any Intensity‡)	**12 SQ-HDM (N=253) n**	**12 SQ-HDM (N=253) %**
All signs/symptoms	221	87.4%
Ear and labyrinth disorders	--	--
Itching in the ear	103	40.7%
Gastrointestinal disorders	**--**	**--**
Itching of the mouth	173	68.4%
Mouth ulcer/sore in the mouth	65	25.7%
Swelling in the back of the mouth†	54	21.3%
Swelling of the lips	54	21.3%
Swelling of the tongue	39	15.4%
Tongue pain	48	19.0%
Tongue ulcer/sore on the tongue	57	22.5%
Nausea (feel like throwing up)	44	17.4%
Stomach pain	42	16.6%
Diarrhea	26	10.3%
Vomiting	7	2.8%
Nervous system disorders	--	--
Food tasting different	21	8.3%
Respiratory, thoracic, and mediastinal disorders	--	--
Throat irritation/tickle	157	62.1%
Throat swelling	37	14.6%

Source: Adapted from BLA 125592/157/6: Study MT-18 CSR, Section 12.3.6, Table 31, p. 81; ISS, Table 2.1.2.6-1, p. 79.
Abbreviations: SOC=System Organ Class, N=number of subjects in safety set, n=Number of subjects with events, %n=percent subjects with events of safety set.
A solicited symptom is defined as a symptom recorded in the subject diary or 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.
*Solicited adverse reactions (modified from World Allergy Organization [WAO] list of local side effects of SLIT) were those reported by subjects within the first 28 days after treatment initiation.
†The percentage of subjects reported for the patient-friendly term of "swelling of the uvula/back of the mouth" includes subjects with an enlarged uvula, edema uvula, palatal swelling/edema, and/or mouth swelling/edema (which can be anywhere in the mouth, not specifically back of the mouth).
‡No severe solicited adverse reactions were reported.

217 subjects (85.8%) reported a solicited symptom that was reported in the eCRF to be possibly IP-related. In terms of onset of IP-related solicited symptoms, the IP-related solicited symptoms reported by the highest proportion of subjects ('itching of the mouth', 'throat irritation/tickle' and 'itching in the ear') all had a median onset of 5 minutes (and an average onset of less than 15 minutes). These symptoms typically occurred in the first few days of treatment initiation, with all 3 symptoms having a median onset of 1 day after first IP intake (and an average onset of approximately 2-3 days). The duration of IP-related solicited symptoms was calculated from the first occurrence to the last occurrence of that symptom, even if there were days in between when the symptom did not occur. The symptoms with the longest median duration (i.e., the time between first and last occurrence of that symptom) were 'itching of the mouth' (21 days), 'itching in the

ear' (18 days) 'throat irritation/tickle' (16 days). These were also the symptoms reported by the highest proportion of subjects.

> *Reviewer Comment:*
> *Adverse reactions were solicited through a Side Effect Report Card during the first 28 days of treatment for this study, Study MT-18 and Study P001 (the pivotal efficacy and supportive safety study in adolescents). While solicited/ active reporting of adverse reactions can lead to increased rates of adverse reactions compared to those obtained via unsolicited/ passive reporting, solicitation of adverse events was conducted to more completely characterize the safety profile of this IP to inform patient use. The increased rates reported here, while high, are not unexpected given the route of administration and allergic properties of the IP.*

Solicited TEAEs (Table 10) were defined as TEAEs with a PT that matched the pre-defined list of solicited terms and which were reported by the investigator in the eCRF. Table 10 lists only the solicited signs/symptoms that were reported by the investigators in the eCRF (solicited TEAEs). Overall, 85% of subjects in the study experienced treatment-emergent solicited AEs (1796 events). The most frequent solicited PTs were 'Oral pruritus', 'Throat irritation', and 'Ear pruritus'. Most of the solicited AEs were mild (1721 events) and some were moderate (75 events) in severity. There were no reports of severe or serious solicited AEs. The majority of all solicited AEs were assessed to be possibly related to IP (1745 events), and most subjects recovered from these TEAEs apart from four subjects. In two subjects, IP was interrupted, and in 2 subjects IP was withdrawn. Two subjects discontinued due to solicited AEs (see Section 6.1.12.7 below).

Table 10. Study MT-18: Investigator/ eCRF-Reported Solicited TEAEs by SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term	**12 SQ-HDM (N=253) n**	**12 SQ-HDM (N=253) %n**	**12 SQ-HDM (N=253) e**
All events	216	85.4%	1796
Ear and labyrinth disorders	--	--	--
All	101	39.9%	270
Ear pruritus	101	39.9%	270
Gastrointestinal disorders	--	--	--
All	204	80.6%	1119
Abdominal pain	3	1.2%	3
Abdominal pain upper	40	15.8%	77
Diarrhea	24	9.5%	30
Enlarged uvula	14	5.5%	38
Glossodynia	41	16.2%	87
Lip edema	11	4.3%	15
Lip swelling	40	15.8%	89
Mouth swelling	14	5.5%	32
Mouth ulceration	38	15.0%	68
Nausea	40	15.8%	83
Mouth edema	21	8.3%	35
Oral pruritus	169	66.8%	421
Swollen tongue	29	11.5%	51

System Organ Class Preferred Term	12 SQ-HDM (N=253) n	12 SQ-HDM (N=253) %n	12 SQ-HDM (N=253) e
Tongue edema	2	0.8%	2
Tongue ulceration	42	16.6%	79
Vomiting	6	2.4%	9
Nervous system disorders	--	--	--
All	16	6.3%	24
Dysgeusia	16	6.3%	24
Respiratory, Thoracic, and Mediastinal disorders	--	--	--
All	139	54.9%	383
Pharyngeal edema	1	0.4%	1
Pharyngeal swelling	33	13.0%	59
Throat irritation	132	52.2%	323

Source: BLA 125592/157/6, Study MT-18 CSR, Section 12.1.5, Table 23, p. 68.
Abbreviations: N=number of subjects in safety set, n=Number of subjects with events, %n=percent subjects with events of safety set, e=number of events.
An adverse event (AE) is considered treatment-emergent if AE start date is on or after the time of first IP administration and no later than 7 days after last IP administration.
A solicited AE is defined as an adverse event coded to one of 24 pre-specified preferred terms and starting no later than 28 days after first treatment and present after first treatment.

Reviewer Comment:
Table 10 (Solicited TEAEs reported in the eCRF/ by the Investigator) is shown here as severity was graded only by the Investigator and because misinterpretation of certain solicited terms by the subjects may have resulted in under-reporting or over-reporting [e.g., some subjects reported ulceration events with durations as short as 3 minutes; this points to a misinterpretation of the solicited terms 'sore in the mouth' (PT: mouth ulceration) and 'sore on the tongue' (PT: tongue ulceration), which may have led to over-reporting of 'ulceration' in the diaries due to the ambiguity surrounding the term 'sore' (pain vs ulcer) and to under-reporting of 'pain' as a symptom.]

Unsolicited TEAEs

In total, 61 subjects (24.1%) reported 108 unsolicited TEAEs during the study. Most subjects who reported an unsolicited TEAE (59 out of 61) recovered by the end of the study without sequalae. Most of the unsolicited TEAEs were mild in severity and 1 was severe: an event of non-serious allergic conjunctivitis assessed as unlikely related to IP. The subject recovered with no changes to IP dose and continued in the study.

The 3 most frequently reported unsolicited TEAEs (reported by ≥2% of the subjects) were 'Oral pain' (4.0%), 'Oral pruritus' (3.2%) and 'Rhinitis' (2.4%). The most frequently reported SOC was 'Gastrointestinal disorders', with 6.7% of subjects experiencing 27 events. The median onset for 'Oral pruritus' and 'Throat irritation' were 8.5 and 5 minutes after the first IP intake, respectively.

No unsolicited treatment-emergent SAEs were reported.

Unsolicited IP-related TEAEs (Unsolicited Adverse Reactions)
Overall, 40 subjects (15.8%) reported 63 unsolicited TEAEs that were assessed as possibly IP-related (58% of all unsolicited TEAEs). These events were mild (14.2% of subjects) or moderate (1.6% of subjects), and none were severe. None of the events were serious. The majority of subjects who experienced an unsolicited IP-related TEAE recovered by the end of the study without sequalae.

One subject reported an unsolicited TEAE of rhinorrhea of mild severity as well as a solicited symptom of abdominal pain of moderate severity leading to IP withdrawal and treatment discontinuation (see below, Section 6.1.12.7). The TEAE was assessed as possibly IP-related. The subject recovered from the event upon treatment discontinuation.

The most frequent unsolicited IP-related AEs (unsolicited adverse reactions) reported over the duration of Study MT-18 in ≥1% of Subjects 12 through 17 Years of Age are shown in Table 11. All of the frequently reported unsolicited IP-related TEAEs were local reactions and belonged to the SOC 'Gastrointestinal disorders' (5.5% of the subjects). The most frequent PTs were 'Oral pain' (3.2%) and 'Oral pruritus' (2.8%).

Table 11. Study MT-18: Most Frequent Unsolicited IP-related TEAEs (≥1% in 12 SQ-HDM group) Occurring During the Entire Study after Initiation of Treatment by SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term	**12 SQ-HDM (N=253) n**	**12 SQ-HDM (N=253) %**	**12 SQ-HDM (N=253) e**
Ear and labyrinth disorders	--	--	--
Ear pruritus	3	1.2%	3
Gastrointestinal disorders	--	--	--
Mouth ulceration	3	1.2%	3
Oral pain	8	3.2%	17
Oral pruritus	7	2.8%	7
Respiratory, thoracic, and mediastinal disorders	--	--	--
Throat irritation	4	1.6%	4

Source: BLA 125592/157/12, Response to FDA Labeling IR#3, Table 12, p. 26.
Abbreviations: N=number of subjects in safety set, n=Number of subjects with events, %n=percent subjects with events of safety set, e=number of events
An adverse event (AE) is considered treatment-emergent if AE start date is on or after the time of first IP administration and no later than 7 days after last IP administration. Solicited events that begin during the first 28 days of treatment and continue beyond the 28 days are also counted as unsolicited events.
System organ class and preferred term coded in MedDRA 24.0

Recurrent TEAEs
Recurrent TEAEs are events that are experienced after each SLIT-tablet intake on consecutive days. Some subjects had more than 1 recurrent event of the same PT, these were counted as separate events. In total, 32 different PTs of recurrent TEAEs were reported.

The duration of recurrent TEAEs ranged between 2 and 154 days. Most recurrent TEAEs had a median duration of up to and including 5 days (25 out of 32). The remaining 7 recurrent TEAEs had a median duration between 6 and 19 days. The TEAE

that was recurring for the longest was 'Rhinitis'. The duration of recurrent TEAEs ranged between 1 to 1320 minutes (22 hours) each day. Most recurrent TEAEs had a median daily duration of up to and including 30 minutes (29 out of 32). The remaining recurrent TEAEs had a median daily duration of 45 and 60 minutes (2 out of 32), except for 1 event of 'Rhinorrhea', which lasted for 5 hours.

Asthma-related Events
No asthma related TEAEs were reported in this study.

Subjects with Asthma

Reviewer Comment:
Safety analyses in the subgroup of subjects who had a medical history of asthma at screening were not pre-specified and, therefore, these analyses were not submitted to the sBLA by the Applicant. The data displayed in Table 12 are based on internal analyses.

