

BLA Clinical Review Memorandum

Application Type	Original Biologics License Application
STN	125592
CBER Received Date	February 9, 2016
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Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
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Review Completion Date / Stamped Date	February 24, 2017
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Applicant	Merck Sharp & Dohme Corp.
Established Name	House Dust Mite (<i>Dermatophagoides pteronyssinus</i> and <i>Dermatophagoides farinae</i>) Allergen Extract
(Proposed) Trade Name	ODACTRA
Pharmacologic Class	Allergenic extract
Formulation(s), including Adjuvants, etc.	Tablet
Dosage Form(s) and Route(s) of Administration	Sublingual
Dosing Regimen	Once daily
Indication(s) and Intended Population(s)	Odactra is an allergen extract indicated as immunotherapy for house dust mite induced allergic rhinitis, with or without conjunctivitis, confirmed by <i>in vitro</i> testing for IgE antibodies to <i>Dermatophagoides pteronyssinus</i> and <i>Dermatophagoides farinae</i> 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

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GLOSSARY

AE	adverse event
ASaT	all subjects as treated
BLA	biologics license application
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CR	complete response
DCP	decentralized procedure
DIS	Division of Inspections and Surveillance
DMS	daily medication score
DSS	daily symptom score
DU	development unit
eCTD	electronic Common Technical Document
EEC	environmental exposure chamber
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
ES	Executive Summary
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FD&C	Federal Food, Drug, and Cosmetic Act
FEV1	forced expiratory volume in 1 second
HDM	house dust mite
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ICS	inhaled corticosteroid
IgE	immunoglobulin E
IgG	immunoglobulin G
IND	investigational new drug application
ISE	integrated summary of efficacy
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NME	new molecular entity
OBE	Office of Biostatistics and Epidemiology
OCOD	Office of Communication Outreach and Development (CBER)
OSE	Office of Surveillance and Epidemiology
PD	pharmacodynamics
PeRC	Pediatric Review Committee (CDER)
PI	package insert
PFT	pulmonary function test
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PREA	Pediatric Research Equity Act
SAE	serious adverse event
SCIT	sublingual immunotherapy
SLIT	sublingual immunotherapy

TCRS total combined rhinitis score
TCS total combined rhinoconjunctivitis score
TNSS total nasal symptom score
US United States
VAS Visual Analogue Scale

1. Executive Summary

Merck Sharp & Dohme Corporation submitted a Biologics License Application (BLA) to the Food and Drug Administration (FDA) for House Dust Mite Allergen Extract sublingual immunotherapy (SLIT) tablets (Odactra). Odactra is a freeze dried tablet that contains an extract of two species of cultivated house dust mites *Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae* (Der f) (b) (4). Odactra also contains fish gelatin, mannitol, and sodium hydroxide as inactive ingredients. The final dose developed for licensure is 12 SQ-HDM where SQ designates the method of standardization based on biological potency, major allergen content, and complexity of the allergen extract. The proposed indication is for the treatment of house dust mite (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 house dust mite allergen extracts. The Applicant seeks licensure of Odactra in persons 18 through 65 years of age.

The Applicant submitted data from 8 clinical studies to the BLA. The demonstration of efficacy for U.S. licensure of Odactra was based on 3 of these 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 allergic rhinitis with or without conjunctivitis and with or without asthma when exposed to house dust and were sensitized to *Der far* and/or *Der pte* as determined by house dust mite specific IgE and skin prick test response to *Der far* and/or *Der pte*. 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 allergic rhinitis, with or without conjunctivitis.

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 house dust mite SLIT tablet (Odactra) in adult and adolescent subjects 12 years of age and older (N=1482) with house dust mite-induced allergic rhinitis with or without conjunctivitis, 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 allergic rhinitis/rhinoconjunctivitis. The efficacy of Odactra was assessed through self-reporting of symptoms and medication use. Based on these self-assessments, the Total Combined Rhinitis Score (TCRS), daily symptom scores (DSS) and daily medication scores (DMS) for rhinoconjunctivitis were calculated. 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 Total

Combined Rhinitis Score (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 $\leq -15\%$ for the point estimate with an upper bound of the 95% confidence interval (CI) $\leq -10\%$ 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%). Since the number of adolescents 12 through 17 years of age included in study P001 was small (N=95), the data provided in this BLA do not establish effectiveness in this population.

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 house dust mite sublingual immunotherapy tablet in adults ages 18 to 65 years with house dust mite-induced allergic rhinitis/rhinoconjunctivitis 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 total combined rhinitis score (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 total combined rhinitis score (TCRS) during the last 8 weeks of treatment based on the full analysis set (FAS) was -18.1% (95%CI, -27.6% , -7.7%).

Study P003 was a Phase 2 randomized, double-blind, placebo-controlled, parallel-assignment, study. The primary objective of the study was to evaluate the safety and efficacy of Odactra compared to placebo in treatment of HDM-induced rhinitis following challenge in an Environmental Exposure Chamber (EEC) in subjects with house dust induced allergic rhinitis/rhinoconjunctivitis 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 *Der far* whole bodies, *Der pter* 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 total nasal symptom scores (TNSS) between treatment and placebo group during the chamber session at Week 24. No pre-specified criteria for success were defined. The primary efficacy analysis (the TNSS) in the EEC at Week 24 showed that the treatment difference relative to placebo was -48.6% (95% CI: -60.2% , -35.3%) in the 12 SQ-HDM group.

Safety

In Study P001, the safety analysis was based on 1482 participants who received at least 1 dose of 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 participants were provided side effect report cards in which they recorded the occurrence of solicited adverse reactions daily during the first 28 days of treatment. The most common solicited adverse reactions reported in $\geq 10\%$ 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 $\geq 1\%$ 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 eosinophilic esophagitis was diagnosed in an Odactra recipient on Day 204 of treatment confirmed by biopsy which resolved with treatment. No cases of confirmed eosinophilic esophagitis 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 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 ($\geq 1.0\%$) 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 DU, 727 received Odactra 6 DU, and 1793 received placebo. Rates of deaths, SAEs, systemic allergic reactions, and eosinophilic esophagitis were less than 1% for each of these outcomes in Odactra recipients. Across 8 clinical studies conducted with different doses of Odactra, eosinophilic esophagitis 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 this age group at this time.

Post-marketing Commitment Study

In addition to routine pharmacovigilance, the Applicant will conduct one postmarketing study in order to better characterize the safety profile of Odactra in the post-licensure setting. The Applicant will conduct an electronic medical records study that will include assessment of multiple adverse outcomes, including the risk of serious allergic reactions and eosinophilic esophagitis in 10,000 patients over 5 years.

Pediatric Assessment

According to the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), this application was required to contain an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups unless the requirement is waived, deferred, or inapplicable. The Applicant submitted a pediatric plan on February 9, 2016, with a request for a partial waiver from the requirements of PREA for children less than 5 years of age and a deferral for studies in children 5 through 17 years of age. The pediatric study requirement in children less than 5 years of age for the proposed indication was waived since necessary studies are impossible or highly impracticable because the number of children younger than 5 years of age with allergic rhinitis/rhinoconjunctivitis who have been diagnostically confirmed with sensitivity to house dust mite is too small (Federal Food, Drug, and Cosmetic Act Section 505B (a)(4)(B)(i)). The pediatric study requirement in children 5 through 17 years of age for the proposed indication was deferred because the drug or biological product is ready for approval in adults before pediatric studies are complete (Federal Food, Drug, and Cosmetic Act Section 505B(a)(3)(A)(i)). Two Phase 3 pediatric studies (a field efficacy study with a design similar to the studies submitted to this BLA; and a study to characterize safety during the first 28 days of use) will be conducted to assess the product in children 5 through 17 years of age.

Risk-Benefit Assessment

The data submitted to this BLA support approval of Odactra for the treatment of house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis in persons 18 through 65 years of age with confirmed HDM allergy. Two field efficacy studies in North American and European populations demonstrated a decrease in allergic symptoms and medication use when Odactra is administered daily for 52 weeks. Study P003, an EEC study, supported these findings and revealed a large decrease in nasal symptom scores as early as 24 weeks after initiation of treatment.

Based on data from 1279 adults 12 through 65 years of age who received at least one dose of Odactra, Odactra is associated with mild to moderate throat irritation/tickle, itching in the mouth, itching in the ear, swelling of the uvula/back of the mouth, swelling of the lips, and swelling of the tongue, throat swelling, nausea, tongue pain, tongue ulcer/sore on the tongue, and stomach pain during the first 28 days of treatment. The estimated rates of outcomes such as anaphylaxis, eosinophilic esophagitis and symptoms requiring use of epinephrine were less than 1% for each of these outcomes.

Taken together, these data support a favorable risk-benefit assessment of Odactra for use in persons 18 through 65 years of age with confirmed HDM induced allergic rhinitis with or without conjunctivitis.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Review of demographic data for subjects in the pivotal study P001 revealed a balanced distribution between the two study arms with overall percentages of 59% female, 76.3% Caucasian, 10.5% Black or African American, 6.7% Asian, and 8.8% Hispanic, and <1% American Indian. Subjects in study P001 were enrolled from North America (US and Canada) and generally reflect the demographics of the US (8). Caucasian (N=908) subjects achieved a percent treatment difference relative to placebo (the average TCRS in the last 8 weeks of treatment) of -22.2%. Non-Caucasian subjects (N=278) achieved an average TCRS of -14.4. Caucasian subjects appear to experience improved symptom control, however, the population size of Non-Caucasian subjects is much smaller and subgroup analysis was not powered to demonstrate efficacy. A post hoc analysis suggests adolescent subjects may experience more improvement in rhinitis symptoms with Odactra than adults. The pool of adults older than 65 was too small to reach conclusions regarding safety and effectiveness in this age group. The percent treatment difference relative to placebo (the average TCRS in the last 8 weeks of treatment) was -22.2% female versus -16.3% male. Female subjects may experience improved symptom control compared to males, however this subgroup analysis was not powered to show differences in efficacy.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Allergic rhinitis is an upper respiratory condition triggered by an IgE-mediated reaction to environmental aeroallergens. Allergic rhinitis is a medical condition that can affect quality of life including work or school performance and lead to or affect other clinical disorders such as asthma, rhinosinusitis, and sleep disorders (3). Quality of life was assessed with a standardized questionnaire in patients with perennial allergic rhinitis compared to healthy individuals in a small study (12). A higher score (out of 100) indicated a better quality of life. Patients with perennial allergic rhinitis scored lower than healthy individuals in many aspects including energy (54.55 versus 71.84), social functioning (73.09 versus 91.3), and physical limitations (60.59 versus 92.03). According to the CDC, 8% of US adults (ages 18 and older) have been diagnosed with "hay fever" or allergic rhinitis; allergic rhinitis affects about 19 million persons in the US (5).

House dust mites are eight-legged, sightless arthropods that live on host skin cells and other debris. These arthropods live in upholstery, carpets 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 (3). House dust mites, particularly two species, *Dermatophagoides farinae* and *Dermatophagoides*

pteronysinus, are ubiquitous in human habitats and are a significant factor underlying perennial allergic rhinitis (4).

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

Treatment for house dust mite induced allergic rhinitis with or without conjunctivitis includes oral antihistamines such as Zyrtec, Benadryl, and Allegra, intranasal antihistamines (Astellin), intranasal anticholinergics (Atrovent Nasal Spray), intranasal steroids (Flonase, Nasacort, QNASL) or subcutaneous immunotherapy (SCIT) with house dust mite allergen extract. Antihistamines or steroid medications treat symptoms but do not modify the course of the disease. Allergen immunotherapy with SCIT has generated data showing that this approach may modify the disease course and decrease medication use (2). There is no U.S.-licensed sublingual immunotherapy for treatment of house dust mite allergic disease.

2.3 Safety and Efficacy of Pharmacologically Related Products

Three sublingual allergen immunotherapy (SLIT) products are approved in the U.S. Oralair© is an extract composed of five grass species for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis. It is approved for use in persons 10 through 65 years of age. Grastek© is an extract composed of Timothy grass pollen for the treatment of Timothy grass (or cross-reactive grass) pollen-induced allergic rhinitis with or without conjunctivitis. Grastek is approved for use in persons 5 through 65 years of age. Ragwitek© is an extract composed of short ragweed pollen for the treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis in persons 18 through 65 years of age.

The most common adverse reactions reported in $\geq 5\%$ of subjects from these products include oral pruritus, throat irritation, ear pruritus, and mouth edema in adult subjects. A small number of subjects experienced systemic reactions for which epinephrine administration was required. Four of these occurred during the Grastek studies and 1 during the Ragwitek study in a safety population of over 1000 adults. Eosinophilic esophagitis (EoE) has been reported with the use of grass pollen SLIT products (7). The package inserts of Grastek, Ragwitek, and Oralair include information about EoE under Contraindications, Warnings and Precautions, and Adverse Reactions. In the US population, the prevalence of EoE is estimated at 56.7/100,000 persons (8).