Table 12. Study MT-18: Summary of Adverse Events in Adolescent Subjects with Asthma at Screening Compared to Adolescent Subjects without Asthma at Screening (Safety Analysis Set)

Category	**Subjects with Asthma** (N=109) n (%)	**Subjects with Asthma** (E= 877) e (%)	**Subjects without Asthma** (N= 144) n (%)	**Subjects without Asthma** (E= 1063) e (%)
At least 1 TEAE	97 (88.9)	877 (100)	126 (87.5)	1063 (100)
TEAE Resulting in IP Dose Modification	--	--	--	--
Not modified	94	872	125	1061
Interrupted	1	2	1	2
Discontinued	2	3	0	0
TEAE Requiring Medication	23 (21.1)	77 (8.8)	30 (20.8)	65 (6.1)
At least 1 Solicited TEAE	95 (87.1)	830 (94.6)	121 (84.0)	966 (90.9)
At least 1 IP-related AE	95 (87.1)	845 (96.4)	123 (85.4)	1018 (95.8)
At least 1 Treatment-Emergent SAE**	0	0	0	0

Source: FDA-generated table using SAS version 9.4.
Abbreviations: N= number of subjects, %N= percent of subjects out of the total number of subjects, E= total number of events, e= number of adverse events, AE= adverse event, TEAE= treatment-emergent adverse event, IP= investigational product, SAE= serious adverse event.

Reviewer Comment:
Internal analyses comparing safety data in the subjects with asthma at screening to subjects without asthma at screening suggest that the safety analyses with regard to the primary safety endpoint (at least 1 TEAE), secondary safety endpoints (at least 1 solicited TEAE, at least 1 IP-related AE, at least 1 treatment-emergent SAE), and TEAEs requiring treatment with medications were comparable between the two subgroups. There were no SAEs reported in this study.

Of the 2 subjects in whom dosing of the IP was interrupted due to a TEAE, 1 had a medical history of asthma and the other did not have a medical history of asthma. Of the 2 subjects who discontinued the study, both had a history of asthma, however, the TEAEs to which the discontinuations were due (1 subject discontinued due to abdominal pain and rhinorrhea and the other subject discontinued due to mouth ulceration) are not lower respiratory tract in nature, and therefore do not suggest association with asthma.

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

No events of SAEs were reported in the study.

6.1.12.5 Adverse Events of Special Interest (AESIs)

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

Systemic allergic reactions including anaphylaxis

*Method*s

- During AE reporting, investigators were requested to answer "yes" or "no" to the question "Was this adverse event a systemic allergic reaction/anaphylaxis?". None of the investigators selected "yes" to this question.
- In addition, the standardized MedDRA query (SMQ) 'Anaphylactic reaction' was used to identify potential systemic allergic reactions among all AEs reported. The method was based on a 2-step algorithm identifying potential systemic allergic reactions as defined by the SMQ.
    - First, a narrow term search was conducted using the PTs that indicate anaphylaxis (category A).
        - No events were captured by the SMQ 'Anaphylactic reaction' narrow terms.
    - Secondly, a broad term search was conducted using PTs that indicate respiratory symptoms including swelling of the mouth/throat (category B), skin-related symptoms and edema (category C), and cardiovascular symptoms (category D). Co-occurring events of more than 1 category (B, C or D) (i.e., more than one symptom from different categories are reported with the same start date) could indicate a potential systemic allergic reaction.

Results

Nine subjects (29 events) were captured by the SMQ 'Anaphylactic reaction' broad terms. Most of these events identified from the search revealed: local site (or near proximity) reactions to IP administration (e.g., 'Lip swelling', 'Swollen tongue', 'Edema mouth') and respiratory reactions ('Cough', 'Pharyngeal swelling'). One skin reaction event of 'Urticaria' was captured. All were mild (20 events) or moderate (9 events) in severity, all were non-serious, and none led to IP discontinuation.

- Based on medical evaluation, of the 9 subjects who were captured by the SMQ 'Anaphylactic reaction' broad term search:
    - 8 subjects experienced only local AEs evaluated not to indicate a potential systemic allergic reaction
    - 1 subject experienced mild urticaria for 15 minutes and mild swelling in the back of the mouth for 5 minutes on Day 3 of treatment. Both events resolved spontaneously without the use of any rescue medication, and IP treatment was continued. As the localization (i.e., local vs. systemic) of the event of urticaria was unknown, it could not be excluded that the subject experienced a systemic allergic reaction, and medical evaluation identified this as a possible systemic allergic reaction.
- As part of the medical evaluation, the 9 subjects that were captured by the SMQ 'Anaphylactic reaction' broad term search were also assessed based on the Sampson criteria (Sampson et al. 2006), and none were identified to be anaphylaxis.

TEAEs treated with epinephrine
No treatment-emergent adverse events requiring treatment with epinephrine were reported in Study MT-18.

Treatment-emergent severe local swelling or edema of the mouth and/or throat
No events of severe local swelling/ edema of the mouth and/or throat were reported in Study MT-18.

Eosinophilic esophagitis (EoE)
No events of EoE were reported in Study MT-18.

Reviewer Comment:
This reviewer agrees with the assessment of 'possible' systemic allergic reaction (as opposed to systemic allergic reaction) based on the details given that the symptoms resolved spontaneously and that the location of the urticaria was not noted (i.e., local/ proximal to the site of administration or distal to the site).

While no cases of EoE occurred in Study MT-18, this is likely due to the short duration of Study MT-18 (28 days) as duration of repeated exposure to the inciting agent(s) that lead to EoE are generally longer. One case in an adolescent subject on Day 204 taking Odactra confirmed by biopsy was considered to be related to IP intake in Study P001, a 52-week study which evaluated efficacy and safety of Odactra in adolescents. The occurrence of EoE was not common in Study P001. It should be noted, however, that the study did not actively solicit for cases of EoE. Therefore, cases may have been underreported. In addition, since the discontinuation rate was high in Study P001 (active treatment arm: 179/741 (24.2%) versus placebo treatment arm: 128/741 (17.3%), a substantial proportion of subjects did not complete 52 weeks of therapy. For this reason, the low number of cases may not accurately reflect the true incidence of EoE in persons who take Odactra daily for 1 year or longer.

6.1.12.6 Clinical Test Results

Not applicable as laboratory testing was only conducted prior to enrollment and was not conducted post-screening.

6.1.12.7 Dropouts and/or Discontinuations

Two subjects discontinued IP due to IP-related solicited TEAEs [rate (%n) = 0.8%]:

- One Caucasian female subject 12 years of age with medical history of allergic rhinitis, atopic dermatitis, allergic asthma, and food allergy experienced moderate 'Abdominal pain' on Day 12 of IP treatment [rate (%n) = 0.4%], which was recurrent over 5 days. On these 5 days, the subject also experienced mild, non-serious 'Rhinorrhea' [rate (%n) = 0.4%]. Study drug was discontinued due to the events of stomach pain and runny nose. The subject spontaneously recovered after stopping IP intake.
- One Caucasian male subject 15 years of age with medical history of allergic asthma and rhinoconjunctivitis experienced a moderate, non-serious 'Mouth ulceration' on Day 10 of IP treatment [rate (%n) = 0.4%], which was recurrent for 2 days. Study drug was discontinued due to the event of mouth ulcer/sore in the mouth. The subject spontaneously recovered after stopping IP intake.

  Reviewer Comment:
  Most adverse events for Odactra occur during the first month of IP intake/ administration. Overall, the IP discontinuation/ study dropout rate (0.8%) in this 28-day study is low.

6.1.13 Study Summary and Conclusions

Summary of Results (Safety) for Study MT-18:

Results related to primary safety endpoint:

- 88% of subjects experienced at least 1 TEAE.

Results related to secondary safety endpoints:

- 85% of subjects experienced at least 1 solicited TEAE.
- 86% of subjects experienced at least 1 IP-related AE.
- There were no treatment-emergent SAEs.

Results related to other safety endpoints:

- There were no investigator reports of systemic allergic reaction.
- There were no reports of systemic allergic reaction as defined by the Sampson criteria.
- There was 1 possible systemic allergic reaction identified through medical evaluation of co- occurring events using the SMQ 'Anaphylactic reaction', broad term algorithm: 1 subject experienced 2 simultaneous events (mild urticaria and mild swelling in the back of the mouth that resolved spontaneously without use of rescue treatment).
- There were no cases of adrenaline/epinephrine use.
- There were no cases of severe local swelling or edema of the mouth and/or throat.
- There were no cases of EoE.
- 2 subjects discontinued treatment due to IP-related TEAEs. 1 subject experienced moderate abdominal pain together with a mild rhinorrhea, and 1 subject had a moderate mouth ulcer. Both subjects recovered after stopping IP treatment.
- The median daily duration of recurrent TEAEs was in most cases up to and including 30 minutes.

Main results related to solicited symptoms:

- 87.4% of subjects reported at least 1 solicited symptom.

- 85.8% of the subjects reported at least 1 IP-related solicited symptom.
- There were no severe IP-related solicited symptoms.

Main results related to unsolicited TEAEs:
- 24.1% of subjects reported at least 1 unsolicited TEAE.
- 15.8% of subjects reported at least 1 IP-related unsolicited TEAE.
- There were no severe IP-related unsolicited TEAEs.

Other safety results:
- There were no SAEs.
- The solicited symptoms reported by the highest proportion of subjects were 'itching of the mouth' (68.4%), 'throat irritation/tickle' (62.1%) and ‘itching in the ear’ (40.7%).
- The IP-related solicited symptoms reported by the highest proportion of subjects (‘itching of the mouth’, ‘throat irritation/tickle’ and ‘itching in the ear’) all had a median onset of 5 minutes after first IP intake.
- The solicited symptoms with the longest median duration (=time between first and last occurrence of that symptom) were ‘itching of the mouth’ (21 days), ‘itching in the ear’ (18 days) ‘throat irritation/tickle’ (16 days). These were also the solicited symptoms reported by the highest proportion of subjects.
- 2 subjects discontinued treatment due to IP-related solicited symptoms or unsolicited TEAEs. 1 subject experienced moderate stomach pain (PT: abdominal pain upper) together with a mild runny nose (PT: rhinorrhea), and 1 subject experienced a moderate sore in the mouth (PT: mouth ulceration). Both subjects recovered from the events/symptoms after treatment discontinuation.
- Of all unsolicited TEAEs that were reported (108 events), 91.6% were mild (99 events), 7.4% were moderate (8 events) and 0.9% were severe (1 event).
- There was 1 severe unsolicited TEAE, which was assessed as unlikely related to IP. The subject recovered with no changes to IP dose.
- 58.3% of the unsolicited TEAEs were assessed as possibly IP-related (63 out of 108 events). Of the IP-related events 93.7% (59 out of 63 events) were assessed as mild and 6.3% (4 out of 63 events) as moderate.
- The most frequently reported unsolicited IP-related TEAEs (reported by ≥2% of subjects) were ‘Oral pain’ (3.2%) and ‘Oral pruritus’ (2.8%).
- 85.8% of subjects reported at least 1 solicited symptom that was assessed as mild, and 10.3% reported at least 1 symptom that was assessed as moderate.

<u>Conclusion: Study MT-18</u>
Prior to completion of MT-18, the safety database included 265 adolescent subjects from different studies with no observations of severe systemic allergic reactions (including anaphylaxis), or severe local swelling/edema of the mouth and/or throat.

Study MT-18 was designed to obtain additional safety data (12 SQ-HDM dose) in adolescents (12 through 17 years of age) with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma to supplement the existing safety database in the age group (12 through 17 years of age). A total of 253 subjects were enrolled to receive treatment with the HDM SLIT-tablet (12 SQ-HDM). The study was conducted according to the study protocol with no deviations impacting the study outcome. The objective of Study MT-18 was to obtain a 1-sided 95% upper confidence limit below 1% for these events in order to exclude the chance of ≥1% of subjects experiencing them. When the safety data from Study MT-18 are added to the overall safety database, this criterion is met. The most common AEs in the study were local allergic reactions related to route of IP

administration, as commonly seen in treatment with other SLIT products. These local AEs were generally mild and lasted no longer than 1-2 hours after IP intake. The proportion of subjects experiencing any IP-related AE was 86% (obtained through both solicited and unsolicited reporting of adverse events). Overall, the HDM SLIT tablet was well tolerated and there were no new or unexpected safety findings observed in this study.

In conclusion, the data from Study MT-18 support the safety of Odactra (acceptable safety and tolerability profile) for use in adolescents (12 through 17 years of age) with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma.

6.2 Study TO-203-3-2

Study TO-203-3-2 was a Phase 2/3, placebo-controlled, randomized, double-blind, multicenter study conducted in Japan evaluating safety and efficacy of the HDM SLIT tablet at 2 doses (6 SQ-HDM, 12 SQ-HDM) compared to placebo in subjects 12 through 64 years of age with HDM-induced allergic rhinitis. Individuals with asthma were excluded from the study. The duration of study treatment was 52 weeks. The sample size of the active treatment arms in total was n=627 and of the placebo arm was n=319. The sample size of the adolescent subjects (12 through 17 years of age) who received the 12 SQ HDM dose was n=107; the sample size of adolescent subjects who received placebo was n=99. Overall, 79 of 107 adolescent subjects completed 52 weeks of treatment with the 12 SQ HDM dose and 73 adolescent subjects completed 52 weeks of treatment with placebo (Table 13). The primary efficacy endpoint was the Total Combined Score (symptom score and medication score).

Table 13. Study TO-203-3-2: Extent of Exposure to 12 SQ-HDM Dose by Duration and Age Group (Safety Analysis Set)

Duration of Exposure	Adolescents (12-17 years) Placebo	Adolescents (12-17 years) 12 SQ-HDM	Adults (18-64 years) Placebo	Adults (18-64 years) 12 SQ-HDM	Total Placebo	Total 12 SQ-HDM
1 day or more	99	107	220	207	319	314
4 weeks or more	99	105	218	202	317	307
3 months (91 days) or more	98	102	210	193	308	295
4 months (122 days) or more	97	101	208	192	305	293
6 months (182 days) or more	97	100	199	189	296	289
9 months (273 days) or more	95	99	197	182	292	281
11 months (335 days) or more	92	99	193	182	285	281
52 weeks (364 days) or more	73	79	140	120	213	199
12 months (365 days) or more	54	48	97	82	151	130

Source: BLA 125592/157/0, ISS, Section 1.2.1.2, Table 1.2.1.2-1, p. 16.
Note: Subjects on 12 SQ-HDM had an up-dosing regimen, the entire duration of treatment is tabulated.

Disposition of adolescent subjects receiving the 12 SQ-HDM dose is shown in Table 14.

Table 14. Study TO-203-3-2: Disposition of Adolescent Subjects 12 through 17 Years of Age Receiving the 12 SQ-HDM Dose (Total Analysis Set)

Disposition	Placebo n (%)	12 SQ-HDM n (%)	Total [a] n (%)
Subjects screened	- (-)	- (-)	454 (-)
Not randomised	- (-)	- (-)	152 (-)
Subjects randomized	99 (-)	107 (-)	302 (-)
Subjects treated	99 (-)	107 (-)	302 (-)
Safety set	99 (100)	107 (100)	302 (100)
Subjects completed	92 (92.9)	99 (92.5)	279 (92.4)
Subjects discontinued	7 (7.1)	8 (7.5)	23 (7.6)
Reason for discontinuation	--	--	--
Adverse event	2 (2.0)	2 (1.9)	6 (2.0)
Lack of efficacy	- (-)	- (-)	- (-)
Physician decision	1 (1.0)	1 (0.9)	2 (0.7)
Pregnancy	- (-)	- (-)	- (-)
Withdrawal by subject	4 (4.0)	5 (4.7)	15 (5.0)
Other	- (-)	- (-)	- (-)

Source: BLA 125592/157/0, ISS, Section 1.2.1.2, Table 1.2.1.2-2, p. 17-18.

In terms of safety monitoring, adverse events (AEs) [name of AE, date of onset, presence/absence of treatment and treatment method, prescription change of IP, seriousness, severity, causal relationship, and outcome] were collected from the start of treatment to the completion of observation after 52 weeks of administration or to the completion of observation on the discontinuation observation day. The following events were also considered AEs (worsening of symptoms because of rhinitis exacerbation was not considered as an AE): for symptoms and signs, occurrence of a new abnormality; for laboratory tests and physiological examinations, clinically significant abnormal changes; any intervention required to treat the worsening of any pre-existing symptoms or laboratory or physiological abnormalities, or judgment of this worsening as medical aggravation. AEs were classified by: Seriousness: “serious” or “non-serious”; Severity: “mild,” “moderate,” or “severe”; Causal relationship: “related,” “possibly related,” or “not related” [AEs classified as “related” or “possibly related” were regarded as “adverse drug reactions (ADRs)”].

A summary of AE types for all treatment arms in subjects 12 through 64 years of age is provided in Table 15.

- Of the 946 subjects in the study, 820 subjects (86.7%) experienced AEs and 453 subjects (47.9%) experienced ADRs.
- No deaths occurred.
- SAEs occurred in 13 subjects (1.4%). A causal relationship to IP was ruled out for all these SAEs.
- Other significant AEs (excluding SAEs) were asthma in 8 subjects (0.8%).
- Adverse events (excluding SAEs and asthma) leading to IP discontinuation occurred in 14 subjects (1.5%), and ADRs leading to IP interruption occurred in 33 subjects (3.5%).

- One event of anaphylactic reaction occurred as an SAE in 1 subject in the placebo group.

Table 15. Study TO-203-3-2: Summary of Adverse Events in Subjects 12 through 64 Years of Age

Parameter	Placebo (n=319) N (%)	6 SQ-HDM (n=313) N (%)	12 SQ-HDM (n=314) N (%)	Active All (n=627) N (%)	Overall (n=946) N (%)
Adverse event	256 (80.3)	280 (89.5)	284 (90.4)	564 (90.0)	820 (86.7)
Adverse drug reaction	54 (16.9)	199 (63.6)	200 (63.7)	399 (63.6)	453 (47.9)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse event	3 (0.9)	5 (1.6)	5 (1.6)	10 (1.6)	13 (1.4)
Serious adverse drug reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other important adverse event (excluding SAE)	14 (4.4)	20 (6.4)	19 (6.1)	39 (6.2)	53 (5.6)
Anaphylactic reaction[*1]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthma[*2]	3 (0.9)	3 (1.0)	2 (0.6)	5 (0.8)	8 (0.8)
Adverse events leading to discontinuation[*3]	6 (1.9)	4 (1.3)	4 (1.3)	8 (1.3)	14 (1.5)
Adverse drug reactions leading to interruption[*4]	5 (1.6)	14 (4.5)	14 (4.5)	28 (4.5)	33 (3.5)

Source: BLA 125592/157/0, Study TO-203-3-2 CSR, Section 12.2.1, Table 12.2-1, p. 132.
Abbreviations: N: Number of subjects with events, %: Incidence
[*1]: Excepted serious adverse events (Anaphylactic reaction occurred as a serious adverse event: 1 subject in the placebo group)
[*2]: Not occurred asthma as serious adverse event
[*3]: Except discontinuation subjects due to serious adverse event and asthma (Serious adverse event leading to discontinuation: 1 subject in the placebo group, 1 subject in the 12 SQ-HDM group; subjects with asthma leading to discontinuation: 2 subjects in the placebo group, 3 subjects in the 6 SQ-HDM group)
[*4]: No interruption due to anaphylactic reaction and asthma occurred
Quotation from 14.3.1.2 (reposted)

The number of common adverse reactions and the number of subjects with common adverse reactions are shown by age in Table 16. The adverse reactions whose incidence in adolescent subjects (younger than 18 years of age) was ≥2% higher than that in adult subjects (18 through 64 years of age) were: oral pruritus (difference: 6.2%), oropharyngeal discomfort (difference: 4.6%), and mouth edema (difference: 3.4%). The adverse reactions whose incidence in adult subjects (18 through 64 years of age) was ≥2% higher than that in adolescent subjects (younger than 18 years of age) were: ear pruritus (difference: 3.9%) and throat irritation (difference: 3.1%). No major differences in the incidence of common adverse reactions were found between adolescent subjects (younger than 18 years of age) and adult subjects (18 through 64 years of age).

Table 16. Study TO-203-3-2: Incidence of Common Adverse Drug Reactions by Age Subgroup

Adverse Drug Reaction (PT)	<18 years (n=203) E	<18 years (n=203) N	<18 years (n=203) %	≥18 years (n=424) E	≥18 years (n=424) N	≥18 years (n=424) %
Mouth Edema	40	39	19.2	75	67	15.8
Oral pruritus	44	38	18.7	59	53	12.5
Throat irritation	23	22	10.8	67	59	13.9
Oropharyngeal discomfort	28	28	13.8	40	39	9.2
Oral discomfort	21	20	9.9	50	44	10.4
Paresthesia oral	21	20	9.9	46	40	9.4
Ear pruritus	10	9	4.4	36	35	8.3
Stomatitis	13	7	3.4	13	9	2.1
Lip swelling	6	5	2.5	12	11	2.6

Source: BLA 125592/157/0, Study TO-203-3-2 CSR, Section 12.2.3.7.1, Table 12.2-14, p. 144.
Abbreviations: E: Number of events, N: Number of subjects with events, %: Incidence.

A summary of other safety results of the study is provided here.

- Asthma occurred in 3 subjects (4 events) in the placebo group, 3 subjects (3 events) in the 6 SQ-HDM group, and 2 subjects (2 events) in the 12 SQ-HDM group. All of these events were non-serious. Of these events, only 1 event in 1 subject in the 6 SQ-HDM group was judged as an ADR. This event resolved on the day of onset without the use of therapeutic drugs, IP administration was discontinued in this subject.
- Adverse events (excluding SAEs and asthma) responsible for discontinuation occurred in 6 subjects (6 events) in the placebo group, 4 subjects (5 events) in the 6 SQ-HDM group, and 4 subjects (6 events) in the 12 SQ-HDM group. Of these events, 4 events in 4 patients were judged as ADRs in the placebo group, and all were judged as ADRs in the active groups.
- Of the ADRs responsible for discontinuation, 2 events in 2 subjects in the placebo group and 1 event in 1 subject in the 6 SQ-HDM group were moderate, and all other events were mild. The outcome was “recovered” for all AEs responsible for discontinuation in the active groups.
- Adverse drug reactions responsible for interruption occurred in 5 subjects (9 events) in the placebo group, 14 subjects (20 events) in the 6 SQ-HDM group, and 14 subjects (22 events) in the 12 SQ-HDM group. Of these events, 1 event in 1 subject in the placebo group, 7 events in 5 subjects in the 6 SQ-HDM group, and 9 events in 6 subjects in the 12 SQ-HDM group were moderate, and all other events were mild.
- Of the moderate ADRs responsible for interruption in the active groups, the most common (in terms of the numbers of events and subjects) event was edema mouth (3 events in 3 subjects). Of the ADRs responsible for interruption in the active groups, the 3 most common (numbers of events and subjects) events were mouth edema (6 events in 6 subjects), stomatitis (5 events in 4 subjects), and oropharyngeal discomfort (3 events in 3 subjects). The outcome was “recovered” for all ADRs responsible for interruption.
- No major differences in the incidence of AEs were found between the treatment groups (80.3%–90.4%). On the other hand, the incidence of ADRs was higher in the

6 SQ-HDM (63.6%) and 12 SQ-HDM (63.7%) groups than in the placebo group (16.9%).

- The 5 most common (in terms of the incidence) ADRs in the active groups were edema mouth (16.9%), oral pruritus (14.5%), throat irritation (12.9%), oropharyngeal discomfort (10.7%), and oral discomfort (10.2%). All of these events were local reactions at the administration site.
- Common (in terms of the incidence) ADRs by SOC in the active groups were "gastrointestinal disorders" (50.2%), "respiratory, thoracic and mediastinal disorders" (26.0%), and "ear and labyrinth disorders" (7.5%). Most of the events categorized into these SOC with a high incidence were local reactions at the administration site.
- No severe ADRs occurred. Of all ADRs reported in the study, 97.3% (914/939 events) were mild.
- In this study, 53.2% (500/939 events) of ADRs occurred within 2 weeks after the start of study treatment and 72.8% (684/939 events) within 4 weeks. In this study, 62.7% (379/604 events) of common ADRs occurred within 2 weeks after the start of study treatment and 82.8% (500/604 events) within 4 weeks.
- The median time to the first onset was 44 days for stomatitis and 1–18.5 days for other common ADRs related to oral findings. The median duration of these events was 2 days for lip swelling, 8 days for stomatitis, and 56–80 days for other events.
- No major differences were found in the incidence of common ADRs between subjects aged younger than 18 years and those aged at least 18 years. The incidence of common ADRs tended to be slightly higher in female subjects than in male subjects.
- No differences were found in the incidence of SAEs, ADR terms (SOC, PT), incidence of ADRs, severity of ADRs, or timing of onset of ADRs between the 6 SQ-HDM and 12 SQ-HDM groups.
- No noteworthy changes were noted in the assessment of laboratory values and vital signs.