For additional details regarding the safety and efficacy data to support each of the SLIT products listed above, please refer to the package insert for each of these products, which can be retrieved at:

<http://www.fda.gov/BiologicsBloodVaccines/Allergenics/ucm391505.htm>.

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

The house dust mite sublingual tablet was approved by an European Medicines Agency (EMA) decentralized procedure (DCP) 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 house dust mite allergic rhinitis and allergic asthma not well

controlled by inhaled corticosteroids and associated with mild to severe house dust mite allergic rhinitis in adults 18 through 65 years of age. Acarizax was approved for the indication of allergic asthma not well controlled by inhaled corticosteroids based on one Phase 3 study (P014/MT-06) with supportive evidence from a Phase 2 study. The Phase 3 trial included 834 adults with house dust mite allergic asthma not well-controlled by daily use of inhaled corticosteroid (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 house dust mite allergic asthma controlled by inhaled corticosteroids (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.

Clinical Reviewer comment: SQ-HDM is an analogous to DU. These units refer to a method of standardization of biological potency, major allergen content and complexity of the allergen extract.

The Applicant, Merck Sharp & Dohme Corp., is seeking an indication for treatment of allergic rhinitis with or without conjunctivitis in the US. (b) (4)

. The Phase 3 trial described above was submitted to the BLA to support the safety of Odactra.

The tablet was approved in September 2015 for use in Japan under the name Miticure for the treatment of allergic rhinitis caused by house dust mites in adults and adolescents 12 years of age and older.

Merck Sharp & Dohme Corporation submitted a safety update report (SUR) to CBER summarizing spontaneous and non-interventional postmarketing reports. The SUR covered the period of September 23, 2015 to April 9, 2016. The purpose of the SUR was to inform CBER of the updated safety profile of the house dust mite SLIT product after licensure in the EU and Japan. This information was not available at the time of the initial BLA submission. The reports are generated from the global Pharmacovigilance database of the Applicant's collaborator, ALK-Abello A/S (Denmark), to document all adverse event reports received for the product.

A total of 149 reports were submitted with 409 adverse events, 30 of which were serious adverse events. The reports are from 4 countries; Germany (N = 111), Japan (N=33), Denmark (N=4), and Austria (N=1). There were no reported deaths. No use of epinephrine or anaphylactic shock was reported. No cases of eosinophilic esophagitis were reported. There were no cases of worsening of asthma symptoms reported.

The serious adverse events included 2 events each of lip swelling, mouth swelling, and swollen tongue. Each of the remaining 24 events was reported once. Those were as

follows: abdominal pain upper, anaphylactic reaction, angioedema, chronic sinusitis, dysphagia, dyspnea, epiglottic edema, erythema, eyelid edema, facial bones fracture, hyperplasia, hypertensive crisis, laryngeal edema, nasal septum deviation, palatal swelling, paresthesia, oral paresthesia, respiratory distress, sinusitis, swelling face, throat irritation, tongue edema, tonsillar hypertrophy, and vomiting.

The Applicant evaluated the SUR for systemic allergic reactions including anaphylactic reactions and identified 2 reports: 1 anaphylactic reaction and 1 case of angioedema. In the first case, the subject experienced moderate anaphylactic symptoms within 10 minutes after the first intake of the product and was treated with antihistamines, intravenous steroids and sodium chloride solution. The subject was reported as recovered. In the second case, a patient developed angioedema and vocal changes after the 6th dose. It was not reported if the subject required medication for treatment. Therapy was discontinued. The Applicant also searched the SUR for reports of local allergic reactions with potential to cause airway compromise. Three reports were identified. The first was reported above; the subject who developed angioedema. One patient experienced laryngeal edema 20 minutes after taking the 6th dose and was treated with antihistamines, steroids, and inhaled β 2-agonist. In third report a patient experienced tongue edema 1 hour after taking the 9th dose of the product. She was treated with intravenous steroids and an antihistamine and was reported as recovered.

Clinical reviewer comment: The number of case reports provided from the post-marketing pharmacovigilance database is small and reported passively, therefore clinical interpretation is limited. The overall safety findings are similar to the safety data submitted to the BLA. These results indicate that no cases of anaphylactic shock, epinephrine use, or cases of eosinophilic esophagitis were reported.

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

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

- March 2014: Type B, End of Phase 2 Meeting
 - CBER agreed that efficacy demonstrated from studies P012, P014, P15, and P003 and safety data from P011, P012, P013, P014, P015, P003, and P008 were adequate to support the 12 DU dose in a proposed Phase 3 study (P001) to evaluate house dust mite sensitive subjects with allergic rhinitis.
 - Data from the EEC study, P003, was not adequate to support efficacy for the purpose of licensure without an additional Phase 3 study (P001).
 - The primary efficacy endpoint for the TCRS in P001 should set the upper bound of the 95% CI as -10% for the treatment difference relative to placebo to define study success.
 - Safety and tolerability data submitted for the meeting supported the inclusion of subjects \geq 12 years of age in P001 with a total planned accrual of 1500 subjects.
 - The Applicant agreed to propose additional pediatric studies for subjects ages 5 through 17 years of age.

- September 2015: Type B, pre-BLA meeting

- CBER agreed that the Applicant could proceed with a BLA submission for adults ages 18 to 65 years of age for the indication of dust mite induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or in vitro testing for *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* IgE antibodies.
- Study P001 did not meet the pre-specified endpoint of $\geq -10\%$ upper bound of the 95% CI for the treatment difference relative to placebo. The upper bound was -9.7% . CBER agreed to review the data in the BLA submission.
- Pooled safety analysis including 1456 subjects who received at least one dose of Odactra 12DU from studies P001, P003, P012, P14, and P015 was acceptable for the submission.
- Adverse events for Study P001, which utilized a side effect report card, would be analyzed separately from studies that did not solicit adverse events. The Applicant noted that the rates of adverse events varied across trials due to the difference in solicitation methods.
- CBER requested individual case report forms for subjects who were diagnosed with or evaluated for eosinophilic esophagitis. The applicant clarified that investigators were informed to consider and report any potential cases of eosinophilic esophagitis. The Applicant agreed to develop an approach to identify any potential cases of eosinophilic esophagitis in the safety database.
- Financial disclosure forms for studies P001, P008, P003, and P015 will be included in the BLA.
- The Applicant was directed to submit a separate meeting request to discuss (b) (4) (b) (4).

Clinical reviewer comment: The Applicant has not submitted a meeting request to discuss a (b) (4)

Post-submission

A total of 64 amendments were submitted. Amendments 6, 7, 9, 10, 18, 24, 30, 32, 48, 57, 59, and 61 were relevant to clinical review. These amendments satisfactorily addressed all clinical information requests sent during the review period. A summary of each amendment is below.

- Amendment 6 Efficacy Information Amendment: Request for post hoc analysis of the primary endpoint of Total Combined Rhinitis Score (TCRS) during the last 8 weeks of treatment from subjects ages 12 to < 18 years, 18 to 65 years, and > 65 years in study P001.
- Amendment 7 Efficacy Information Amendment: Request to revise Integrated Summary of Safety to include all studies conducted using the 12DU dose of Odactra.
- Amendment 9 Efficacy Information Amendment: Request to revise Integrated Summary of Safety and Integrated Summary of Efficacy to include all studies conducted using the 12DU dose of Odactra analyzed by subgroup.
- Amendment 10 Efficacy Information Amendment: Request to provide the 95% CI the difference in the TCRS of the treatment relative to placebo for the subgroups referred to in amendment 6.

- Amendment 18 Efficacy Information Amendment: Request to clarify the evaluation for potential cases of eosinophilic esophagitis.
- Amendment 24 Efficacy Information Amendment: Request for data pertaining to pregnancies that occurred during conduct of studies P012, P014, P001, P015 and P003. Request for additional post hoc analyses of P001 study results including sensitivity analysis by age subgroup.
- Amendment 30 Efficacy Information Amendment: Request for additional post hoc analysis of P001 study results. Request to provide rationale for the claim that the product is not systemically absorbed. Request to provide rationale for seeking licensure in adults 18 to 65 years of age based on pivotal study P001 which includes subjects 12 years of age and older.
- Amendment 32 Efficacy Information Amendment: Request to provide the percent treatment difference relative to placebo with the 95% confidence interval for the
- key secondary efficacy endpoints using the FAS-MI population in study P015
- Amendment 48 Efficacy Information Amendment: Request for clarification regarding safety analysis conducted in studies P015, P014, and P012
- Amendment 57 Efficacy Information Amendment: Request to clarify pharmacovigilance plan for a post market claims-based study and a post-market electronic health record
- Amendment 59 Efficacy Information Amendment: Request to clarify Financial Disclosures from covered studies
- Amendment 61 Efficacy Information Amendment: Request to clarify postmarketing Safety Update Report (SUR)

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized to accommodate the conduct of a complete clinical review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The Bioresearch Monitoring Discipline (BiMo) inspections were completed at one domestic, and one foreign clinical study site conducting study P05607/001-00. The reviewer, Mr. King, stated that a review of the Establishment Inspection Report did not reveal problems that would impact the data submitted to the application. Please see Mr. King's full review for further information.

3.3 Financial Disclosures

Table 1. Financial Disclosures for 4 Covered Studies Submitted as the Basis for Licensure

Covered clinical study (name and/or number): P001, P003, P008, P015		
Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>895</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u> (of those identified via efforts at due diligence)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 895

Clinical reviewer note: The Applicant did not include financial disclosure information for the other clinical studies because these studies are not considered covered clinical studies per 21CFR54.2. These studies are either phase 1 studies (MT-01, MT-03) or studies performed to evaluate allergic asthma as an endpoint (MT-02, MT-04). Per 21CFR54.2 Financial Disclosure by Clinical Investigators, studies that the FDA relies on to establish that the product is effective or a study in which a single investigator makes a significant contribution to the demonstration of safety are considered covered clinical studies (P008, P003, P001, P015). This approach was discussed and agreed upon during the pre-BLA meeting Sept. 8, 2015. The Applicant reports due diligence in their effort to identify and contact all investigators from each study.

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

4.1 Chemistry, Manufacturing, and Controls

A complete review of the chemistry, manufacturing, and controls (CMC) data submitted to the BLA was conducted by Dr. Khurana.

Allergen potency in Odactra is described by the development unit (DU). The package insert will state allergen potency as SQ-HDM. DU is equivalent to SQ-HDM. The potency of the tablet is determined using the (b) (4)

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.

Please see Dr. Khurana's review for further details.

4.2 Assay Validation

N/A

4.3 Nonclinical Pharmacology/Toxicology

The Applicant submitted 8 toxicology studies to the BLA; 2 general toxicology studies, 1 reproductive study, and 5 genotoxicology studies. These studies were reviewed by Dr. Al-Humadi

The first general toxicology study was performed in mice. Mice received daily sublingual administration of house dust mite extract over 26 weeks in doses of 0.9, 3.5, or 14 DU. The doses were well-tolerated. The second general toxicology study was performed in

rabbits. This was an oral mucosal irritation study conducted during a 7 day period. Rabbits were administered repeated sublingual doses of 12 or 24 DU. The toxicology reviewer notes no significant safety issue was identified.

The reproductive and developmental toxicity study was performed in mice that were administered 12.5, 25, or 50 DU of Odactra subcutaneously. These doses were given daily during the gestation period (Days 6 through 17). No effects were observed in dams. An increased incidence of fused sternbrae was observed in the fetuses whose dams received 50 DU compared to controls. No data was submitted regarding the incidence of fused sternbrae for 12.5 or 25 DU of Odactra. Fused sternbrae occurred in 2/105 (1.9%) of fetuses in the placebo group and 4/104 (3.9%) of fetuses in the Odactra group. According to the toxicology review by Dr. Al-Humadi, the upper limit of the historical data for this anomaly at the test facility is 2/140 (1.4%) fetuses based on data from 4 studies conducted between 2003 and 2013.

Clinical reviewer comment: The toxicology reviewer raised the question as to whether this finding should be described in section 8.1 of the Prescribing Information. The BLA review committee discussed the finding. No other embryonic abnormality was observed that would indicate a dysfunction in skeletal development. The dose response relationship between Odactra and the incidence of fused sternbrae could not be evaluated because data from the low- and mid-dose groups were not available. The rates from the historical data were not derived based on robust data with narrow confidence intervals. A clear dose-response relationship was not demonstrated. In addition, clinical experience with allergen extracts administered subcutaneously for immunotherapy in pregnant women supports the safety of this product (2). Based on these points, the review committee concluded that the isolated finding of fused sternbrae in a single murine study did not represent a potential safety signal and thus, would not be included in Section 8.1 of the package insert.

Five genotoxicology studies included mutation analysis in *Salmonella typhimurium*, *Escherichia coli*, cultured human peripheral blood lymphocytes, and cells from rat liver, stomach, and bone marrow. One study reported treatment with (b) (4) of house dust mite extract induced structural chromosome aberrations *in vitro* in cultured human peripheral blood lymphocytes at a concentration of 2250 µg/mL after 20 hours of exposure without a liver metabolic activation system (The concentration of Odactra 12 DU will have (b) (4) of extract by (b) (4)). The four other genotoxicology studies did not reveal any evidence of chromosomal aberration or mutation

Clinical Reviewer comment: The BLA review committee discussed the finding of HDM induced structural chromosome aberrations. The finding was isolated to a single study and was not consistent across the 4 other genotoxicology studies. In addition, the test substance used was not the same as Odactra. There is no known association between licensed HDM allergenic extracts which have been administered subcutaneously to humans and cancer. Based on these considerations, the review committee determined that these findings are unlikely to be of clinical relevance. Section 13.1 of the package insert was labeled accordingly.

Please see the toxicology review by Dr. Al-Humadi for further details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action of allergen immunotherapy has not been established.

Clinical Reviewer comment: Allergen immunotherapy is intended to train the immune system to suppress allergic symptoms. Although the mechanism of action has not been established, possible mechanisms include the action of regulatory T cells that promote tolerance to environmental allergens and suppresses allergic inflammation by secreting inhibitory cytokines, a change from a type 2 T helper cell (associated with allergic inflammation) to a type 1 T helper cell cytokine profile, and allergen-specific immunoglobulin G₄ (IgG₄) production which may block the action of IgE-dependent allergic inflammation (2).

4.5 Statistical

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

Please see Dr. Zhong Gao's review for further details.

4.6 Pharmacovigilance

A complete review of the pharmacovigilance plan (PVP) was conducted by Dr. Rohan.

In addition to routine pharmacovigilance, the Applicant will conduct one postmarketing phase 4 study entitled: "Post-Market Electronic Health Records (EHR) Based Study of Serious Allergic Reactions and Eosinophilic Esophagitis in Marketed Use of Odactra in the United States." This study is based on electronic medical records from a large US integrated health system and will aim to accrue 10,000 patients over a 5 year period. Annual accrual rates will be assessed at the end of each year and compared against projected rates. This study will assess the first in-office exposure to Odactra and all subsequent exposures and outcomes (i.e. serious allergic reactions and eosinophilic esophagitis).

Clinical reviewer comment: The general design of this study was discussed and agreed upon with the Applicant.

Although the rates of eosinophilic esophagitis in the pre-licensure clinical studies were low, the true frequency of eosinophilic esophagitis following treatment with Odactra is unknown because the size of the pre-licensure safety database was too small to accurately characterize the rate. In addition, studies submitted pre-licensure such as P001 did not include active surveillance specifically for the occurrence of eosinophilic esophagitis. Another limitation of the pre-licensure safety database is that it did not provide data on the rate of eosinophilic esophagitis when Odactra is administered for more than 1 year (i.e., 3 to 5 years). Since house dust mite is a perennial allergen, it is likely that patients will take Odactra year round. This feature distinguishes Odactra from other approved SLIT products which treat patients with seasonal allergens. Obtaining post-marketing safety data to better estimate the rate of eosinophilic esophagitis would be useful because it can inform the public regarding the risk of eosinophilic esophagitis

with longer duration of use. Another reason for the postmarketing study is to better estimate the risk of serious or systemic allergic reactions prompting epinephrine use. This information would inform need for epinephrine following treatment with Odactra.

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

5.1 Review Strategy

The BLA submission included 8 studies (listed in Section 5.3). Three of these studies were completed under IND 15015; P001, P003, and P008. Trials not completed under IND were conducted by ALK-Abello A/S in Europe. These include P011, P012, P013, P014, and P015). Three of these studies were reviewed to support efficacy, the Phase 3 North American field study (P001), the Phase 3 European field study (P015), and the Phase 2 environmental chamber study (P003). Trial P008 is not included in the efficacy review because it is a Phase 1 dose-finding study.

Four studies were submitted to support safety; P011, P013, P012, P014 in addition to P001, P003 and P015. The studies considered pivotal to support the safety of the product were: P001, P015, P003 and P014 although all 8 studies were reviewed.

Study P014, a Phase 3 study done in European asthmatic subjects will be described briefly to evaluate safety in allergic subjects with mild to moderate asthma taking Odactra who often have concomitant allergic rhinitis.

Clinical reviewer comment: Studies not conducted under IND are accepted based on certain conditions outlined by the FDA. Per 21CFR 312.120, these non-IND studies were determined to be well-designed, well-conducted studies that were conducted in accordance with Good Clinical Practice (GCP).

The following subheadings will be deleted from the review for the following reasons:

- Section 5.4 Consultations because no consultations outside of the review division were necessary. An advisory committee meeting was not held because the discussion in a previous Allergenic Products Advisory Committee (APAC) regarding licensure of SLIT products was adequate to inform the review and evaluation of the submitted BLA.
- Section 4.4.2 and 4.4.3 because Pharmacodynamic and Pharmacokinetic studies were not required for this product.
- Section 8.5.3 Product-Demographic Interactions, Section 8.5.4 Product Disease interactions, Section 8.5.8 Immunogenicity, Section 8.5.9 Person to Person Transmission were not applicable to this product.

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

The following files served as the basis for the clinical review of STN 125592/0:

STN 125592 Sections:

- Section 1.2 Cover Letters
- Section 1.3.4 Financial Certification and Disclosures
- Section 1.9 Pediatric Administrative Information
- Section 1.14 Labeling
- Section 5 Clinical Study Reports

Amendments to this initial submission were reviewed as indicated in Section 2.5.

5.3 Table of Studies/Clinical Trials

Study	Design (Length of Study)	Subjects per treatment arm	Age (years)	Countries (number of sites)
P008 NCT01678807	Randomized, placebo controlled, double-blind Phase 1 (28 days)	6DU (65), 12DU (65), placebo (65)	12-17	US (19)
P011/MT-01	Randomized, double-blind, placebo-controlled Phase 1 (28 days)	1DU (9), 2DU (9), 4DU (9), 8DU (9), 16DU (9), 32DU (9), placebo (17)	18-65	Denmark (1)
P013/MT-03	Randomized, double-blind, placebo-controlled Phase 1 (28 days)	0.5DU (9), 1DU (9), 3DU (9), 6DU (9), 9DU (9), 12DU (9), placebo (18)	5-14	Spain (4)
P003 NCT01644617	Randomized, double-blind placebo-controlled Phase 2 (26 weeks)	6DU (42), 12DU (41), placebo (41)	≥ 18	Austria (1)
P012/MT-02	Randomized, double-blind, placebo-controlled Phase 2/3 (12 months)	1DU (146), 3DU (159), 6DU (156), placebo (143)	≥ 14	EU (81)
P001 NCT01700192	Randomized, double-blind, placebo-controlled Phase 3 (12 months)	12DU (743), placebo (738)	12-85	North America (182)
P015/MT-06, NCT01454544	Randomized, double-blind, placebo-controlled Phase 3 (12 months)	6DU (336), 12DU (318), placebo (338)	18-65	EU (100)
P014/MT-04	Randomized, double-blind, placebo-controlled Phase 3 (13-18 months)	6DU (275), 12DU (282), placebo (277)	≥18	EU (109)

DU: development unit, which is equivalent to standardized quality house dust mite (SQ-HDM)
EU: European Union

5.4 Literature Reviewed

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: Protocol P001, NCT01700192

A one-year randomized, double-blind, placebo-controlled, parallel assignment Phase 3 trial evaluating the efficacy and safety of the house dust mite sublingual allergen immunotherapy tablet (Odactra) in children and adult subjects with house dust mite-induced allergic rhinitis/rhinoconjunctivitis with or without asthma.

6.1.1 Objectives (Primary, Secondary)

The primary objective of protocol P001 was to evaluate the efficacy of Odactra compared to placebo in the treatment of HDM-induced allergic rhinitis/rhinoconjunctivitis based on the average total combined rhinitis score (TCRS) during the last 8 weeks of treatment and to evaluate the safety and tolerability of Odactra administered sublingually once daily.

Secondary objectives include the comparison of the average rhinitis daily symptom score (DSS), average rhinitis daily medication score (DMS), average total combined rhinoconjunctivitis score (TCS), and average allergic rhinitis/rhinoconjunctivitis symptoms assessed by Visual Analogue Scale (VAS) during the last 8 weeks of treatment.

6.1.2 Design Overview

Study P001 was a Phase 3, one year double-blind, placebo-controlled, randomized, multicenter trial was conducted at 182 sites. Of these sites, 157 were located in the United States (US) and 25 in Canada. The study population consisted of 1482 subjects 12 years of age and older with HDM-induced allergic rhinitis/rhinoconjunctivitis with or without asthma. Subjects were randomized in a 1:1 ratio (741 subjects per cohort) to receive treatment or placebo.

Subjects were treated with one 12 DU sublingual tablet of Odactra or placebo each day for 52 weeks. A run-in period of up to 6 weeks was performed first. During the run-in period, subjects discontinued their allergy medications and recorded their symptoms in an electronic diary (e-diary). Subjects were eligible for randomization when they met the entry criterion of a documented average rhinitis daily symptom score of at least 6, or a score of at least 5 with 1 symptom being severe, on 5 of 7 consecutive calendar days during the run-in period. At selected sites, subjects were not required to perform run-in symptom scoring, rather historical information from prior HDM chamber challenge testing was used as a qualifying symptomatic entry criterion. The minimum induction period was 6 months (maximum 10 months) before treatment effects were measured. Including the 8-week efficacy assessment period, subjects were on treatment for a minimum of approximately 8 months (and maximum of approximately 12 months).

Efficacy assessments were performed during the last 8 weeks of treatment and at a time when seasonal allergens would not interfere with the allergic rhinoconjunctivitis symptom assessment which was based on symptom and medication usage. All subjects could restart their symptomatic allergy medications following the establishment of symptom score eligibility during the run-in period, and subjects were provided with rescue medications for their allergy symptoms during the last 12 weeks of the trial.

Symptom scores included 4 rhinitis (runny nose, stuffy nose, sneezing, itchy nose) and 2 conjunctivitis (itchy eyes, and watery eyes), were recorded daily in the morning during the run-in period and from Visit 9 through Visit 11 on a scale of 0 (no symptoms) to 3 (severe symptoms). Asthma daily symptom scores were also reported (cough, wheeze, and chest tightness/shortness of breath, scored from 0 to 3 for a total of 9), but were not part of the scoring system for primary endpoint.

Table 2. Symptom scores based on severity for Study P001

0 = no symptoms	No sign/symptom evident
1 = mild symptoms	Sign/symptom is clearly present but minimal awareness; easily tolerated
2 = moderate symptoms	Definite awareness of sign/symptom, which is bothersome, but tolerable
3 = severe symptoms	Sign/symptom is hard to tolerate; may cause interference with activities of daily living and/or sleeping

Source: Adapted from STN125592/0; Clinical Study Report P001

Medication scores were tabulated as shown in the chart below.

Table 3. Medication scores for Study P001

Medication	Dosing Instructions	Score/Dose Unit	Maximum Daily Score
Rhinitis Daily Medication Score (Rhinitis DMS)			
Loratadine 10mg tablet	1 tablet daily	4	4
Mometasone 50µg/ dose nasal spray	2 sprays per nostril daily	2	8
Conjunctivitis Daily Medication Score (Conjunctivitis DMS)			
Loratadine 10mg tablet	1 tablet daily	1	2
Olopatadine 0.1% eye drops	1 drop in each eye twice a day	1.5	6

Source: Adapted from STN125592/0; Clinical Study Report P001

6.1.3 Population

Adolescents and adults 12 years of age and older participated in this study. 1482 subjects with HDM-induced allergic rhinitis/rhinoconjunctivitis with or without asthma were randomized in a 1:1 ratio (741 subjects per cohort) to receive treatment or placebo.

Subjects had a clinical history of HDM-induced allergic rhinitis or rhinoconjunctivitis of at least one year in duration. As part of the entry criteria, subjects had a positive skin prick test (SPT) of least 5 mm larger than the saline control after 15 to 20 minutes) to *D. pteronyssinus* (b) (4) and/or *D. farinae* (b) (4) and specific immunoglobulin E (IgE) against *D. pteronyssinus* and/or *D. farinae* of at least 0.7 kU/L. Subjects who had asthma were included. Asthmatic subjects had 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 β 2 agonists and 12-hour washout of long-acting beta2 agonists).

Females of childbearing potential had a negative urine pregnancy testing and agreed to remain abstinent or use an acceptable method of birth control as defined in the study protocol.

Inclusion criteria:

1. Be \geq 12 years of age on the day of signing informed consent.
2. Have 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 have received anti-allergy treatment during the previous year before the Screening Visit.