> *Reviewer Comment:*
> *Safety data in the adolescent subgroup receiving the 12 SQ-HDM dose in this study were not reported separately from the safety data in the adult subgroup (Study TO-203-3-2 CSR), as the objective of this study was not to specifically evaluate safety of Odactra in the adolescent age subgroup. However, in general the safety profile of Odactra was shown not to be significantly different between adults and adolescents.*
>
> *Safety results obtained in the study are also similar to those of Study MT-18, in that the most adverse reactions were local in nature (proximal to the site of administration), no serious AEs related to the IP were noted, none to 1 anaphylactic reaction occurred in the study population, and the discontinuation rate in the 12 SQ-HDM group (4 subjects) and in the overall study was acceptable. As safety results in the study population (full age range) in both dose arms in this study appear to be similar to those of Study MT-18, these data do not raise concerns regarding the safety of Odactra in adolescents 12 through 17 years of age.*

7. INTEGRATED OVERVIEW OF EFFICACY

Not Applicable.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety evaluations included solicited adverse reactions, unsolicited treatment-emergent adverse events and adverse reactions, SAEs, AESIs, and deaths. All summaries of adverse events were based on the safety analysis populations in each of the studies. To be able to compare and evaluate safety across studies in this sBLA, the safety analysis set definition was aligned across studies to include all randomized subjects who received at least one dose of study treatment. Subjects were included in the safety set based on the highest dose received.

AEs reported in the 5 studies included in this sBLA (MT-03, P008, P001, TO-203-3-2, MT-18) were coded using different MedDRA versions (MT-03: v10.1; P008: v16.0; P001: v18.0; TO-203-3-2: v15.0; MT-18: v23.0). To be able to compare and evaluate AEs across studies in this sBLA, all AEs were recoded to MedDRA version 24.0.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety of Odactra in adolescents 12 through 17 years of age at the 12 SQ-HDM dose was evaluated in two Phase 1 clinical studies: Study MT-03 (multiple-dose, double-blind, placebo-controlled, safety study conducted in Europe in children 5 through 11 years of age and adolescents 12 through 14 years of age) and Study P008 (randomized, multiple-dose, double-blind, parallel-group, placebo-controlled safety study conducted in the U.S. in adolescents 12 through 17 years of age) and three Phase 3 clinical studies: Study P001 (pivotal, randomized, double-blinded, placebo-controlled safety and efficacy study conducted in North America in adolescents 12 through 17 years of age and adults 18 through 85 years of age), Study MT-18 (open-label safety study conducted in Europe in adolescents 12 through 17 years of age), and Study TO-203-3-2 (safety and efficacy study conducted in Japan in adolescents 12 through 17 years of age and adults 18 through 64 years of age).

Please see Table 2 (Section 5.3) for a summary of key elements of the Phase 3 studies. Phase 1 Study MT-03 was a staggered dose-escalation, double-blind, placebo-controlled study investigating safety and tolerability of the HDM SLIT-tablet in children (5−14 years of age) with HDM-induced mild to moderate asthma with or without allergic rhinitis. Each cohort of subjects was exposed to one dose of HDM SLIT-tablet (doses ranged from 0.5 to 12 SQ-HDM) followed by an approximately 7-day interval where safety data from that cohort was collected and evaluated, before another cohort of subjects was exposed to a higher dose. A total of 3 adolescent subjects (12–14 years of age) were exposed to 12 SQ-HDM and all of them completed daily treatment for 28 days. Phase 1 Study P008 was a randomized, multiple-dose, double-blind, parallel-group, placebo-controlled study to investigate safety and tolerability of the HDM SLIT-tablet in adolescent (12−17 years of age) subjects with HDM-induced allergic rhinitis/rhinoconjunctivitis with or without asthma. 65 adolescent subjects were exposed to 12 SQ-HDM. Of these, 62 received treatment for the full treatment period of 28 days.

In the below sections, safety data are generally presented by study and, for the 2 studies including both adolescents and adults (P001 and TO-203-3-2), by age group (12−17 years vs at least 18 years of age). Subgroup analyses by age group were performed

post hoc for this sBLA. The rationale for presenting the data in this way is based on the differences between the studies in treatment duration (from 28 days to 1 year), study design (placebo-controlled vs open-label design), and method of AE collection (with or without solicitation of AEs during the first 28 days).

The below sections will focus on safety data from the three Phase 3 studies. However, for the presentation of extent of exposure and severe and systemic events of interest sections below, the adolescent safety data on 12 SQ-HDM are pooled from all 5 studies (MT-03, P008, P001, TO-203-3-2, MT-18). This is based on the rationale that pooled data may better characterize the safety profile of the adolescent age group with regard to rare severe and systemic events of interest.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The overall adolescent exposure to Odactra 12 SQ-HDM across all completed studies in the clinical development program is shown in Table 17. A total of 522 adolescent subjects were exposed to a least one dose of 12 SQ-HDM, and of these, 504 subjects received treatment for at least 4 weeks (28 days). Approximately half of these were included in Study MT-18.

Table 17. Studies MT-03, P008, P001, TO-203-3-2*, MT-18: Extent of Adolescent Exposure to 12 SQ-HDM Dose by Study and Duration (All Adolescents Exposed to Odactra 12 SQ-HDM)

Duration of Exposure	MT-03	MT-18	P001	P008	TO-203-3-2	Overall
1 day or more	3	253	94	65	107	522
4 weeks or more	3	248	86	62	105	504
3 months (91 days) or more	-	-	81	-	102	183
4 months (122 days) or more	-	-	81	-	101	182
6 months (182 days) or more	-	-	77	-	100	177
9 months (273 days) or more	-	-	56	-	99	155
11 months (335 days) or more	-	-	2	-	99	101
52 weeks (364 days) or more	-	-	-	-	79	79
12 months (365 days) or more	-	-	-	-	48	48

Source: BLA 125592/157/6, Summary of Clinical Safety, Section 1.2, Table 4, p. 12.
* In TO-203-3-2, subjects on 12 SQ-HDM had an up-dosing regimen. For all subjects, the entire duration of treatment is tabulated.

Demographic and baseline characteristics are presented by study and, for Study P001 and Study TO-203-3-2, by age group in the following subsections.

Study P001
Within age groups (i.e., the adult age group and the adolescent age group), the treatment arms were well balanced with respect to age, gender, race, ethnicity, baseline FEV1 (% of predicted), baseline sensitizations (HDM only vs other sensitizations in

addition to HDM), duration of HDM-induced AR/C, asthma status and asthma duration, ICS use at baseline, baseline IgE levels, and baseline HDM wheal size. Regardless of age group, most subjects were white and approximately 20% of subjects were Black or African American or multi-racial. Most subjects were sensitized to 1 or more allergens in addition to HDM (76% of subjects in both age groups). All subjects had HDM-induced AR/C, and the duration of HDM-induced AR/C (number of years) was similar across treatment groups within each age group (a mean duration of 8.3 years among the adolescents and 20.1 years among the adults). Subjects were included in P001 based on a serum-specific IgE to HDM (*D. farinae* or *D. pteronyssinus*) of at least 0.7 kU/L, and for 20% of adolescents and 32% of adults, the highest HDM-specific IgE level was in the range of 0.7 to <3.5 kU/L. Within each age group, no major differences between treatment groups were observed with respect to baseline IgE levels.

Across age groups, only minor differences were noted; in the adolescent age group females comprised a smaller proportion of subjects, the HDM-specific IgE levels were higher (specifically, 27% of adolescents had an HDM-specific IgE level in the range of 50 to 100 kU/L or greater compared to 6% of adults), and the proportion of subjects with asthma at baseline was higher (40% of adolescent subjects reported asthma at baseline compared to 30% of adults, with no differences between treatment groups in either age group), as compared to the adult age group.

Study TO-203-3-2

Across age groups, the treatment groups were well-balanced with respect to demographics (except race, as all subjects in this study were Asian). Most adolescent subjects were male (62%) while most adult subjects were female (65%), with no significant differences between treatment groups in either age group. The age distribution was similar across treatment groups for adolescents as well as adults. Within age groups, the treatment groups were well balanced with respect to age, gender, baseline sensitizations (HDM only vs other sensitizations in addition to HDM), duration of HDM-induced AR/C, and baseline IgE levels. All subjects had HDM-induced AR/C, and the duration of HDM-induced AR/C (in years) was similar across treatment groups within each age group (mean duration of 6.2 years among adolescents and 11.8 years among adults).

Across age groups, only minor differences were noted; in the adolescent age group females comprised a smaller proportion of subjects and the HDM-specific IgE levels were higher, as compared to the adult age group.

In contrast to Study P001, only Asian subjects were included, and patients with asthma or ICS use were excluded. Additionally, the inclusion criterion on specific IgE to HDM was different in this study (serum IgE level ≥ 3.5 kU/L) as compared to Study P001 (serum IgE level ≥ 0.7 kU/L) and accordingly, a higher proportion of subjects in the higher baseline IgE classes (serum IgE ≥ 50 to 100 kU/L or greater) was noted as compared to Study P001. In Study TO-203-3-2, for most adult subjects (78%) the highest HDM-specific IgE level was in the range of 3.5 to 17.5 kU/L or 17.5 to 50 kU/L, whereas most adolescent subjects (88%) had an HDM-specific IgE level in the range of 17.5 to 100 kU/L or greater.

> *Reviewer Comment:*
> *A limitation of this study, from a single study standpoint, was that all subjects were Asian. However, since Asians are often underrepresented in studies*

conducted in Europe and North America, data from this study provides ethnic diversity in the context of the clinical development program.

Study MT-18
For a detailed description of demographics and baseline characteristics, see Section 6.1.10.1.1.

8.2.3 Categorization of Adverse Events

See Section 8.1 for categorization of adverse events that were collected for these studies.

AE solicitation
With regard to the first category listed in Section 8.1 (solicited adverse reactions), in P001 and MT-18, potential local side effects of SLIT were assessed using solicitation of 15 pre-specified symptoms/signs via a subject side effect report card/ diary for 28 days after initial administration of treatment. (This procedure of solicitation was not performed in TO-203-3-2 as this is not a requirement by Pharmaceuticals and Medical Device Agency in Japan.) Entries on the report card/ diary were discussed with the Investigator at each study visit; entries were then reported on the eCRF based on the Investigator's medical evaluation/ assessment (and subsequently coded as specific PTs).

In Study P001, the report card/diary prompted subjects to record 'Yes' or 'No' as to whether they experienced any of the 15 pre-specified symptoms/signs of SLIT within 60 minutes of taking study drug, whereas in Study MT-18 no specific time limit for reporting was specified.