3. 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)) at the Screening Visit.
4. 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).
5. 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. A subject receiving anti-allergy medication is required to washout of their medication before and during the Run-in period of the trial until the required symptom threshold is met.
6. 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).
7. Have a negative urine pregnancy test at Screening, Run-in, and Randomization Visits (female subjects of childbearing potential). A female subject who is of reproductive potential agrees to remain abstinent or use (or have their partner use) an acceptable method of birth control within the projected duration of the trial. Acceptable methods of birth control are: intrauterine device, hormonal contraception, diaphragm with spermicide, contraceptive sponge, condom, vasectomy, as per local regulations or guidelines.
8. A female subject who is not of reproductive potential is eligible without requiring the use of contraception. A female subject who is not of reproductive potential is defined as: one who has either 1) reached natural menopause (defined as 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone levels in the postmenopausal range as determined by the laboratory, or 12 months of spontaneous amenorrhea), 2) 6 weeks postsurgical documented total hysterectomy and/or bilateral salpingo-oophorectomy, or 3) bilateral tubal ligation.
9. Subject or the subject's legal representative understands the trial procedures, alternative treatments available, risks involved with the trial, and voluntarily agrees to participate by giving written informed consent.
10. Be able to adhere to dose and visit schedules.
11. Be able to read, understand, and complete questionnaires and diaries.
12. Provide written informed consent/assent for the trial

Exclusion criteria:

1. Has a clinically relevant history of symptomatic allergic rhinoconjunctivitis caused by animal dander, molds, and/or cockroach (e.g., present in the home, job, daycare) or other perennial allergen during the Run-in and efficacy assessment periods (i.e., HDM peak period).
2. Has a clinical history of symptomatic seasonal allergic rhinoconjunctivitis and/or asthma due to an allergen to which the subject is sensitized and regularly exposed and which could potentially overlap with the Run-in and HDM peak periods.
3. Has any nasal condition that could confound the efficacy or safety assessments (e.g., nasal polyposis).
4. Has received an immunosuppressive treatment within 3 months before the Screening Visit.
5. Has unstable or severe asthma, as judged by the clinical Investigator, or a subject who has experienced a life-threatening asthma attack or an occurrence

- of any clinical deterioration of asthma that resulted in emergency treatment, hospitalization due to asthma, or treatment with systemic corticosteroids (but allowing short-acting beta2 agonists) at any time within the last 3 months before Screening and Run-in Visits.
6. Has asthma requiring high-dose ICS within the last 6 months before Screening Visit.
 7. Has a history of anaphylaxis with cardiorespiratory symptoms with prior immunotherapy, unknown cause, or inhalant allergen.
 8. Has a history of chronic urticaria and/or angioedema within the last 2 years before Screening and Run-in Visits.
 9. Has a clinical history of chronic sinusitis during the past 2 years before the Screening and Run-in Visits.
 10. Is pregnant or expecting to conceive within the projected duration of the trial.
 11. Is nursing at randomization.
 12. Has had previous immunotherapy treatment with any HDM allergen for more than 1 month within the 5 years before Screening Visit 1.
 13. Has had previous exposure to the study drug.
 14. Is receiving ongoing treatment with any specific immunotherapy at the time of the Screening Visit 1.
 15. Has a known history of allergy, hypersensitivity, or intolerance to investigational medicinal products (except for *D. pteronyssinus* and/or *D. farinae*), rescue medications, or self-injectable epinephrine
 16. Is unable to meet medication washout requirements before Screening Visit 1 or is taking prohibited medications

Clinical Reviewer comment: These criteria appropriately define a house dust mite allergic population for study inclusion. Unlike the clinical setting where subjects are typically diagnosed by skin prick testing (SPT) or specific IgE, subjects were considered HDM allergic if they had both positive SPT and HDM specific IgE antibodies. The proposed indication is for treatment of subjects who have HDM allergy based on either of these results. The cutoff for a positive test is at the lower limit for both SPT and specific IgE; combining these results may confer greater specificity on trial subjects.

Asthmatics enrolled in this trial did not have severe or unstable asthma and could not enroll if their asthma was not well controlled (i.e. recent use of oral steroids, recent hospitalization, or history of severe exacerbation). An FEV1 of at least 80% ensures that asthmatic individuals had good lung function prior to enrollment. This limits generalizability of safety data to persons with severe or unstable asthma.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study treatments were either a placebo tablet or Odactra. The placebo tablet contained only excipients; gelatin, mannitol, and sodium hydroxide but no allergen extract. Odactra and placebo were matched in appearance and were packaged identically so that treatment blind was maintained. In addition to excipients, Odactra contains house dust mite extract. Odactra is measured in 12 DU of standardized allergen extract of two species of cultivated house dust mite, *Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae* (Der f). (b) (4)

. The major allergen content in Der p and Der f of the

group 1 and group 2 major allergens (Der p 1, Der p 2, Der f 1 and Der f 2) is measured in relation to the in-house reference standard.

6.1.5 Directions for Use

Subjects took the first dose of the study treatment at the study site and were observed for allergic reactions for 30 minutes. If subjects tolerated the first dose in clinic, subjects were directed to take one sublingual tablet daily at home. Subjects were advised not to swallow during the first minute and not to eat or drink for 5 minutes after tablet administration.

Clinical Reviewer Comment: The subject instructions are in alignment with the directions for use in the package insert.

6.1.6 Sites and Centers

Study P001 was conducted at 182 sites. 157 sites were located in the United States (US) and 25 in Canada.

6.1.7 Surveillance/Monitoring

During the screening period (- 52 weeks to -7 days prior to randomization, Visit 1), subjects provided informed consent, a medical history and physical exam with vital signs, pulmonary function test (PFT), concomitant medication review, and urine pregnancy test. During the run-in period (-6 weeks to -5 days, Visit 2), concomitant medication was reviewed, pregnancy testing was completed, electronic diary use was reviewed, and peak flow meters were dispensed.

On Day 1 (randomization, Visit 3), subjects underwent medication review and were provided with self-injectable epinephrine and an anaphylaxis plan. Subjects underwent a limited physical exam with vital signs, oropharyngeal exam, pregnancy testing, and PFTs for asthmatic subjects. Subjects were observed for 30 minutes after taking the first tablet. During treatment phase (including randomization and 2 telephone contacts the following 2 days after the first dose was given in clinic, Visits 4 through 11), there were 9 visits total. Vital signs, medication compliance, rescue medication use, vital signs, pregnancy testing, and PFTs (for asthmatics) were evaluated on visits 6 through 11. A final follow-up telephone call was placed 2 weeks following the last study visit and cessation of the study drug (Visit 12).

In this study, an adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. AEs were evaluated by their relation.

Subjects completed a Side Effect Report Card daily for the first 28 days of treatment and used the Side Effect Report Card to record symptoms during the first 60 minutes after dosing. This report card was returned to the site at Visit 6. The subject was solicited for the occurrence of the following local adverse reactions were recorded: taste alteration, mouth ulcer, mouth swelling, itching in the mouth, itching in the ear, swellings of the lips, swelling of the tongue, tongue pain, tongue ulcer, throat irritation, throat swelling,

stomach pain, nausea, diarrhea and vomiting. These events were characterized in terms of time to onset, duration, and recurrence.

Other events of clinic interest included an overdose of the study drug, elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) laboratory values systemic events of interest were systemic allergic reactions such as anaphylaxis, anaphylactic reactions, anaphylaxis, and/or systemic allergic reactions, events treated with epinephrine, and severe local swelling or edema of the mouth and/or throat. Information on unsolicited adverse events, serious adverse events and deaths was collected throughout the study and for 2 weeks after the last dose of study drug was taken.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

The treatment difference of Odactra compared to placebo of the average total combined rhinitis score (TCRS) during the last 8 weeks of treatment between Visit 10 and Visit 11. The primary efficacy endpoint was calculated as the treatment difference relative to placebo by $[(\text{treatment} - \text{placebo})/\text{placebo} * 100]$. The pre-specified criteria for efficacy were demonstration of a point estimate difference between treatment and placebo of $\leq -15\%$ and an upper bound of the 95% CI of that difference of $\leq -10\%$.

Clinical Reviewer comment:

The pre-specified criteria for success were agreed upon between CBER and the Applicant at the End of Phase 2 (EOP2) meeting.

The primary endpoint was amended prior to unblinding of the trial. The primary endpoint was changed to the TCRS from a score that also evaluated conjunctivitis symptoms in addition to rhinitis symptoms. This change was made because conjunctivitis symptoms tend to be less prominent in subjects with allergic symptoms induced by HDM. Conjunctivitis symptoms were also removed from the secondary endpoints.

The TCRS was proposed by the Applicant based on the recommendations of the European Medicines Agency (EMA) and World Allergy Organization (WAO) because the TCRS is evaluated based on both the severity of allergic rhinitis symptoms and rescue medication use meant to alleviate those symptoms. In particular, the Applicant cited EMA recommendations that symptom scores be collected on a daily basis during a pre-defined assessment period (1).

Study P001 includes subjects ages 12 to 85 years and the primary efficacy endpoint analysis is based on subjects in this age group. This approach was agreed upon during the EOP2 meeting.

Secondary Efficacy Endpoints

1. Average rhinitis DSS during the last 8 weeks of treatment
2. Average rhinitis DMS during the last 8 weeks of treatment
3. Average TCS during the last 8 weeks of treatment
4. Average allergic rhinitis/rhinoconjunctivitis VAS score during the last 8 weeks of treatment

Exploratory Efficacy Endpoints

1. Average asthma DSS during the last 8 weeks of treatment
2. Percentage of minimal symptom days (defined as a day without the use of any rescue medication and with a rhinoconjunctivitis DSS of ≤ 2) during the last 8 weeks of treatment
3. Average rhinoconjunctivitis symptoms assessed by RQLQ(S) 12+ during the last 8 weeks of treatment
4. Average EQ-5D-5L domain scores and EQ-VAS during the last 8 weeks of treatment
5. Immunological assessments, including *D. farinae* and *D. pteronyssinus* specific IgE, IgG4, and IgE-BF at Run-in, Week 4, Week 20, and final week of dosing (Visit 11)
6. WPAI+CIQ:AS outcome at Visits 2, 3, and 6
7. To confirm expression of biomarkers previously identified in a Odactra Phase II trial by evaluating mRNA content in nasal scrapes at Day 1 (randomization), Week 4, Week 20, and the final week of dosing
8. To determine site-to-site variance in the nasal scrape collection procedure through monitoring of common mRNA transcripts collected in nasal scrapes Day 1 (randomization), Week 4, Week 20, and the final week of dosing

Safety Endpoints

Tier 1 Safety Endpoint(s)

1. Proportion of subjects reporting pre-specified local application site reactions, including lip swelling/edema; mouth edema; palatal edema; swollen tongue/edema; oropharyngeal swelling/edema; pharyngeal edema/throat tightness; oral pruritus; throat irritation; tongue pruritus; ear pruritus;
2. Proportion of subjects reporting anaphylaxis and/or systemic allergic reactions;
3. Proportion of subjects with events treated with epinephrine.
4. Proportion of subjects with
 - a. any AE,
 - b. any SAE,
 - c. any drug-related AE
 - d. serious and drug-related AE
 - e. specific AEs or system organ classes (SOCs) (incidence $\geq 1\%$ subjects in 1 of the treatment groups)
5. Proportion of subjects who discontinue due to an AE
6. Proportion of subjects with upper respiratory viral infections
7. Laboratory tests, vital signs, and AEs that were not classified as any of the above safety endpoints.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The total target sample size was about 1500 with subjects randomized 1:1 to receive the study treatment or placebo for up to 52 weeks. Randomization was stratified according to asthma status (yes/no) and age (12-17 years) and ≥ 18 years).

The expected dropout rate was 14% (changed in a protocol amendment from 17%) which estimated about 645 subjects per treatment group. Unless otherwise stated in the application, all statistical tests were conducted at $\alpha = 0.05$ (2-sided) level. The primary and key secondary endpoints were tested in a stepwise procedure, where statistical

conclusions were made on the key secondary efficacy endpoints only if statistical significance was demonstrated in the primary efficacy endpoint.

Randomization occurred using an interactive voice response systemic or integrated web response system managed centrally by the applicant.
Please see the statistical review for a detailed description of the statistical analysis.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Below are the definitions of each population to be analyzed. Subjects with insufficient efficacy data (i.e., subjects with no e-diary data during the efficacy assessment period) were not evaluable for efficacy analyses in this period.

Full Analysis Set (FAS)

This population served as the primary population for the evaluation of efficacy data. The FAS population considered all randomized subjects who received at least 1 dose of study drug. There were 1481 subjects in the FAS (Odactra N= 740; placebo N=741).

Per Protocol (PP)

This population was used for supportive analysis of the primary and key secondary efficacy endpoints. The PP population excluded subjects due to important protocol deviations that may have substantially affected the results of the primary and key secondary efficacy endpoints. A total of 185 subjects were excluded from analysis. 174 subjects were excluded prior to the original database lock, and an additional 11 subjects were excluded due to protocol violations identified after the original database lock and unblinding.

Below is a list of major protocol violations that lead to exclusion of a subject.

- Subjects with chronic sinusitis during the previous 2 years
- Subjects treated with HDM immunotherapy for more than 1 month within 5 years before screening
- Subjects unable to meet medication washout requirements before Visit 9
- Subject who was randomized in the trial more than once
- Subject who participated in the same trial at another site
- Subject did not meet the symptom threshold requirement before randomization
- Subjects with a negative skin prick test response to HDM (*D. pteronyssinus* and *D. farinae*) (difference against saline control < 5 mm)
- Subjects with serum-specific IgE to HDM (*D. pteronyssinus* and *D. farinae*) <0.7 kU/L
- Subjects with overall treatment compliance <75%
- Subjects who took prohibited medications as defined in the protocol, with the exception of antihistamines. Subjects who took antihistamines or short-acting nasal decongestants (other than Applicant-provided rescue medications) were considered protocol violators if they took the medication for 2 or more consecutive days between Visit 10 and Visit 11
- Subjects who had their blinded treatment randomization code broken

All-Subjects-as-Treated (ASaT)

This population was evaluated as the safety analysis population. This population consisted of all randomized subjects who received at least 1 dose of study drug. Any subjects randomized to the placebo group who took Odactra in error were included in the Odactra group, as pre-specified in the handling convention for cross-treated subjects. At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study drug was required for inclusion in the analysis of each specific parameter.

6.1.10.1.1 Demographics

The demographics of study P001 are shown below in Table 4.

Table 4. Demographic Characteristics of Randomized Subjects: Study P001

	Odactra N (%)	Placebo N (%)	Total N (%)
Number of subjects	741	741	1482
Gender:			
Male	296 (39.9)	311 (42)	607 (41)
Female	445 (60.1)	430 (58)	875 (59)
Age (years):			
12 to <18	94 (12.7)	95 (12.8)	189 (12.8)
18 to 65	636 (85.8)	632 (85.3)	1268 (85.6)
>65	11 (1.5)	14 (1.9)	25 (1.7)
Race:			
White	567 (76.5)	564 (76.1)	1131 (76.3)
Asian	48 (6.5)	51 (6.9)	99 (6.7)
Black or African American	80 (10.8)	75 (10.1)	155 (10.5)
Multi-racial	39 (5.3)	46 (6.2)	85 (5.7)
American Indian or Alaska Natives	6 (0.8)	4 (0.5)	10 (0.7)
Unknown	1 (0.1)	1 (0.1)	2 (0.1)
Ethnicity:			
Hispanic/Latino	68 (9.2)	63 (8.5)	131 (8.8)
Non-Hispanic/Latino	662 (89.3)	657 (88.7)	1319 (89)
Unknown	11 (1.5)	21 (2.8)	32 (2.2)

Adapted from 125592/0: Clinical Study Report Table 10-5

Clinical Reviewer comment: More female subjects participated in study P001 than male subjects. CDC data suggests more adult females report 'hay fever' than adult males (8.7% versus 6.6%) (5). Other possible explanations for this imbalance may be due to differences in allergic sensitization or health-care utilization.

The Applicant seeks an indication in persons 18 through 65 years of age although the study includes small numbers of persons outside this age range. Since these numbers are small, data from this study will be insufficient to establish safety and effectiveness in persons <18 or >65 years of age.

The majority of subjects enrolled in this study were White (77%). For this reason, the generalizability of the data from this study to non-White populations may be limited.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The mean duration of the diagnosis of allergic rhinitis/rhinoconjunctivitis in all randomized subjects was 18.6 years. The percentage of subjects who were only sensitized to HDM was 24% while the remaining subjects had sensitivity to HDM as well as other environmental aeroallergens. 31% of subjects had asthma (30.8% in the treatment group and 31.3% in the placebo group).

Clinical Reviewer comment: This population is representative of individuals with allergic rhinitis in both sensitivity to other aeroallergens and diagnosis of asthma (2, 13). The majority of subjects enrolled in this study were sensitized to additional allergens, other than HDM. The Applicant attempted to mitigate the impact of concomitant allergies to seasonal allergens by performing the efficacy assessments during the last 8 weeks of treatment at a time when seasonal allergens would not interfere with the allergic rhinoconjunctivitis symptom assessment.

6.1.10.1.3 Subject Disposition

The table below outlines subject disposition.

Table 5. Study P001: Subject Disposition

Disposition	Odactra 12DU N (%)	Placebo N (%)	Total N (%)
Number of subjects (N)	741	741	1482
Study Disposition:			
FAS¹	740 (99.9)	741 (100)	1481 (99.9)
PP²	651 (87.9)	645 (87)	1296 (87.4)
ASaT³	743* (100.3)	738 (99.6)	1481 (99.9)
Treated	740 (99.9)	741 (100)	1481 (99.9)
Completed	561 (75.7)	613 (82.7)	1174 (79.2)
Discontinued:	179 (24.2)	128 (17.3)	307 (20.7)
Adverse event	73 (9.9)	18 (2.4)	91 (6.1)
Lack of Efficacy	1 (0.1)	0	1 (0.1)
Lost to follow-up	45 (5.7)	29 (3.9)	71 (4.8)
Non-compliance	0	5 (0.7)	5 (0.3)
Physician decision	2 (0.3)	3 (0.4)	5 (0.3)
Pregnancy	1 (0.1)	4 (0.5)	5 (0.3)
Progressive disease	1 (0.1)	0	1 (0.1)
Technical problem	0	1 (0.1)	1 (0.1)
Withdrawal by subject	56 (7.6)	64 (8.6)	120 (8.1)

Adapted from 125592/0: Clinical Study Report Table 10-2

*Three subjects randomized to placebo received the incorrect treatment during the trial.

DU: development unit

¹FAS: full analysis set

²PP: per protocol

³ASaT: all subjects as treated

Clinical reviewer comment: Please see Section 6.1.11.4 for a discussion on subject study discontinuation due to adverse events. The 2 subjects who discontinued the study in the Odactra group due to physician decision did so due to adverse events. Subject number 220366 suffered from numerous fractures that were not resolved at the time of discontinuation. Subject number 120168 was discontinued due to pericarditis.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary efficacy analysis was the Total Combined Rhinitis Score (TCRS) during the last 8 weeks of treatment using the FAS population. The pre-specified criteria for efficacy were demonstration of a point estimate of $\leq -15\%$ and an upper bound of the 95% CI of that difference of $\leq -10\%$.

Table 6. Efficacy Analysis of the Primary Endpoint of the TCRS in the Full Analysis Set Population and Per Protocol Population in Subjects Ages ≥ 12 Years: Study P001

Treatment	N	Baseline Mean DSS (SD)	Mean TCRS (SD)	Median TCRS(Lower Quartile, Upper Quartile)	% Treatment Difference Relative to Placebo (95% CI)
FAS					
Odactra 12 DU	566	7.94 (1.72)	4.67 (3.55)	4.10 (2.00, 6.40)	-17.2 (-25.0, -9.7)
Placebo	620	7.94 (1.76)	5.49 (3.82)	4.95 (2.70, 7.55)	---
PP					
Odactra 12 DU	498	7.94 (1.74)	4.56 (3.53)	4.00 (2.00, 6.30)	-16.7 (-25.5, -8.5)
Placebo	536	7.95 (1.74)	5.29 (3.68)	4.80 (2.50, 7.30)	---

Adapted from 125592/0 Clinical Study Report Table 11-2 and Table 11-3

CI: confidence interval

FAS: full analysis set

PP: per protocol

SD: standard deviation

Treatment difference relative to Placebo based on medians was calculated by (Odactra – Placebo)/Placebo*100%

Clinical Reviewer comment: The primary efficacy endpoint result met the pre-specified criteria for success with respect to the point estimate ($\leq -15\%$), although the upper bound of the 95% CI for this point estimate was not $\leq -10\%$.

Over half of subjects in the trial did not use rescue medication, therefore the effect of the daily rhinitis medication score (DMS) on the TCRS would be to lower this score for both the treatment and placebo group, making it more difficult to detect a treatment difference. Only 24% of subjects were sensitized only to HDM. Subjects sensitized to other perennial allergens such as cockroach, cat, dog, or some fungi may have experienced symptoms due to exposure to these allergens in addition to HDM exposure, interfering with symptom control provided by the study treatment. Additionally, daily exposure to the HDM allergen is not predictable (unlike seasonal allergens) or consistent and varies throughout the year based on many environmental factors including humidity, the presence of carpeting and upholstery, the use allergen-proof bedding covers, and general cleanliness. Due to the potential impact on the efficacy analysis of variations in daily exposure to HDM allergen and perennial nature of HDM allergen, the EEC study (P003) provided critical supportive data to support efficacy of Odactra in adults.

The increased number of dropouts due to adverse events in the treatment group compared to placebo may have impacted the efficacy results of this trial. Subjects in the treatment group who dropped out may have had more severe symptoms related to HDM sensitivity and increased reactions to the HDM allergen. These subjects may have benefited from treatment. Those who stayed in the study may have been less sensitive and therefore reported less symptom improvement.

The table below shows data from a post hoc analysis of the primary efficacy endpoint by age subgroups based on the FAS population (subjects 12 through < 18 years of age, 18 through 65 years of age, and > 65 years of age).

Table 7. Post Hoc Efficacy Analysis of the Primary Endpoint of the TCRS in the Full Analysis Set Population: Study P001

Treatment	N	Baseline Mean DSS (SD)	Mean TCRS (SD)	Median TCRS(Lower Quartile, Upper Quartile)	% Treatment Difference Relative to Placebo (95% CI)
Age 12 to < 18 years					
Odactra 12 DU	76	7.06 (1.60)	3.64 (2.69)	3.3 (1.35, 5.10)	-22.4 (-42.6, -8.1)
Placebo	84	7.82 (1.64)	4.83 (3.42)	4.3 (2.50, 6.55)	---
Age 18 to 65 years					
Odactra 12 DU	482	7.93 (1.74)	4.77 (3.61)	4.20 (2.10, 6.60)	-16.0 (-23.2, -5.3)
Placebo	529	7.96 (1.78)	5.60 (3.90)	5.00 (2.70, 7.70)	---
Age > 65 years					
Odactra 12 DU	8	7.09 (1.74)	8.40 (3.92)	6.50 (5.50, 11.85)	28.7
Placebo	10	7.86 (1.69)	5.53 (1.89)	5.05 (4.40, 6.70)	---

Adapted from 125592/0.10 Efficacy Information Amendment, Table 1

CI: confidence interval

DSS: daily symptom score

SD: standard deviation

Treatment difference relative to Placebo based on medians was calculated by (Odactra – Placebo)/ Placebo*100%

Baseline was calculated as the average symptom score obtained during the last 7 consecutive days of diary entries prior to subjects satisfying the run-in

The table below shows supportive data for the primary efficacy endpoint calculated for 3 age groups in the PP population.

Table 8. Post Hoc Efficacy Analysis of Primary Endpoint of the TCRS in the Per Protocol Population: Study P001

Treatment	N	Baseline Mean DSS(SD)	Mean TCRS (SD)	Median TCRS (Lower Quartile, Upper Quartile)	% Treatment Difference Relative to Placebo (95% CI)
Age 12 to < 18 years					
Odactra 12 DU	71	8.07 (1.61)	3.57 (2.69)	3.20 (1.30, 5.00)	-26.4 (-49.5, 2.8)
Placebo	78	7.80 (1.64)	4.87 (3.49)	4.35 (2.40, 6.40)	---
Age 18 to 65 years					
Odactra 12 DU	422	7.92 (1.76)	4.67 (3.58)	4.05 (2.00, 6.70)	-17.3 (-27.8, -8.3)
Placebo	451	7.97 (1.76)	5.35 (3.73)	4.90 (2.50, 7.40)	---
Age > 65 years					
Odactra 12 DU	5	7.44 (2.17)	9.80 (4.48)	10.00 (5.80, 13.70)	108.3
Placebo	7	8.09 (1.82)	5.56 (2.22)	4.80 (4.10, 7.40)	---

Adapted from 125592/0.10 Efficacy Information Amendment, Table 2

CI: confidence interval

DSS: daily symptom score

SD: standard deviation

Treatment difference relative to Placebo based on medians was calculated by $(\text{Odactra} - \text{Placebo}) / \text{Placebo} * 100\%$

Baseline was calculated as the average symptom score obtained during the last 7 consecutive days of diary entries prior to subjects satisfying the run-in criteria

Clinical Reviewer comment:

Study P001 was not powered to demonstrate efficacy in the age subgroups shown. A post hoc analysis of efficacy in persons 18 through 65 years of age was performed because this is the age range for which the Applicant seeks use. In a post hoc analysis of subjects 18-65 years of age, the point estimate was < -15% based on both the FAS and PP analysis sets. The adolescent population has a higher point estimate for efficacy compared to the adult population. Since these data suggest that efficacy may have been driven by the adolescents, data from 2 additional trials in adults (P003 and P015) were critical to provide support on the efficacy of Odactra in adults. Please see Integrated Summary of Efficacy for additional discussion. The efficacy data from adults over 65 years of age are not sufficient to support licensure in older adults.