Severity
The overall intent of severity grading was the same across the studies although the exact definitions varied between the studies. The differences were most notable between studies conducted by different Applicants (i.e., ALK [Studies MT-03 and MT-18], Merck [Studies P001 and P008], and Torii [Study TO-203-3-2]). An overview of the different severity definitions is provided in Table 18.

Table 18. Studies MT-03, P008, P001, TO-203-3-2, MT-18: Definitions of Adverse Event Severity

Study	Mild	Moderate	Severe
TO-203-3-2	No disruption of daily activities	Deteriorates or affects daily activities	Inability to perform daily activities or results in death
P008, P001	Awareness of sign, symptom, or event, but easily tolerated (for pediatric studies, awareness of symptom, but easily tolerated)	Discomfort enough to cause interference with usual activity (for pediatric studies, definitely acting like something is wrong)	Incapacitating with inability to work or do usual activity (for pediatric studies, extremely distressed or unable to do usual activities)
MT-03, MT-18	Transient symptoms, no interference with the subject's daily activities	Marked symptoms, moderate interference with the subject's daily activities	Considerable interference with the subject's daily activities, unacceptable

Source: BLA 125592/157/0 and 6, Study TO-203-3-2 CSR, Section 9.5.1.4.5; P001 CSR, Appendix 16.1.1, Table 8; Study P008 CSR, Appendix 16.1.1.1, Table 5; Study MT-03 CSR, Section 5.7.1; Study MT-18 CSR, Section 9.5.2.1.

Causality

For causality assessments of AEs in this sBLA, IP-related AEs were defined as:

- Study MT-03: events reported as “possibly related” by the investigator
- Study P008, P001: events reported as "related" by the investigator
- Study TO-203-3-2: events reported as "possibly related" or "related" by the investigator
- Study MT-18: events reported as "possibly related" by the investigator

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

Pooled safety data should be interpreted with caution.

Studies P001 and MT-18 are the only studies that utilized a Side Effect Report Card to solicit adverse reactions for the first 28 days. Unsolicited adverse events were recorded for the entire study duration.

All other studies recorded unsolicited adverse events.

8.4 Safety Results

A summary of TEAEs in adolescents who received Odactra 12 SQ-HDM or placebo from the five clinical studies in which adolescents were evaluated (Studies MT-03, P008, P001, MT-18, and TO-203-3-2) is shown in Table 19.

Table 19. Studies MT-03, P008, P001, MT-18, and TO-203-3-2: Summary of Treatment-Emergent Adverse Events in Adolescent Subjects 12 through 17 Years of Age in (Safety Analysis Set)

Characteristic	Odactra 12 SQ-HDM (N=522) N (%)	Placebo (N=262) N (%)
Subjects with one or more AEs	452 (86.6)	187 (71.4)
Intensity	--	--
Mild	444 (85.1)	177 (67.6)
Moderate	80 (15.3)	45 (17.2)
Severe	7 (1.3)	3 (1.1)
Unknown	61 (11.7)	4 (1.5)
No AEs	70 (13.4)	75 (28.6)
With drug-related AEs	413 (79.1)	80 (30.5)
With serious AEs	0	2 (0.8)
With serious drug-related AEs	0	0
Discontinued due to an AE	17 (3.3)	3 (1.1)
Discontinued due to a drug-related AE	17 (3.3)	1 (0.4)
Discontinued due to a serious AE	0	1 (0.4)
Discontinued due to a serious drug-related AE	0	0
Deaths	0	0

Source: BLA 125592/157/16, Response to FDA IR#10, Table 1, p. 3.
Abbreviations: AE= adverse event, SQ-HDM=Standardized Quality- House Dust Mite (unitage), N: number of subjects, (%): percentage of subjects in population.
Subjects who discontinued, discontinued both the study and the treatment.

This table is based on both solicited and unsolicited adverse events (data on solicited adverse reactions were not solicited consistently in all studies; this table contains both sets of data.).

8.4.1 Deaths

No deaths were reported in any of the studies.

8.4.2 Nonfatal Serious Adverse Events

Data on SAEs are presented for each study separately.

Study P001
In the adolescent age group, no SAEs were reported by subjects in the 12 SQ-HDM treatment group. In the placebo group, 2 subjects reported one SAE each in the SOC 'Psychiatric disorders'. Both events were severe, but neither was judged to be IP-related and both subjects recovered from the events.

- One subject, 16 years of age, receiving treatment with placebo, reported depression at Day 321 of treatment; this event was graded as severe and considered an SAE, was assessed as not related to the IP, the dose of the IP was not changed; the adverse event resolved after 6 days.
- One subject, 17 years of age, receiving treatment with placebo, reported Bipolar I Disorder at Day 226 of treatment, this event was graded as severe and considered an SAE, was assessed as not related to the IP, the IP was withdrawn; the adverse event resolved after 9 days.

Reviewer Comment:
The overall proportion of subjects reporting SAEs was low and similar across age groups. In comparison to the adolescent age group, in the adult age group the SAEs were reported across multiple SOCs without any apparent pattern within the individual SOCs. Approximately half of the events were severe, all but 2 subjects (1 reporting 'hepatic cancer' and the other reporting 'alcohol abuse') recovered and 3 events led to treatment discontinuation.

Study MT-18
No SAEs were reported in this study.

Study TO-203-3-2
No SAEs were reported in the adolescent age group.

Reviewer Comment:
In comparison to the adolescent age group, the proportion of subjects in the adult age group experiencing SAEs was low. In the adult age group, 1 SAE was reported as 'anaphylactic reaction' in the placebo group. None of the SAEs were deemed as IP-related and the outcome was “recovering” or “recovered” for all events.

8.4.3 Study Dropouts/Discontinuations

In all studies, discontinuation from treatment also led to discontinuation from the study.

Study P001
The overall pattern of TEAEs leading to treatment discontinuation was similar across age groups. Across age groups, the proportion of subjects discontinuing treatment due

to a TEAE was higher in the 12 SQ-HDM treatment group (10% of adolescents; 10% of adults) as compared to the placebo treatment group (1% of adolescents; 3% of adults). The pattern with regards to type of TEAEs leading to treatment discontinuation was similar across age groups. Across age groups, the majority of TEAEs leading to treatment discontinuation were IP-related and for the events reported in the adolescent age group treated with 12 SQ-HDM, all events were IP-related (these were: ear pruritus 1%, enlarged uvula 1%, glossodynia 1%, lip swelling 1%, mouth swelling 1%, mouther ulceration 1%, nausea 2%, mouth edema 1%, palatal swelling 1%, swollen tongue 2%, tongue pruritus 1%, pharyngeal edema 1%, throat irritation 4%). The majority of all IP-related TEAEs leading to treatment discontinuation were local reactions related to study product administration, and the vast majority of all events across age groups were mild or moderate in severity; within the adolescent age group, 2 of the events, reported by 1 subject ('throat irritation' and 'tongue pruritus') were severe. All adolescent subjects reporting TEAEs leading to treatment discontinuation recovered from the events (for 1 subject, no outcome information was available. Across age groups, both the proportion of subjects discontinuing treatment due to IP-related TEAEs and the type of IP-related TEAEs most often leading to treatment discontinuation (e.g., 'throat irritation' and 'mouth swelling') were similar.

Study MT-18

Please see Section 6.1.12.7.

Two subjects discontinued IP and discontinued the study due to TEAEs (0.8%)- these were both solicited TEAEs. The solicited symptoms leading to treatment discontinuation (‘mouth ulcer/sore in the mouth’ (PT: mouth ulceration) and ‘stomach pain’ (PT: abdominal pain upper)) were both moderate and assessed to be IP-related. One of the symptoms (‘mouth ulcer/sore in the mouth’) was a local reaction. Neither of the solicited symptoms were serious, and both subjects recovered from the events upon treatment discontinuation.

Study TO-203-3-2

The overall pattern of TEAEs leading to discontinuation was similar across age groups. Across age groups, the proportion of subjects discontinuing treatment due to TEAEs was low and similar across treatment groups; 2% of adolescents and 1% of adults treated with 12 SQ-HDM and 2% of adolescents and 3% of adults treated with placebo discontinued treatment due to one or more TEAEs. Across age groups, the majority of TEAEs leading to treatment discontinuation were IP-related and for the TEAEs reported in the adolescent age group treated with 12 SQ-HDM, all events were IP-related (these were: nausea 1%, tongue pruritus 1%, chest discomfort 1%). None of the events reported in the adolescent age group were severe and all subjects recovered from the events.

8.4.4 Common Adverse Events

Solicited Adverse Reactions

The most common solicited adverse reactions occurring in ≥10% of adolescent subjects taking Odactra were: throat irritation/tickle, itching in the mouth, itching in the ear, tongue pain, stomach pain, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat swelling, nausea, tongue ulcer/sore on the tongue, and mouth ulcer/sore in the mouth, and diarrhea.

Solicited adverse reactions occurring within 28 days after initiation of treatment with Odactra in adolescents 12 through 17 years of age in Study P001 and Study MT-18 are shown in Table 20 and Table 21, respectively. Most of the solicited adverse reactions were assessed as mild to moderate in severity, occurred very early in treatment, and resolved without complication.

Table 20. Study P001: Solicited* Adverse Reactions Within 28 Days After Initiation of Treatment with Odactra or Placebo in Adolescent Subjects 12 through 17 Years of Age (Safety Analysis Set)

System Organ Class Adverse Reaction (Any Intensity‡)	**Odactra (N=94)**	**Placebo (N=95)**
Ear and labyrinth disorders	--	--
Itching in the ear	50.0%	11.6%
Gastrointestinal disorders	--	--
Itching in the mouth‡	73.4%	14.7%
Tongue pain	24.5%	4.2%
Stomach pain	23.4%	15.8%
Swelling of the uvula/back of the mouth†	20.2%	3.2%
Swelling of the lips	20.2%	1.1%
Swelling of the tongue	19.1%	3.2%
Nausea‡	17.0%	9.5%
Tongue ulcer/sore on the tongue	12.8%	4.2%
Mouth ulcer/sore in the mouth	10.6%	3.2%
Diarrhea	7.7%	2.1%
Vomiting‡	4.3%	--
Nervous system disorders	--	--
Taste alteration/food tastes different	4.3%	4.2%
Respiratory, thoracic, and mediastinal disorders	--	--
Throat irritation/tickle‡	73.4%	35.8%
Throat swelling	18.1%	8.4%

Source: BLA 125592/157/9, Applicant Response Document to FDA Labeling IR #9, Section 2, Table 18, p. 75.
*Solicited adverse reactions (modified from World Allergy Organization [WAO] list of local side effects of SLIT) were those reported by subjects within the first 28 days after treatment initiation.
†The percentage of subjects reported for the patient-friendly term of "swelling of the uvula/back of the mouth" includes subjects with an enlarged uvula, palatal swelling, and/or mouth swelling/edema (which can be anywhere in the mouth, not specifically back of the mouth).
‡Of those subjects reporting any intensity of itching in the mouth, nausea, throat irritation/tickle, or vomiting in the Odactra group, 1 subject (1.1%) reported severe intensity of the reaction. Adverse reactions were categorized as severe according to the definition 'incapacitating with inability to work or do usual activity', as assessed by the investigator.