Sensitivity Analyses of the Primary Endpoint

Multiple sensitivity analyses were provided using 4 models for subjects ages ≥ 12 years for the primary efficacy endpoint during the last 8 weeks of treatment. The ANCOVA model (with observed data only) provided an alternative approach to the primary non-parametric approach to analyze the data. The other 3 sensitivity analyses, ANCOVA model with multiple imputation and with LOCF imputation as well as the LDA method, assessed the impact of missing data on the primary analysis result. The analyses were conducted due to the high number of drop outs in the Odactra group. Please see 6.1.11.4 and the statistical review. These included the analysis of covariance (ANCOVA) model, longitudinal data analysis (LDA) model, multiple imputation method using missing data in both treatment groups were imputed using the sample distribution of TCRS observed from the placebo group, and the last observation carried forward (LOCF) method. These analyses are in the table below.

Table 9. Sensitivity Analyses for the average Total Combined Rhinitis Score (TCRS) for the Full Analysis Set: Study P001

Treatment	N	Baseline Mean DSS(SD)	Least Square Mean	% Treatment Difference Relative to Placebo (95% CI)
Average TCRS ANCOVA¹ Model				
Odactra 12DU	566	7.94 (1.72)	4.67	-17.5 (-25.2, -8.8)
Placebo	620	7.94 (1.76)	5.49	---
Average TCRS LDA² Model				
Odactra 12DU	566	7.94 (1.72)	4.66	-18.4 (-31.0, -6.5)
Placebo	620	7.94 (1.76)	5.42	---
Average TCRS Multiple Imputation Method				
Odactra 12DU	740	7.95 (1.75)	4.67	-12.3 (-17.8, -6.9)
Placebo	741	7.92 (1.75)	5.49	---
Average TCRS LOCF³ Method				
Odactra 12DU	566	7.94 (1.72)	4.67	-17.3 (25.2, -8.5)
Placebo	620	7.94 (1.76)	5.48	---

Adapted from STN 125592/0: Clinical Study Report Table 11-4.

¹ANCOVA: analysis of covariance

²LDA: longitudinal data analysis

³LOCF: last observation carried forward

CI: confidence interval

DSS: rhinitis daily symptom score

SD: standard deviation

Treatment difference relative to placebo based on LS means was calculated by (Odactra – Placebo)/ placebo*100%

Baseline was calculated as the average symptom score obtained during the last 7 consecutive days of diary entries prior to subjects satisfying the run-in criteria

Clinical reviewer comment: The sensitivity analyses demonstrate the consistency of the treatment effect of Odactra.

6.1.11.2 Analyses of Secondary Endpoints

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

These scores are presented for subjects ≥12 years of age.

Rhinitis Daily Symptom Score

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

Table 10. Secondary Endpoint of Rhinitis Daily Symptom Score (DSS) for the Full Analysis Set: Study P001

Treatment	N	Baseline Mean DSS(SD)	Mean DSS (SD)	Median DSS (Lower Quartile, Upper Quartile)	% Treatment Difference Relative to Placebo (95% CI)
Odactra 12 DU	566	7.94 (1.72)	3.83 (2.64)	3.83 (1.90, 5.30)	-15.5 (-24.4, -7.3)
Placebo	620	7.94 (1.76)	4.83 (2.80)	4.20 (2.30, 6.25)	---

Adapted from STN 125592/0: Clinical Study Report Table 11-5

CI: confidence interval

DSS: rhinitis daily symptom score

SD: standard deviation

Treatment difference relative to placebo based on medians was calculated by (Odactra – Placebo)/ Placebo*100%

Baseline was calculated as the average symptom score obtained during the last 7 consecutive days of diary entries prior to subjects satisfying the run-in criteria

Rhinitis Daily Medication Score

The DMS is presented in the table below for the FAS population. The Applicant reports that rescue medications were not utilized by the majority of subjects; 337 (59.5%) and 336 (54.2%) subjects in the Odactra 12 DU and placebo treatment groups, respectively, had a rhinitis DMS equal to zero. The zero-inflated log-normal model was used due to this issue, as pre-specified in the protocol, to analyze the average rhinitis DMS for the FAS population during the last 8 weeks of treatment.

Table 11. Secondary Endpoint of Rhinitis Daily Medication Score (DMS) of the Full Analysis Set: Study P001

Treatment	N	Zero Value of Rhinitis DMS n (%)	Mean DMS(Standard Deviation)	Estimated Mean (95% CI)	% Treatment Difference Relative to Placebo (95% CI)
Odactra 12 DU	566	337 (59.5%)	0.84 (1.817)	0.65 (0.45, 0.85)	-18.4 (-41, -4.3)
Placebo	620	336 (54.2%)	1.03 (2.074)	4.20 (0.56, 1.02)	---

Adapted from STN 125592/0: Clinical Study Report Table 11-6

CI: confidence interval

SD: standard deviation

Treatment difference relative to placebo based on medians was calculated by (Odactra – Placebo)/ Placebo*100%

Baseline was calculated as the average symptom score obtained during the last 7 consecutive days of diary entries prior to subjects satisfying the run-in criteria

Clinical Reviewer comment: The majority of subjects did not use rescue medication during the efficacy evaluation period (the last 8 weeks). The number of subjects who had a rhinitis DMS equal to zero was 337 (59.5%) for Odactra and 336 (54.2%) placebo. Due to this issue, the zero-inflated log-normal model was used, as pre-specified in the protocol. The average rhinitis DMS was lower in the Odactra groups compared with placebo, however, the treatment difference was not statistically significant between Odactra and placebo.

Total Combined Rhinoconjunctivitis Score (TCS)

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

Table 12. Secondary Endpoint of Total Combined Rhinoconjunctivitis Score (TCS) for the Full Analysis Set: Study P001

Treatment	N	Baseline Mean DSS (SD)	Mean TCS(SD)	Median TCS (Lower Quartile, Upper Quartile)	% Treatment Difference Relative to Placebo (95% CI)
Odactra12 DU	566	11.15 (2.84)	6.40 (5.16)	5.50 (2.50, 8.80)	-16.7 (-24.6, -4.0)
Placebo	620	11.27 (2.89)	7.62 (5.48)	6.60 (3.60, 10.40)	---

Adapted from STN 125592/0: Clinical Study Report Table 11-7

CI: confidence interval

DSS: daily symptom score = rhinitis DSS + conjunctivitis DSS only for the TCS analysis

SD: standard deviation

Treatment difference relative to placebo based on medians was calculated by (Odactra – Placebo)/ Placebo*100%

Baseline was calculated as the average symptom score obtained during the last 7 consecutive days of diary entries prior to subjects satisfying the run-in criteria

6.1.11.3 Subpopulation Analyses

Subgroup analyses of the average TCRS during the last 8 weeks of treatment included age, gender, race, asthma status, ICS use, allergen sensitivity, geographic location, and the occurrence of local application site reactions. Study P001 was not powered to show efficacy in specific subgroups. Age subgroups are presented in the primary efficacy endpoint section; the table below presents data specific to gender, race, and geographic location.

Table 13. Subgroup Analyses for Full Analysis Set of the TCRS: Study P001

Treatment	N	Baseline Mean DSS(SD)	Mean TCRS (SD)	Median TCRS (Lower Quartile, Upper Quartile)	% Treatment Difference Relative to Placebo
Gender: Male					
Odactra 12 DU	239	7.8 (1.71)	4.4 (3.49)	3.6 (1.80, 5.90)	-16.3
Placebo	268	7.7 (1.65)	4.9 (3.56)	4.3 (2.25, 6.60)	
Gender: Female					
Odactra 12 DU	327	8.0 (1.73)	4.9(3.59)	4.2 (2.30, 6.80)	-22.2
Placebo	352	8.1 (1.82)	6.0 (3.95)	5.4 (3.20, 8.25)	
Race: Caucasian					
Odactra 12 DU	428	7.8 (1.70)	4.8 (3.48)	4.2 (2.30, 6.70)	-17.6
Placebo	480	7.9 (1.68)	5.6 (3.80)	5.1 (2.80, 7.70)	
Race: Non-Caucasian					
Odactra 12 DU	138	8.3 (1.76)	4.2 (3.74)	3.9 (1.30, 5.60)	-14.4
Placebo	140	8.2 (1.98)	5.1 (3.87)	4.5 (2.35, 7.20)	
Subjects with Asthma					
Odactra 12 DU	163	7.9 (1.76)	4.5 (3.52)	3.9 (1.90,6.70)	-22.0
Placebo	190	7.9 (1.68)	5.8 (4.01)	5.0 (3.10, 7.90)	
Subjects with ICS Use (Asthmatics)					
Odactra 12 DU	44	8.0 (1.59)	3.9 (2.71)	3.7 (2.05, 5.60)	-24.0
Placebo	50	7.9 (1.62)	5.4 (4.12)	4.8 (2.80, 7.00)	
Subjects sensitized to HDM + other allergens					
Odactra 12 DU	424	8.0 (1.75)8.0	4.6 (3.59)5.3	4.0 (2.10, 6.60)4.8	-17.7
Placebo	478	(1.78)	(3.74)	(2.60, 7.30)	
US					
Odactra 12 DU	400	7.9 (1.69)	5.1 (3.65)	4.4 (2.30, 7.00)	-15.4
Placebo	450	7.9 (1.74)	5.9 (3.86)	5.2 (3.00, 8.00)	
Northern US					
Odactra 12 DU	254	7.9 (1.66)	4.8 (3.72)	4.1 (2.10, 6.20)	-22.6
Placebo	294	7.9 (1.74)	5.9 (3.90)	5.3 (3.10, 8.00)	
Southern US					
Odactra12 DU	146	8.0 (1.74)	5.6 (3.47)	5.1 (3.00, 7.60)	-1.0
Placebo	156	8.0 (1.73)	5.7 (3.80)	5.1 (2.90, 7.80)	
Canada					
Odactra 12 DU	166	8.0 (1.80)	3.7 (3.11)	3.4 (0.90, 5.30)	-17.1
Placebo	170	8.0 (1.83)	4.5 (3.53)	4.1 (1.90, 6.40)	

Adapted from STN 125592/0: Clinical Study Report Table 14.2.1.1.2

DSS: daily symptom score

SD: standard deviation

Treatment difference relative to placebo based on medians was calculated by (Odactra - Placebo)/ Placebo*100%.

Baseline was calculated as the average symptom score obtained during the last 7 consecutive days of diary entries prior to subjects satisfying the run-in criteria

Clinical Reviewer comment: The percent treatment difference relative to placebo generally follows a trend towards symptomatic improvement in all subgroups listed above except for the subjects residing in the Southern US. The warm, humid climate of the Southern US is ideal for the Dermatophagoides pteronyssinus and Dermatophagoides farinae species. However, subjects residing in the Southern US

experience a longer period of seasonal allergen exposure which may have interfered with rhinitis symptom control. In addition, the climate conditions may tend to exacerbate other perennial allergens (e.g., mold), which would tend to also tend to interfere with rhinitis symptom control.

6.1.11.4 Dropouts and/or Discontinuations

Section 6.1.10.1.3 provides a table detailing dropouts and discontinuations for trial P001. The number of discontinuations was higher in the treatment group as compared with placebo, 179/741 (24.2%) versus 128/741 (17.3%). A higher number of subjects discontinued treatment in the Odactra group was due to adverse events, 73 (9.9%) versus 18 (2.4%) placebo subjects. Of these 73 subjects who received Odactra, 5 (6.8%) reported severe adverse events, all of which were related to Odactra. No serious adverse events that resulted in discontinuation.

Clinical Reviewer comment: The safety analysis set includes any subject who received at least 1 dose of Odactra. The majority of these reactions (75.9%) were mild to moderate in severity. The high rate of discontinuations due to adverse events should be reflected in product labeling.

The increased number of dropouts due to adverse events in the treatment group compared to placebo impacts the effectiveness results of this trial (See 6.1.11.1.)

6.1.11.5 Exploratory and Post Hoc Analyses

See section 6.1.11.1 for a review of post hoc analyses of efficacy in age subgroups.

6.1.12 Safety Analyses

6.1.12.1 Methods

A total of 1481 subjects (743 Odactra; 738 placebo) were included in the safety analyses. Three subjects who were originally randomized to placebo but who received Odactra during the trial were counted in the treatment group. Mean duration of treatment was 241 days in the safety (All Subjects as Treated (ASaT)) population. The range was 1 to 368 days.

Adverse events (AEs) were assessed throughout the trial including during the run-in period, randomization period, through telephone contact during the trial and 2 weeks after the last study visit, during the treatment phase, efficacy assessment period, and final study visit. AEs were recorded in the eCRF by the investigator. A side effect report card was completed by subjects for the first 28 days of treatment and filled out within the first 60 minutes of study drug intake. Adverse events were assessed by their intensity, severity, and relation to the study treatment. Unsolicited AEs, SAEs, and deaths were monitored throughout the study.

Clinical reviewer comment: In the package insert, solicited and unsolicited data are analyzed separately for ages 18 through 65 years because the data collection methods for the 2 sets of data differ.

6.1.12.2 Overview of Adverse Events

The table below summarizes adverse events in the safety population.