Table 21. Study MT-18: Solicited* Adverse Reactions Within 28 Days After Initiation of Treatment with Odactra in Adolescent Subjects 12 through 17 Years of Age (Safety Analysis Set)

System Organ Class Adverse Reaction (Any Intensity‡)	**Odactra (N=253)**
Ear and labyrinth disorders	--
Itching in the ear	40.7%
Gastrointestinal disorders	--
Itching in the mouth	68.4%
Mouth ulcer/sore in the mouth	25.7%
Tongue ulcer/sore on the tongue	22.5%
Swelling of the lips	21.3%
Swelling of the uvula/back of the mouth†	21.3%

System Organ Class Adverse Reaction (Any Intensity‡)	**Odactra (N=253)**
Tongue pain	19.0%
Nausea	17.4%
Stomach pain	16.6%
Swelling of the tongue	15.4%
Diarrhea	10.3%
Vomiting	2.8%
Nervous system disorders	--
Food tasting different	8.3%
Respiratory, Thoracic, and Mediastinal disorders	--
Throat irritation/tickle	62.1%
Throat swelling	14.6%

Source: Adapted from BLA 125592/157/6, ISS, Section 2.1.2, Table 2.1.2.6-1, p. 79.
Abbreviations: n=number of subjects, %=percentage of subjects in safety set.
*Solicited adverse reactions (modified from World Allergy Organization [WAO] list of local side effects of SLIT) were those reported by subjects within the first 28 days after treatment initiation.
†The percentage of subjects reported for the patient-friendly term of "swelling of the uvula/back of the mouth" includes subjects with an enlarged uvula, edema uvula, palatal swelling/edema, and/or mouth swelling/edema (which can be anywhere in the mouth, not specifically back of the mouth).
‡No severe solicited adverse reactions were reported.

Reviewer Comment:
A comparison of the solicited adverse reactions in adolescents from Study P001 and Study MT18 reveals that all 15 pre-specified solicited adverse reactions occurred in both studies and that most of the adverse reactions were reported at a slightly lower frequency by subjects/ investigators in Study MT-18. Of note, in Study P001, the report card/diary prompted subjects to record 'Yes' or 'No' as to whether they experienced any of the 15 pre-specified symptoms/signs of SLIT within 60 minutes of taking the IP or placebo, whereas in Study MT-18 no specific time limit for reporting after taking the IP was specified.

The adverse reactions that were reported at similar rates between the two studies were swelling of the uvula/ back of the mouth, swelling of the lips, and nausea.

The adverse reactions that were reported at higher rates in Study MT-18 were: tongue ulcer/ sore on the tongue, mouth ulcer/ sore in the mouth, diarrhea, and taste alteration/ food tasting different.

Unsolicited Adverse Events

Most Frequently Reported Unsolicited TEAEs (reported by at least 2% of subjects in any 12 SQ-HDM group)

Study P001
Overall, the pattern of the most frequently reported unsolicited TEAEs, both with regards to type of reported events and the frequency by which they were reported, was similar across age groups. Across age groups, the overall proportion of subjects reporting the most frequent TEAEs was higher in the 12 SQ-HDM treatment group (94% of adolescents, 87% of adults) as compared to placebo (68% of adolescents, 58% of adults). Across age groups, the most frequently reported TEAEs were among the symptoms/signs which were solicited during the first 28 days of treatment. The most

frequently reported TEAEs were all local reactions related to study product administration and reported by a higher proportion of subjects in the 12 SQ-HDM treatment group as compared to the placebo group.

In the adolescent group, the 5 most frequently reported PTs were (12 SQ-HDM vs placebo): 'throat irritation' (71% vs 36%), 'oral pruritus' (73% vs 15%), 'ear pruritus' (50% vs 12%), 'glossodynia' (24% vs 4%) and 'abdominal pain upper' (23% vs 15%). In addition, for 'oral pruritus' and 'abdominal pain upper', the number of TEAEs in relation to the number of subjects reporting the events was higher in the 12 SQ-HDM treatment group as compared to the placebo group.

Study MT-18
Regarding the most frequently reported unsolicited TEAEs, the most frequently reported PTs (reported as % subjects with the event) were ‘oral pain’ (4%), ‘oral pruritus’ (3%) and ‘rhinitis’ (2%). The most frequently reported SOC was ‘Gastrointestinal disorders’, with 7% of subjects reporting 27 events.

Study TO-203-3-2
Overall, the pattern of the most frequently reported unsolicited TEAEs, both with regards to type of reported events and the frequency by which they were reported, was similar across age groups. Across age groups, the overall proportion of subjects reporting the most frequent TEAEs was higher in the 12 SQ-HDM treatment group (88% of adolescents, 87% of adults) as compared to placebo (78% of adolescents, 70% of adults). The most frequently reported PTs were a mix of local reactions related to study product administration and pharyngitis-related events. The local reactions were all reported by a higher proportion of subjects in the 12 SQ-HDM treatment group as compared to the placebo group whereas pharyngitis-related events were reported by a similar proportion of subjects across treatment groups.

In the adolescent age group, the 5 most frequently reported PTs were (12 SQ-HDM vs placebo): 'nasopharyngitis' (26% vs 28%), 'oral pruritus' (22% vs 1%), 'pharyngitis' (21% vs 10%), 'laryngopharyngitis' (16% vs 17%) and 'throat irritation' (13% vs 2%).

In the adult age group, the 5 most frequently reported TEAEs were (12 SQ-HDM vs placebo): 'nasopharyngitis' (36% vs 36%), 'laryngopharyngitis' (18% vs 11%), 'oral pruritus' (15% vs 1%), 'oral discomfort' (11% vs 1%) and 'throat irritation' (11% vs 0%).

> *Reviewer Comment:*
> *In contrast to Studies P001 and MT-18, the most frequently reported TEAEs (which includes the most frequently reported IP-related TEAEs, see section below) in Study TO-203-3-2 were not all local reactions related to IP administration. In addition, the proportion of subjects reporting local reactions, across age and treatment groups, was lower in Study TO-203-3-2 as compared to Studies P001 and MT-18. Safety data results in Studies P001 and MT-18 are likely due to the active solicitation of local signs/symptoms for the first 28 days after IP administration, a method used to characterize the safety profile of the product as much as possible.*

IP-Related TEAEs

Study P001
Overall, the pattern of unsolicited IP-related TEAEs, both with regards to type of events and frequencies by which the events were reported, was similar across age groups.

Across age groups, the overall proportion of subjects reporting an IP-related TEAE as well as the total number of reported TEAEs was higher in the 12 SQ-HDM treatment group as compared to the placebo group. Similarly, the proportion of subjects discontinued due to an IP-related TEAE was higher in the 12 SQ-HDM treatment group as compared to the placebo group. The vast majority of all IP-related TEAEs were mild or moderate in severity and the proportion of 12 SQ-HDM-treated subjects reporting severe, IP-related TEAEs was the same in both age groups (2%).

Across age groups, the most frequently reported IP-related TEAEs were all local reactions related to study product administration and reported by a higher proportion of subjects in the 12 SQ- HDM treatment group as compared to the placebo group. In the 12 SQ-HDM treatment group, the most frequently reported IP-related TEAEs were the same (adolescents; adults); 'oral pruritus' (73%; 60%), 'throat irritation' (69%; 61%), 'ear pruritus' (50%; 50%). These 3 treatment-related TEAEs were also among the most frequently reported TEAEs in adolescent and adult subjects in the placebo group.
All of the most frequently reported IP-related TEAEs were solicited symptoms/signs.

Study MT-18
Sixteen percent of the subjects reported an unsolicited IP-related TEAE. The majority of these were mild in severity, a few were moderate, and no events were severe. No unsolicited IP-related SAEs were reported. The proportion of subjects discontinuing due to an unsolicited IP-related TEAE was low which was similar to Study TO-203-3-2 and lower than Study P001. In Study MT-18, 1 subject discontinued the study due to an unsolicited IP-related TEAE. In total, 2 subjects discontinued the study due to unsolicited IP-related TEAEs or solicited symptoms. The most frequently reported unsolicited IP-related TEAE (reported as ≥2% subjects with the event) were local reactions related to IP administration: ‘oral pain’ (3%) and ‘oral pruritus’ (3%).

Study TO-203-3-2
Overall, the pattern of IP-related TEAEs, both with regards to type of events and frequencies by which the events were reported, was similar across age groups.

Across age groups, the proportion of subjects reporting an IP-related TEAE as well as the total number of reported TEAEs was higher in the 12 SQ-HDM treatment group as compared to the placebo group. The vast majority of all events were mild in severity, a few were moderate and no events in either age group were severe. No IP-related SAEs were reported. Across age and treatment groups, the proportion of subjects discontinuing due to an IP-related TEAE was low and the proportion of adolescent subjects in the 12 SQ-HDM treatment group discontinuing due to an IP-related TEAE was similar to in Study MT-18 and lower than in Study P001.

Across age groups, the most frequently reported IP-related TEAEs were all local reactions related to IP administration and reported by a higher proportion of subjects in the 12 SQ-HDM treatment group as compared to the placebo group. In the 12 SQ-HDM treatment group, the most frequently reported IP-related TEAEs were the same

(adolescents; adults); 'oral pruritus' (22%; 15%) and 'throat irritation' (13%; 11%). One difference between the adolescent and adult age groups was that 'oropharyngeal discomfort' was reported by a higher proportion of adolescent subjects (11%) as compared to adult subjects (3%).

8.4.5 Clinical Test Results

Not applicable, as no overall clinical laboratory evaluations were performed as there was no blood collection at the end of study and thus, no comparisons to baseline values were possible.

8.4.6 Systemic Adverse Events

For this sBLA, systemic adverse events were denoted as severe and systemic events of interest and were defined (with the term 'treatment-related' used synonymously with the term 'IP-related') as:

- IP-related systemic allergic reactions (both when identified directly by investigators and when identified as per the modified Sampson criteria)
    - the assessment of systemic allergic reactions was based on pooled data from all adolescent subjects exposed to 12 SQ-HDM or placebo and the events were identified by 2 measures:
        - events directly reported by investigators were identified using the SMQ 'Anaphylactic reaction', narrow terms
        - events fulfilling the modified Sampson criteria were identified through medical evaluation of co-occurring events identified using the SMQ 'Anaphylactic reaction', broad term algorithm
- IP-related events treated with epinephrine
- IP-related severe local swelling or edema of the mouth/throat.

Data on severe and systemic events of interest for the 12 SQ-HDM dose (n=522) or placebo (n=270) are presented across all adolescent subjects included in any of the 5 studies in which adolescent subjects were exposed to 12 SQ-HDM (Table 22). In the population of 522 adolescent subjects exposed to 12 SQ-HDM, the observed rates were 0% for all three sub-categories of the severe and systemic events of interest.

Based on these observed rates, the upper bound of the 95% CI of the incidence proportion of all combined severe and systemic events of interest is 0.70% for the 12-SQ-HDM treatment group and 1.4% for the placebo treatment group, respectively.

> *Reviewer Comment:*
> *Although the point estimate for the incidence of severe and systemic events of interest is 0% in the studies conducted in adolescents, the calculated 95%CI range suggests that there is a 95% chance that the incidence of these events would fall into the range of 0 and 0.7% in subjects receiving Odactra as the number of observations (number of subjects/ patients receiving Odactra) increases beyond the number of observations in these pre-licensure studies. Taking the total number of subjects in each group into account, the confidence interval calculations in Table 22 were verified.*

Table 22. Studies MT-03, P008, P001, TO-203-3-2, MT-18: Incidence of Severe and Systemic Adverse Events of Interest in Adolescents in All Adolescents Exposed to Odactra 12 SQ-HDM or Placebo (Safety Analysis Set)

Severe and Systemic Events of Interest	12 SQ-HDM (N=522) n (%) 95% CI	Placebo (N=270) n (%) 95% CI
IP-related Systemic Allergic Reactions	--	--
Directly reported by investigator [a]	0 (0) [0.0%; 0.7%]	0 (0) [0.0%; 1.4%]
Based on modified Sampson criteria [b]	0 (0) [0.0%; 0.7%]	0 (0) [0.0%; 1.4%]
IP-related Events treated with Epinephrine	0 (0) [0.0%; 0.7%]	0 (0) [0.0%; 1.4%]
IP-related severe local swelling or edema of the mouth/throat [c]	0 (0) [0.0%; 0.7%]	0 (0) [0.0%; 1.4%]
Total Severe and Systemic Events of Interest	**0 (0) [0.0%; 0.7%]**	**0 (0) [0.0%; 1.4%]**

Source: BLA 125592/157/6, SCS, Section 2.1.5.3, Table 24, p. 72.
Abbreviations: n=number of subjects with event, %n=percent subjects of safety set, N=number of subjects in safety set, CI=confidence interval.
[a.] Based on MedDRA SMQ 'Anaphylactic reaction' narrow terms.
[b.] Based on medical evaluation of co-occurring events identified through MedDRA SMQ 'Anaphylactic reaction' broad terms, for fulfilment of the criteria for anaphylaxis according to Sampson et al. 2006.
[c.] Events identified via the PTs: Dysphagia, Dysphonia, Epiglottic edema, Laryngeal dyspnea, Laryngeal obstruction, Laryngeal edema, Laryngotracheal edema, Mouth swelling, edema mouth, Oropharyngeal edema, Oropharyngeal swelling, Palatal edema, Palatal swelling, Pharyngeal edema, Pharyngeal swelling, Sensation of foreign body, Suffocation feeling, Swollen tongue, Throat tightness, Tongue edema, Tracheal edema.

The following is a list of adverse events within each of the sub-categories (for Studies P001, MT-18, and TO-203-3-2) that were excluded from Table 22 (rationale included in the brief narratives below):

- IP-related systemic allergic reactions (both when identified directly by investigator and when identified as per modified Sampson criteria)
    - Study P001:
        - One adolescent subject treated with 12 SQ-HDM reported a systemic allergic reaction (PT 'anaphylactic reaction') not considered IP-related by the investigator. The subject had a medical history of peanut allergy and reported the event after eating a cookie containing peanuts. The event was moderate in severity, non-serious and the subject recovered from the event.
        - A total of 20 subjects were identified to have reported 65 co-occurring events, i.e., events affecting at least 2 organ systems, with the same start date, based on the SMQ 'Anaphylactic reaction' broad term algorithm. After medical evaluation of these co-occurring events, no events were evaluated to fulfil the criteria for diagnosis of anaphylaxis as per modified Sampson criteria, thus, the observed rate of IP-related systemic allergic reactions as per modified Sampson criteria was 0%.
    - Study MT-18: One adolescent subject taking 12 SQ-HDM experienced mild urticaria for 15 minutes and mild swelling in the back of the mouth for 5 minutes on Day 3 of treatment. Both events resolved spontaneously without the use of any rescue medication, and IP treatment was

continued. As the localization (i.e., local vs. systemic) of the event of urticaria was unknown, it could not be excluded that the subject experienced a systemic allergic reaction, and medical evaluation identified this as a possible systemic allergic reaction (see Section 6.1.12.5) (this event was not reported in the SCS or ISS or Table 22 as this event was not characterized to be “of interest” due to spontaneous resolution of the events).

- IP-related events treated with epinephrine
  - Study TO-203-3-2: One subject treated with 12 SQ-HDM reported epinephrine use due to an event of mild 'pharyngitis'. This event was not considered IP-related by the investigator.
- IP-related severe local swelling of the mouth and /or throat with the potential to compromise airways
  - no events were reported

8.4.7 Local Reactogenicity

See Section 8.4.4, as most of the common adverse events 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 EoE in subjects taking SLIT products, selected upper gastrointestinal tract AEs were reviewed.

EoE was not assessed in the Phase I studies (MT-03 and P008).

There were no cases of EoE identified in Study MT-18 or Study TO-203-3-2.

Two cases reporting an adolescent subject undergoing evaluation for EoE, 1 taking Odactra 12 SQ-HDM and 1 taking placebo, were identified in Study P001. These events are summarized below.

1. One 13-year-old subject taking Odactra 12 SQ-HDM in Study P001 was diagnosed with EoE on Day 204 based on an upper endoscopy showing 10-20 eosinophils per high powered field in both the mid and distal esophagus. The subject was treated with swallowed fluticasone, omeprazole, and continued in the study.
2. One 14-year-old subject taking placebo was evaluated for potential EoE via a stomach biopsy on Day 198 that showed 30 eosinophilic per high powered field. The subject was treated with high dose lansoprazole. A repeat endoscopy on Day 296 showed no eosinophils in the mid or distal esophagus and only 2 eosinophils per high powered field in the proximal esophagus. The subject was ultimately diagnosed with gastroesophageal reflux disease. This subject completed the study.

Reviewer Comment:
Overall, in all three Phase 3 studies evaluating Odactra in adolescents, 1 adolescent study subject developed IP-related EoE.

Asthma-related events (included under AESIs as these events are of special interest)

Study P001
In the adolescent age group, no subjects treated with 12 SQ-HDM reported any TEAEs related to asthma. Four subjects in the placebo group experienced asthma related TEAEs. All events were nonserious, non-treatment-related and all but 1 moderate event were mild in severity.

Study MT-18
No asthma related TEAEs were reported in this study.

Study TO-203-3-2
No asthma related TEAEs were reported in this study.

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.

Study P001
Data on overdose was not specified by age subgroup (i.e., all data below are on the full age range of the study population).

A total of 4 subjects had overdoses that were identified; the dosage of overdose for each of these subjects was 2 tablets. Two subjects reported overdoses (each subject took 1 extra tablet) with drug-related AEs (1 subject had 2 AEs, oral pruritus and throat irritation, and the other subject had an AE of oral pain). The Applicant classified these overdoses with drug-related AEs as SAEs. All 3 AEs were assessed as mild in intensity by the Investigator and did not meet ICH criteria for seriousness.

Fifty-six subjects had overdoses that were not associated with an adverse effect; these overdoses were similarly reported in the treatment and placebo groups. The vast majority of overdoses were accidental and not associated with AEs. Two placebo-treated subjects had intentional overdoses (2 tablets/day), which were considered by the Investigator to be nonserious, not related to study drug, and mild in intensity.

Study MT-18
No overdoses were reported during Study MT-18.

Study TO-203-3-2
Eleven subjects received IP doses higher than those specified in the study: 5 subjects in the placebo group and 6 subjects in the active groups. Although mild oral pruritus occurred in 1 subject in the 12 SQ-HDM group, the subject recovered on the day of onset without any therapy. No effects of overdose were observed in other subjects.

8.5.2 Time Dependency for Adverse Events

See individual sections for data on timing of various adverse events.

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 the safety data in adolescents finds that the Odactra safety profile in the adolescent population is acceptable.

Adverse reactions expectedly occurred in the treatment group more often than placebo. The most common solicited adverse reactions occurring in ≥10% of adolescent subjects taking Odactra were throat irritation/tickle, itching in the mouth, itching in the ear, tongue pain, stomach pain, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat swelling, nausea, tongue ulcer/sore on the tongue, and mouth ulcer/sore in the mouth, and diarrhea. Throat irritation, oral pruritus, ear pruritus, and lip swelling have also been reported as the most common adverse reactions for licensed SLIT products. The majority of these events were assessed as mild to moderate in severity, occurred very early in treatment, and resolved without complication.

No deaths occurred in the five clinical studies in which adolescents were evaluated. None of the reported serious adverse events were related to Odactra and there were no serious unexpected adverse events. No systemic allergic reactions including anaphylaxis considered ‘related to the IP’ by the investigator occurred; there was one possible case of systemic allergic reaction noted in Study MT-18 due to two co-occurring allergic adverse events that resolved spontaneously without the use of any rescue

medication within 15 minutes of onset. One case of EoE in an adolescent in the treatment group was identified (Study P001).

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 subject 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 adolescents in any of the 5 studies in which adolescents were evaluated.

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 (see also Section 2.5)

The study reviewed in this supplemental BLA submission was a PMR under the Pediatric Research Equity Act (PREA; Section 505B of the Federal Food, Drug, and Cosmetic Act), which requires that FDA consider the utility of studying use of an investigational drug product in all pediatric subpopulations.

On 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 through 65 years of age. The deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act as outlined in the March 1, 2017 Approval Letter were as follows:

> 1. Deferred pediatric study (Study 1) under PREA to evaluate safety and efficacy of Odactra in pediatric subjects 5 through 17 years of age with HDM-induced allergic rhinitis/rhinoconjunctivitis with or without asthma.
> 2. Deferred pediatric study (Study 2) under PREA to evaluate safety of Odactra in pediatric subjects 5 through 17 years of age with HDM-induced allergic rhinitis/rhinoconjunctivitis with or without asthma.

Following discussions between the Applicant and CBER regarding the deferred pediatric studies, CBER agreed that for the age group 12 through 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 concurred with a revised, staged development approach which included two separate studies for the two age groups, children 5 through 11 years of age and adolescents 12 through 17 years of age, as follows:

1. Study MT-18: an open-label 28-day safety study to evaluate safety and tolerability of Odactra in adolescents 12 through 17 years of age with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma over 28 days of treatment.
2. Study MT-12: a Phase 3, double-blind, parallel-group, placebo-controlled study to evaluate safety, tolerability, and efficacy of Odactra in children 5 through 11 years of age with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma.

The CSRs of Study MT-18 and Study TO-203-3-2 were submitted under sBLA 125592/157 on December 22, 2021. After review of the data, the Division concluded that the safety data from Study MT-18, the safety data from Study T0-202-3-2, and the efficacy and safety data from Study P001 (previously reviewed under STN 125592/0) support approval of Odactra in adolescents 12 through 17 years of age.

The following language was proposed for Section 8.4 (Pediatric Use) of Section 8 (Use in Specific Populations) of the Prescribing Information (PI): The safety and effectiveness of Odactra have been established in adolescents 12 through 17 years of age. The safety and effectiveness have not been established in persons below 12 years of age.

On December 13, 2022, a meeting with the PeRC was held in which the findings in the adolescent population from Study MT-18, Study TO-203-3-2, and Study P001 were discussed. The Division also proposed the following and PeRC agreed with this proposal:

1. Release of the Applicant from PMR#1 and PMR#2 (listed in the March 1, 2017 Approval Letter).
2. 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 through 11 years of age with HDM-induced allergic rhinitis/rhinoconjunctivitis with or without asthma).

Reviewer Comment:
The PSP was discussed throughout clinical development with CBER's PeRC, who agreed with the interactions that occurred between the Division and the Applicant on the various revisions of the PSP including the Applicant's rationale for requests for waivers and deferrals.

During the December 13, 2022 meeting with PeRC, the Division noted that review of the adolescent safety data from Studies P001, MT-18, and TO-203-3-2, supports approval of Odactra for use in the adolescent population (no new safety signals were identified that would require additional evaluation in this age group). PeRC agreed with the assessments provided by the Division with regard to the adequacy of the safety and efficacy data to support approval of Odactra for licensure in adolescents 12 through 17 years of age.

As noted above, during the discussion of the results of the data analyses in the adolescent population from Study MT-18, Study TO-203-3-2, and Study P001 on December 13, 2022, the Division proposed that the Applicant be released from PMR Studies 1 and 2 (as listed in the March 1, 2017 Approval Letter) and that a new PREA PMR be issued for Study MT-12 (a Phase 3, double-blind, parallel-group, placebo-controlled study to evaluate safety, tolerability, and efficacy of

Odactra in children 5 through 11 years of age with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma). PeRC concurred with the Division's request for release of the Applicant from PMR Studies 1 and 2 and issuance of a new PREA PMR for evaluation of Odactra in children 5 through 11 years of age (Study MT-12).

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

Data submitted to the BLA demonstrate the benefit of Odactra for the treatment of HDM-induced allergic rhinitis with or without conjunctivitis in adolescents 12 through 17 years of age. Study P001 demonstrated a consistent treatment effect in the adolescent population and showed a statistically significant TCRS reduction compared to placebo during the efficacy assessment period. The duration of treatment effect after discontinuing Odactra has not been studied.