Table 14. Summary of Adverse Events in All Subjects as Treated (ASaT) for Study P001

	Odactra 12 DU N (%)	Placebo N (%)
Subjects in population	743	738
One or more adverse event	676 (91)	539 (73)
Severe adverse events	13 (1.7)	2 (0.3)
Serious adverse event	11 (1.5)	7 (0.9)
Drug related adverse event	627 (84)	301 (40.8)
Serious drug related adverse event*	2 (0.3)	0
Discontinued due to an adverse event	73 (9.8)	19 (2.6)

Adapted from STN 125592/0: Clinical Study Report Table 12-2

DU: development unit

* These events were reported as a serious adverse event due to an overdose defined as taking > 1 tablet a day. These events did not meet ICH criteria for seriousness

A brief summary of drug-related severe adverse events assessed by investigator is below. All of these events resolved with the exception of insomnia.

Odactra treatment group

1. Oral pruritus and nausea
2. Asthma exacerbation (described below)
3. Dyspnea and throat tightness
4. Dysphagia and laryngeal discomfort
5. Nasal edema
6. Stomatitis
7. Oral pruritus
8. Throat irritation and tongue pruritus
9. Ear and oral pruritus
10. Headache, oral discomfort, throat irritation, dysphagia
11. Dyspepsia
12. Abdominal distention and pain
13. Ear pruritus, dry throat

Placebo group

1. Fatigue, headache
2. Insomnia

Eosinophilic esophagitis

Two adolescent subjects were evaluated for eosinophilic esophagitis.

One subject diagnosed with eosinophilic esophagitis was in the Odactra treatment group. On Day 204 the subject underwent an upper GI endoscopy with biopsy performed on showing mid and distal esophagitis with 10-20 eosinophils per high powered field. The subject was treated with omeprazole and swallowed fluticasone and subsequently completed the trial. This event was reported as resolved.

A second subject was evaluated for eosinophilic esophagitis in the placebo group. The subject underwent 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 per high

powered field in the proximal esophagus. The subject was diagnosed with gastroesophageal reflux disease. This subject completed the trial.

Clinical Reviewer Comment: The occurrence of eosinophilic esophagitis was not common in this study. It should be noted, however, that the study did not actively solicit for cases of eosinophilic esophagitis. Therefore, cases may have been underreported. In addition, since the discontinuation rate was high in this study, a substantial proportion of subjects did not complete 52 weeks of therapy. For this reason, the low number of cases shown here may not accurately reflect the true incidence of eosinophilic esophagitis in persons who take Odactra daily for 1 year or longer.

Subjects with asthma

The majority of AEs in subjects with asthma were mild or moderate in severity. No AEs in subjects with asthma met the criteria for an SAE. The most common AEs were ear pruritus, upper abdominal pain, glossodynia, lip and tongue swelling, nausea, and oral pruritus. One subject in the Odactra group had a severe asthma exacerbation treated from Days 27 to 32 with inhaled steroid and a long-acting beta agonist. The event resolved on Day 32. This event was assessed by the Investigator as related to study drug and was discontinued from the study drug and the trial. The episode resolved on Day 32 with treatment.

Adverse events in subjects with asthma are summarized in the table below

Table 15. Any Adverse Event in Subjects with Mild to Moderate Asthma (All Subjects as Treated): Study P001

	Subjects with Asthma	Subjects with Asthma	Subjects without Asthma	Subjects without Asthma
	Odactra 12DU N (%)	Placebo N (%)	Odactra 12DU N (%)	Placebo N (%)
Subjects in population	229	231	514	507
One or more AEs*	212 (92.6)	184 (79.7)	464 (90.3)	355 (70)
Drug-related AEs	197 (86)	103 (44.6)	427 (83.1)	198 (39.1)
Discontinued due to an AE	29 (12.7)	8 (3.5)	44(8.6)	11 (2.2)

Adapted from STN 125592/0: Clinical Study Report Table 12-19.

DU: development unit

*Any unsolicited adverse event in subjects with asthma

Clinical reviewer comment: Overall, subjects with asthma reported slightly more unsolicited adverse events in both Odactra and placebo groups than subjects without asthma. More subjects with asthma discontinued due to any AE than subjects without asthma. One subject experienced a severe asthma exacerbation that led to discontinuation from the trial. The most common AEs in asthmatic subjects were similar to the most common AEs in all subjects.

Unsolicited local adverse events and solicited adverse reactions are presented in the table below in MedDRA terms.

Table 16. Local Adverse Events in All Subjects 12 Years of Age and Older as Treated: Study P001

	Odactra 12 DU N (%)	Placebo N (%)
Subjects in population	743	738
Lip Swelling/Edema	151 (20.3)	19 (2.6)
Mouth Swelling/Edema	75 (10.1)	12 (1.6)
Palatal Swelling/Edema	89 (12)	11 (1.5)
Swollen Tongue/Edema	133 (17.9)	17 (2.3)
Oropharyngeal Swelling/Edema	1 (0.1)	0
Pharyngeal Edema/Throat Tightness	113 (15.2)	24 (3.3)
Oral Pruritus	468 (63)	109 (14.8)
Throat Irritation	506 (68.1)	172 (23.3)
Tongue Pruritus	36 (4.8)	7 (0.9)
Ear Pruritus	382 (51.4)	92 (12.5)

Adapted from STN 125592/0: Clinical Study Report Table 12-9
DU: development unit

Clinical Reviewer comment: Adverse reactions were solicited through a Side Effect Report Card during the first 28 days of treatment. Study P001 is the only study in the submission that solicited adverse reactions. Therefore, adverse reactions appear increased in study P001 as compared with the other protocols reviewed in this application. See Table 17 below for solicited adverse reactions.

Table 17. Solicited Adverse Reactions in Subjects Ages 18 through 65 years in All Subjects as Treated: Study P001

Adverse Reaction (Patient-Friendly Term)	Study Population: Study 1 Adverse Reactions of Any Intensity	Study Population: Study 1 Adverse Reactions of Any Intensity	Study Population: Study 1 Adverse Reactions That Were Severe	Study Population: Study 1 Adverse Reactions That Were Severe
	Odactra (N=640)	Placebo (N=631)	Odactra (N=640)	Placebo (N=631)
Ear and labyrinth disorders				
Itching in the ear	51.7%	11.7%	0.3%	-
Gastrointestinal disorders				
Itching in the mouth	61.3%	14.1%	0.2%	-
Swelling of the uvula/back of the mouth [†]	19.8%	2.4%	-	-
Swelling of the lips	18.0%	2.7%	-	-
Swelling of the tongue	15.8%	2.1%	-	-
Nausea	14.2%	7.1%	-	-
Tongue pain	14.2%	3.0%	-	-
Tongue ulcer/sore on the tongue	11.6%	2.1%	-	-
Stomach pain	11.3%	5.2%	0.2%	-
Mouth ulcer/sore in the mouth	10.3%	2.9%	-	-
Diarrhea	6.9%	3.6%	-	-
Vomiting	2.5%	1.4%	-	-
Nervous system disorders				
Taste alteration/food tastes different	10.0%	3.6%	-	-

Adverse Reaction (Patient-Friendly Term)	Study Population: Study 1 Adverse Reactions of Any Intensity	Study Population: Study 1 Adverse Reactions of Any Intensity	Study Population: Study 1 Adverse Reactions That Were Severe	Study Population: Study 1 Adverse Reactions That Were Severe
	Odactra (N=640)	Placebo (N=631)	Odactra (N=640)	Placebo (N=631)
Respiratory, thoracic and mediastinal disorders				
Throat irritation/tickle	67.0%	20.8%	0.3%	-
Throat swelling	13.6%	2.4%	0.2%	-

Adapted from STN 125592/0: Package Insert

The median time to onset of these adverse reactions following initiation of treatment with Odactra varied from 1 to 7 days. The median duration of these adverse reactions that occurred on the first day of treatment initiation varied from 30 to 60 minutes. These adverse reactions recurred for a median of 2 to 12 days. Severe adverse reactions occurred in <1% of subjects taking Odactra.

Severe local adverse events in the ASaT population occurred in 8 subjects all receiving Odactra, 7 of those subjects had drug-related local application site reactions. The severe local application site reactions included oral pruritus (3 subjects; 1 subject had 2 separate events), throat irritation (3 subjects), ear pruritus (2 subjects), throat tightness (1 subject), tongue pruritus (1 subject), and pharyngeal edema (1 subject). Three subjects had more than 1 severe local application site reaction. Three subjects discontinued from the trial due to severe local application site reactions (1 subject had throat tightness; 1 subject had oral pruritus; and 1 subject had throat irritation and tongue pruritus). None of these events were considered SAEs and all resolved. Two subjects with severe local adverse events were treated with epinephrine; 1 event (throat tightness) was assessed as related to study drug and 1 event (pharyngeal edema) was assessed as not related to study drug.

6.1.12.3 Deaths

No deaths occurred during the trial

6.1.12.4 Nonfatal Serious Adverse Events

In the Odactra group, 11(1.5%) SAEs were reported versus 7(0.9%) in the placebo group.

Two subjects each took 2 tablets of Odactra once, instead of the advised daily dose of one tablet. These events were reported as serious adverse events due to an overdose defined as taking > 1 tablet a day.

SAEs assessed as not related to the study drug are below. Some subjects had one or more SAE.

Odactra group

1. Pericarditis
2. Tympanic membrane perforation

3. Diverticulitis
4. Infected bite
5. Peritonitis
6. Concussion
7. Osteoarthritis
8. Spontaneous abortion
9. Alcohol abuse
10. Ureteric Calculus
11. Deep vein thrombosis
12. Hypertensive emergency

Placebo group

1. Small intestine obstruction
2. Cholelithiasis
3. Anaphylactic reaction due to food allergy
4. Hepatic cancer
5. Bipolar I disorder
6. Depression

No drug-related serious adverse events occurred as assessed by study investigators.

Clinical reviewer comment: This reviewer agrees with the assessment that the SAEs listed above are unrelated to the study treatments.

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

6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESIs) were pre-specified and included anaphylaxis or systemic allergic reactions, events treated with epinephrine, severe local edema of the mouth or throat, an overdose of the study product (>1 tablet per day) or elevated AST or ALT ≥ 3 times the upper limit of normal, total bilirubin > 2X normal or alkaline phosphatase <2 times normal.

AESIs are presented in the table below.

Table 18. Adverse Events of Special Interest

Adverse Events of Special Interest	Odactra 12DU N (%)	Placebo N (%)	Total N (%)
Total Subjects in Population	743	738	1481
Subjects With ≥ 1 AESI	31 (4.2)	35 (4.7)	66 (4.5)
Overdose	25 (3.4)	31 (4.2)	56 (3.8)
Abnormal Liver Function Lab Values	0	0	0
Anaphylaxis/Systemic Allergic Reactions	3 (0.4)	3 (0.4)	6 (0.4)
Events Treated with Epinephrine	4 (0.5)	3 (0.4)	7 (0.5)
Severe swelling/edema of the mouth/throat	2 (0.3)	0	2 (0.1)

A summary of systemic allergic or local allergic reactions including anaphylaxis is below.

Events related to study drug

1. One subject had a systemic allergic reaction that included facial flushing, itchy palms and swollen throat. This reaction occurred on Day 1 in the investigator's office after 10 minutes of dosing. The subject was treated with intramuscular epinephrine. The reaction was assessed as moderate. The subject recovered and was discontinued from the trial.

Unrelated to study drug

2. One subject experienced an anaphylactic reaction after consuming a food containing peanuts on Day 18, 2 days after the last dose of Odactra. The subject was treated with an antihistamine. The subject was discontinued from the study on Day 16 due to mouth ulceration.
3. One subject taking Odactra experienced an allergy flare reported as a hypersensitivity reaction from a dust exposure on Day 245 and was treated with an oral antihistamine. The event was assessed as moderate.
4. One subject on placebo had a drug hypersensitivity reaction (hives) to Bactrim on Day 147.
5. One subject on placebo had throat tightness, difficulty swallowing, and an itchy face. The subject was treated with epinephrine and continued in the study. The event was assessed as mild.
6. One subject on placebo had an anaphylactic reaction 24 hours after the last dose of study drug. The subject self-administered epinephrine. This event was classified as a serious adverse event. The subject had a history of food allergy, however the exact trigger was not identified.

A summary of events treated with epinephrine is below.

Events related to study drug

1. One subject had multiple local oral reactions including oral itching and throat irritation on Days 1 to 2 as well as severe throat tightness on Day 7, 30 minutes after Odactra administration and self-administered epinephrine. The subject recovered and was discontinued from the trial. This event was assessed as mild.
2. One subject taking Odactra developed moderate throat and chest discomfort 30 minutes after drug intake on Day 128. The subject self-administered epinephrine and the event resolved. The subject continued in the study.
3. Please see narrative 1, above.

Events unrelated to study drug

4. One subject in the Odactra group developed pharyngeal edema after an exposure to environmental dust. This occurred 1 day after her last dose of Odactra. The subject self-administered epinephrine and the event resolved. The subject was continued in the study.
5. One subject in the placebo group self-administered epinephrine due to moderate pharyngeal edema as a result of a food reaction.
6. Please see narratives 5 and 6 above.