Most subjects undergoing treatment with Odactra report mild to moderate adverse reactions with low risk of serious reactions. One adolescent subject using Odactra experienced symptoms suggestive of a possible systemic allergic reaction related to the drug; however, the two concurrent symptoms resolved spontaneously within 15 minutes without rescue medication or medical intervention. One case of EoE was reported in an adolescent subject taking Odactra 12 SQ-HDM. The most common reactions were throat irritation/tickle, itching in the mouth, itching in the ear, tongue pain, stomach pain, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat swelling, nausea, tongue ulcer/sore on the tongue, and mouth ulcer/sore in the mouth, and diarrhea. Based on the submitted data, the risks of treatment with Odactra appear to be modest and adverse reactions tend to be self-limited. However, because of the small risk of systemic allergic reactions and local allergic reactions, patients should be prescribed auto-injectable epinephrine. In addition, while 1 case of EoE was noted to occur in the adolescent populations evaluated, EoE remains a known risk with sublingual AIT products. To mitigate this risk, product labeling (PI and MG) is used to communicate the potential for development of EoE.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 23 below summarizes the risk-benefit considerations for Odactra in adolescents 12 through 17 years of age.

Table 23. Summary of Risk-Benefit Analysis of Odactra in Adolescents 12 through 17 years of age

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Allergic rhinitis with or without conjunctivitis (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 developed nations (Schuler Iv and Montejo 2021). • AR/C can have a major impact on quality of life (QOL) and can cause significant impairment of daily function due to symptoms including decreased energy, productivity, and social functioning. AR/C is often associated with rhinosinusitis, sleep disturbances, and asthma (which typically develops after AR/C). • The total direct medical cost of allergic rhinitis is about $3.4 billion (medication and medical visits) (Meltzer and Bukstein 2011). • House dust mite-induced AR/C is a perennial and common disease affecting children and adolescents. Prevalence of HDM sensitivity in the U.S. is reported to be 30% among adolescents (10 to 19 years of age) and 28% in the general population (6 to 59 years of age) based on the NHANES survey, with age identified as a predictor of HDM sensitization (Arbes et al. 2005).	• AR/C is prevalent in the U.S. pediatric population. • AR/C impacts QOL which can lead to significant disruption in daily activities and function. • In a subset of patients, AR/C precedes and contributes to allergic asthma. • House dust mite-induced AR/C, a perennial allergic disease, commonly affects not only adults, but also children and adolescents in the U.S.
Unmet Medical Need	• Currently available treatment for HDM-induced AR/C includes allergen avoidance (which is difficult to achieve and sustain), pharmacologic therapy (which treats symptoms but not the underlying cause, has side effects, and can be cost-prohibitive), and SCIT with HDM extract (which causes a substantial burden on the individual due to: the level of discomfort associated with injections and local and systemic allergic reactions, the frequency of administration of the injections, the inconvenience of mandatory administration in a monitored healthcare setting with staff trained to treat systemic allergic reactions, and the risk of local and systemic allergic reactions). • No perennial sublingual immunotherapy (SLIT) product is licensed for use in the adolescent population in the U.S. for the treatment of house dust mite-induced AR/C.	• There is an unmet medical need for safe and effective treatments of house dust mite-induced AR/C. • SLIT is a non-invasive therapy and can be administered at home with proper instruction. • As SLIT can be conveniently administered at home with proper instruction, its availability may increase the use of immunotherapy to treat AR/C in adolescents. • Odactra may have a significant impact on overall QOL in this population.

Clinical Benefit	• Phase 3 Study P001 was a double blind, randomized, controlled, field efficacy and safety study evaluating Odactra for a treatment duration of 12 months in adolescents and adults 12 through 85 years of age. Although it is uncertain whether the treatment effect of Odactra is maintained beyond one or multiple courses of treatment, the post-hoc efficacy analysis in the adolescent population resulted in a relative treatment difference of the total combined rhinitis score for active treatment compared to placebo of -22.4% (95% CI: -42.6%, -8.1%).	• Although, the duration of effectiveness on therapy beyond one year and effectiveness after discontinuation of Odactra have not been characterized, a therapeutic benefit was seen over a treatment period of 12 months. • The totality of evidence for treatment with Odactra in adolescents 12 through 17 years of age supports its' effectiveness for treatment of HDM-induced AR/C and suggests clinically meaningful benefit. • SLIT may be disease-modifying.
Risk	• The most substantial risks of treatment with Odactra are life-threatening local (e.g., pharyngeal edema) and systemic allergic reactions including anaphylaxis. However, these events were rare (in Phase 3 studies in adolescents, these adverse events occurred at a rate of 0%). • The most common adverse reactions occurring in ≥ 10% of adolescent subjects in Studies P001 and MT-18 were throat irritation/tickle, itching in the mouth, itching in the ear, tongue pain, stomach pain, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat swelling, nausea, tongue ulcer/sore on the tongue, and mouth ulcer/sore in the mouth, and diarrhea. Most reactions were mild to moderate in severity and resolved relatively quickly and without sequelae. • In the clinical studies in adolescents of 1 year duration (P001 and TO-203-3-2), one adolescent subject taking Odactra (12 SQ-HDM) developed EoE.	• The risk of serious systemic allergic reaction with Odactra is low. • Local reactions are common, but generally mild to moderate and self-limited. • EoE is known to be associated with SLIT products. Further studies are needed to characterize the incidence of EoE in patients taking SLIT products. • The safety profile of Odactra in adolescents is acceptable and is justified by the clinical benefit.
Risk Management	• The Odactra PI includes a boxed warning about severe allergic reactions. • A prescription for injectable intramuscular epinephrine for emergency treatment of systemic allergic reactions should be given to any individual for whom Odactra is prescribed; patients should be educated on the technique of epinephrine auto-injector self-administration. • Patients should be warned about the potential risk of eosinophilic esophagitis and directed to contact a health care professional if any signs or symptoms of eosinophilic esophagitis occur.	• Use of product labeling (PI and MG) and the PVP plan to communicate the potential for serious local adverse reactions, severe systemic allergic reactions, and EoE and to educate patients or parents/ guardians on how to manage these risks could adequately mitigate the risk of local adverse reactions, systemic allergic reactions, and EoE.

11.2 Risk-Benefit Summary and Assessment

Allergic rhinitis with or without conjunctivitis (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 developed nations (Schuler Iv and Montejo 2021). Many children are diagnosed with AR/C by the age of 6 years, and 80% of all individuals with AR/C develop symptoms before 20 years of age (Meltzer et al. 2009). Among adolescents 13 to 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 to 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 QOL.

HDM 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 to 19 years of age) and 28% in the general population (6 to 59 years of age) based on the NHANES survey, with age identified as a predictor of HDM sensitization (Arbes et al. 2005), and HDM sensitization rates across 7 inner city metropolitan areas in the U.S. showing an average of 62% of inner-city children with 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). In addition, the disease may result in a lower QOL for patients (Meltzer et al. 2012), which, in the adolescent population, 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).

Currently available therapies for HDM-induced AR/C include allergen avoidance measures (hard to achieve and sustain), medications for symptomatic treatment (which provide symptomatic treatment only), and SCIT with HDM allergenic extract. SCIT is burdensome for several reasons: the level of discomfort associated with SCIT; the inconvenience of the frequency of administration of the injections; the inconvenience of delivery of SCIT (which is required to occur in a monitored healthcare setting due to the risk of systemic allergic reactions associated with SCIT); and the risks of occurrence of local and systemic allergic reactions associated with SCIT. Sublingual immunotherapy, however, can be taken at home after the first dose with appropriate patient counseling, decreasing the burden of clinic visits for patients.

Data submitted to the BLA demonstrate the benefit of Odactra for the treatment of HDM-induced AR/C in adolescents 12 through 17 years of age. Study P001 demonstrated a consistent treatment effect in the adolescent population and showed a statistically significant TCRS reduction compared to placebo during the efficacy assessment period. The duration of treatment effect after discontinuing Odactra has not been studied.

Most subjects undergoing treatment with Odactra report mild to moderate adverse reactions with low risk of serious reactions. One adolescent subject using Odactra experienced symptoms suggestive of a possible systemic allergic reaction related to the drug. One case of EoE was reported in an adolescent subject taking Odactra 12 SQ-HDM. The most common reactions were throat irritation/tickle, itching in the mouth,

itching in the ear, tongue pain, stomach pain, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat swelling, nausea, tongue ulcer/sore on the tongue, and mouth ulcer/sore in the mouth, and diarrhea. Based on the submitted data, the risks of treatment with Odactra appear to be modest and adverse reactions tend to be self-limited. However, because of the small risk of systemic allergic reactions and local allergic reactions, patients should be prescribed auto-injectable epinephrine. In addition, while 1 case of EoE was noted to occur in the adolescent populations evaluated, EoE remains a known risk with sublingual AIT products. To mitigate this risk, product labeling (PI and MG) is used to communicate the potential for development of EoE.

While the duration of treatment effect after discontinuation of Odactra has not been studied, the addition of Odactra as the first sublingual AIT product for treatment of perennial HDM allergy to the currently available treatments for HDM allergy provides another treatment option for adolescents 12 through 17 years of age with HDM-induced AR/C in the U.S. that is effective with an acceptable safety profile and that is possibly less burdensome than currently available treatment options. Given the clinical benefit associated with the consistent treatment effect and the modest risks of treatment with Odactra observed in Studies P001, MT-18, and TO-203-3-2, the overall risk-benefit assessment for Odactra is favorable for its intended use in the adolescent population.

11.3 Discussion of Regulatory Options

Although Study MT-18 had limitations (28 days in duration, lack of placebo comparator given the open-label study design, descriptive analyses), the safety data from this study and from Study TO-203-3-2 supplement the existing safety database for Odactra in the adolescent population (existing safety database for adolescents from Study P001). The safety and efficacy profile of Odactra was established in 1279 adults 18 through 65 years of age in 4 double-blind, placebo-controlled, randomized clinical studies. In addition, Odactra has been licensed in the U.S. for use in persons 18 through 65 years of age since 2017, and the safety of Odactra has been evaluated in post-marketing studies (these data are described in the currently approved PI for Odactra).

Overall, the safety data from Studies P001, MT-18 and TO-203-3-2 and the efficacy data from Study P001 are sufficient to support approval of Odactra 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 by skin testing to licensed HDM allergen extracts in adolescents 12 through 17 years of age; therefore, consideration of other regulatory options was not necessary.

11.4 Recommendations on Regulatory Actions

The data submitted to this supplemental BLA support licensure of Odactra in adolescents 12 through 17 years of age.

11.5 Labeling Review and Recommendations

CBER recommended, and the Applicant agreed to, several revisions to the PI intended to clarify and more clearly describe the clinical data in the adolescent population. Section 6 Adverse Reactions was revised to display safety data in the adolescent population from Study P001 and Study MT-18 separately from adult data from clinical

studies conducted in the adult population. Specific revisions to Section 6 resulted in inclusion of solicited adverse reaction data (for the first 28 days after initial administration of Odactra) and unsolicited adverse reaction data for the duration of the studies (as opposed to unsolicited adverse event data over 28 days) for the adolescent population from Study P001 and Study MT-18. The MG was revised to include adverse events in adolescents 12 through 17 years of age. Language in the PI and MG was adapted from adults only to include adults and adolescents (and their parents/guardians).

Since EoE is known risk associated with SLIT products, the PI lists EoE under Section 5 Warnings and Precautions. Although the occurrence of systemic allergic reactions including anaphylaxis observed in pre-licensure clinical studies was not common, treatment with Odactra may require use of epinephrine. For this reason, the PI includes a Black Box Warning and a MG, both of which emphasize the potential risk for severe allergic reactions and need for access to auto-injectable epinephrine.

The PI submitted by the Applicant was in the format required by FDA's Final Rule titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" to establish requirements for Pregnancy and Lactation Labeling.

11.6 Recommendations on Post-Marketing Actions

Additional post-marketing safety studies are not recommended. Routine pharmaco-vigilance measures are adequate.