Clinical reviewer comment: In the Odactra group 3 (0.4%) allergic reactions resulting directly from the study treatment necessitated the use of epinephrine. The events related to Odactra did not qualify as anaphylaxis according to consensus guidelines for the

diagnosis of anaphylaxis because these subjects met only one of the required criteria (skin-mucosal tissue involvement after exposure to a likely allergen (in this case house dust mite)), not two or more which would include the following: respiratory compromise, reduced blood pressure, or persistent gastrointestinal symptoms (15).

6.1.12.6 Clinical Test Results

Exploratory clinical laboratory testing followed the change from Visit 2 (baseline) to Visits 6 (Week 4), 8 (Week 20), and 11 (last week of dosing) for IgE and IgG4 against *D. farinae* and *D. pteronyssinus*. In the Odactra group, there was a steep rise in serum specific IgE across both HDM species while there was little change in the placebo group. Higher IgE values were seen in the Odactra group compared to the placebo group at Visit 8 with a decrease in IgE after Visit 8. During the treatment period there was a steep increase in IgG4 across both HDM species and higher log10 transformed IgG4 values were seen in the Odactra group compared to the placebo group at Visit 8 and at Visit 11.

Clinical reviewer comment: The trends in IgE and IgG₄ in the Odactra group are consistent with documented trends in both biomarkers during allergen immunotherapy (2). It is not yet clear whether these biomarkers can reliably predict treatment efficacy.

6.1.12.7 Dropouts and/or Discontinuations

In the study population, 92 (6.2%) subjects had AEs resulting in the discontinuation of study drug. Of these subjects, 82 had at least 1 AE assessed with maximum intensity of mild or moderate. The most frequently reported AEs leading to discontinuation of Odactra were throat irritation (20 subjects), mouth swelling (15 subjects), oral pruritus (14 subjects), and ear pruritus (14 subjects).

6.1.13 Study Summary and Conclusions

Study P001 was Phase 3, one year double-blind, placebo-controlled, randomized, multicenter trial that evaluated the efficacy and safety of daily HDM sublingual immunotherapy in the treatment of HDM-induced allergic rhinitis/rhinoconjunctivitis. Subjects were enrolled from 182 sites in the US and Canada with 157 sites in the US.

In trial P001, 1482 subjects 12 years of age and older were randomized 1:1 treatment to placebo. The study enrolled similar numbers of male and female subjects across treatment and placebo groups. There were more females than males in the study overall. Of the 1482 subjects randomized, 1174 completed the study; 561 in the treatment group and 613 in the placebo group.

The primary efficacy endpoint was the percent treatment difference relative to placebo of the average TCRS during the last 8 weeks of treatment in the FAS population in subjects 12 years of age and older. The relative treatment difference between the groups was -17.2% (95% CI: -25.0%, -9.7%). Post hoc analysis for the FAS population in adults ages 18 through 65 years was -16.0% 95% CI (-23.2, -5.3) and in the PP population, the data showed a point estimate of -17.3% 95% CI of (-27.8, -8.3). The point estimate was met based on the pre-specified analysis in the FAS population, however the pre-specified criterion for study success was not met. Potential reasons for this finding were considered and discussed in Section 6.1.11.

The most frequently reported solicited adverse reactions were consistent with other licensed aeroallergen sublingual immunotherapy products. The majority of these

reactions occurred within 7 days of the first dose and resolved. Three subjects (0.4%) of the Odactra group had allergic reactions that required the use of epinephrine. No subjects had severe anaphylaxis. No deaths related to the study drug occurred during the trial.

6.2 Trial #2 Protocol P015/MT-06, NCT01454544

A Phase 3 one-year, randomized, double-blind, placebo-controlled, parallel assignment trial evaluating the efficacy and safety of the house dust mite sublingual immunotherapy tablet in adult subjects with house dust mite-induced allergic rhinitis with or without asthma

6.2.1 Objectives (Primary, Secondary)

The primary objective of protocol P015 was to evaluate the efficacy of Odactra given once daily (12 DU or 6 DU) compared to placebo in the treatment of HDM allergic rhinitis. The primary endpoint was the difference in the average TCRS during the last 8 weeks of treatment between treatment and placebo arms.

Relevant secondary objectives include the average allergic rhinitis score (DSS), average allergic medication score (DMS), the average total combined rhinoconjunctivitis score during the efficacy evaluation period, the last 8 weeks of treatment, and the safety and tolerability of Odactra.

6.2.2 Design Overview

Study P015 was a Phase 3, one year double-blind, placebo-controlled, randomized, multi-center trial was conducted at 100 sites in 12 countries in Europe. The study population consisted of 992 subjects ages 18 through 65 years with HDM-induced allergic rhinitis with or without asthma randomized in a 1:1:1 ratio (n=318 12DU, n= 336 6DU, n= 338 placebo).

After an initial screening evaluation (Visit 1), subjects underwent a 15 day baseline evaluation period with daily diary recordings. During the screening evaluation, subjects recorded information on daily rhinitis symptoms and medication use. These baseline scores were used for inclusion criteria and the efficacy assessments. Subjects were randomized into the study and began therapy at Visit 2. The first dose of the study treatment was administered under medical supervision and subjects were observed at least 30 minutes afterwards for a reaction. For 10 months, subjects recorded symptoms for 1 week after each clinic visit (Visits 3-6). The efficacy assessment period occurred during the last 8 weeks of the trial (Visits 7-8). During this time subject recorded symptoms and medication use daily.

Clinical reviewer comment: Study P015 was not designed to obtain data on the rate of solicited adverse reactions with a Side Effect Report Card as did Study P001. All adverse event data is unsolicited. The efficacy assessment period and primary endpoint (the percent treatment difference in the average TCRS compared to placebo during the last 8 weeks of treatment) is defined in the same manner as in study P001.

Rhinitis and Conjunctivitis symptom scores were calculated as follows,

A total of 4 rhinitis symptoms (runny nose, blocked nose, sneezing, itchy nose) and 2 conjunctivitis symptoms (gritty feeling/red/itchy eyes, watery eyes) were measured on a scale from 0-3.

Table 19. Symptom Scores for Study P015

0 = no symptoms	No sign/symptom evident
1 = mild symptoms	Sign/symptom is clearly present but minimal awareness; easily tolerated
2 = moderate symptoms	Definite awareness of symptom that is bothersome but tolerable
3 = severe symptoms	Symptom is hard to tolerate; causes interference with activities of daily living and/or sleeping

Source: Adapted from STN125592/0: Clinical Study Report P015

Medication scores were calculated as below.

Table 20. Medication Scores for Study P015

Medication	Dosing Instructions	Score/Dose Unit	Maximum Daily Score
Rhinitis Medication Score			
Desloratadine 5mg tablet	1 tablet daily	4	4
Budesonide 64µg/ dose nasal spray	2 sprays per nostril daily	2	8
Conjunctivitis Medication Score			
Desloratadine 5mg tablet	1 tablet daily	1	2
Azelastine 0.05% eye drops	1 drop in each eye twice a day	1.5	6

Source: Adapted from STN125592/0: Clinical Study Report P015

6.2.3 Population

Adults ages 18 through 65 years participated in this study.

Inclusion criteria

1. Written informed consent obtained before entering the trial
2. Subject 18-65 years of age, with a clinical history consistent with moderate to severe persistent HDM allergic rhinitis (with or without asthma) for at least one year prior to trial entry, with allergic rhinitis symptoms despite having received symptomatic treatment
3. Moderate to severe HDM allergic rhinitis symptoms during the baseline period defined as a daily total rhinitis symptom score of at least 6 or a score of at least 5 with one symptom being severe, during at least 8 days of the 15-days baseline period
4. Use of symptomatic medication for treatment of HDM allergic rhinitis during at least 8 days of the 15-days baseline period
5. Presence of one or more of the following ARIA quality of life items due to HDM allergic rhinitis during the baseline period (Bousquet et al. 2008):
 - a. Sleep disturbance
 - b. Impairment of daily activities, leisure and/or sport
 - c. Impairment of school or work
6. If asthma, daily use of ICS should be ≤ 400 mcg budesonide or equivalent³ (i.e. corresponding to GINA treatment steps 1 or 2)

7. Positive skin prick test response (wheal diameter ≥ 3 mm) to *D. pteronyssinus* and/or *D. farinae*
8. Positive specific IgE against *D. pteronyssinus* and/or *D. farinae* (defined as \geq IgE Class 2; i.e. ≥ 0.70 kU/L)
9. Subject one of the following: male, infertile female, female, with a negative pregnancy test and willingness to practice appropriate contraceptive methods until treatment with IMP has been discontinued
10. Subject willing and able to comply with trial protocol

Exclusion criteria

1. A clinically relevant history of symptomatic seasonal allergic rhinoconjunctivitis and/or asthma caused by an allergen to which the subject is regularly exposed and overlapping with the 8-week efficacy assessment period
2. A clinically relevant history of symptomatic allergic rhinoconjunctivitis caused by mold or by animal hair and dander to which the subject is regularly exposed.
3. Reduced lung function (defined as FEV1 < 70% of predicted value after adequate pharmacologic treatment)
4. A clinical history of uncontrolled asthma⁷ within 3 months prior to screening.
5. Symptoms of or treatment for upper respiratory tract infection, acute sinusitis, acute otitis media or other relevant infectious process at randomization.
6. Any nasal condition that could confound the efficacy or safety assessments (e.g. nasal polyposis)
7. Inflammatory conditions in the oral cavity with severe symptoms such as oral lichen planus with ulcerations or severe oral mycosis at randomization
8. Previous treatment with immunotherapy with HDM allergen or a cross-reacting allergen for more than 1 month within the last 5 years. Initiation of subcutaneous immunotherapy is acceptable, if treatment has been discontinued before reaching maintenance dose
9. Ongoing treatment with any allergy immunotherapy
10. History of anaphylaxis with cardio-respiratory symptoms (food allergy, drugs or an idiopathic reaction)
11. History of 2 or more episodes of generalized urticaria during the last 2 years.
12. History of drug induced (incl. immunotherapy) facial angioedema or a family (parents and siblings) history of hereditary angioedema
13. Any clinically relevant chronic disease (≥ 3 months duration) (e.g. cystic fibrosis, malignancy, type I diabetes mellitus, malabsorption or malnutrition, renal or hepatic insufficiency)
14. Systemic disease affecting the immune system (e.g. autoimmune disease, immune complex disease, or immune deficiency disease).
15. Severe inflammatory disease (e.g. rheumatoid arthritis, systemic lupus erythematosus, immune deficiency diseases or multiple sclerosis)
16. Immunosuppressive treatment (ATC code L04 or L01) within 3 months prior to the screening visit (except steroids for allergic rhinitis and asthma).
17. Current treatment with tricyclic antidepressants; catechol-O-methyl transferase inhibitors and mono amine oxidase inhibitors
18. Use of medication listed in "Prohibited Concomitant Medication" within the specified timeframes
19. Use of any investigational product within 30 days/5 half-lives of the product (which ever longest) prior to randomization.
20. History of allergy, hypersensitivity or intolerance to the excipients of the investigational product or to the symptomatic medications

21. History of alcohol or drug abuse within the past 2 years
22. Being immediate family of the investigator or trial staff, defined as the investigator's/staff's spouse, parent, child, grandparent or grandchild

6.2.4 Study Treatments or Agents Mandated by the Protocol

The study treatment consisted of a placebo tablet or Odactra. Odactra is a 1:1 mixture of allergen extracts derived from two species of cultivated HDM (*D. pteronyssinus* and *D. farinae*) and excipients. The placebo tablet contained only excipients. The excipients used are gelatin (fish source), mannitol, and sodium hydroxide. The tablets are identical in appearance and packaging. Odactra is measured in 6 or 12 DU of standardized allergen extract of two species of cultivated house dust mite, *Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae* (Der f) (b) (4)

The major allergen content in Der p and Der f of the group 1 and group 2 major allergens (Der p 1, Der p 2, Der f 1 and Der f 2) is measured in relation to the in-house reference standard.

Randomization was performed by ALK for study P015. A randomization list was generated by an independent statistician. The list was divided in blocks of 6, each block comprising 2 sets of each of the 3 different treatments (Odactra 12 DU, 6 DU, or placebo). Randomization codes were kept strictly confidential, accessible only to authorized personnel until the time of un-blinding. The randomization codes could only to be broken when the clinical database had been locked and all protocol deviations had been identified and evaluated.

6.2.5 Directions for Use

Subjects took the first dose of the study treatment at the study site and observed for allergic reactions for 30 minutes. If subjects tolerated the dose in clinic, subjects were directed to take one sublingual tablet daily at home. The tablet was placed under the tongue. Swallowing was avoided for 1 minute afterwards. Eating or drinking was not allowed for 5 minutes after tablet administration.

6.2.6 Sites and Centers

Study P015 was conducted at 100 sites in 12 countries in Europe (Austria, Bosnia and Herzegovina, Croatia, Czech, Denmark, France, Germany, Latvia, Poland, Romania, Serbia, and Ukraine). This study was not conducted under IND.

6.2.7 Surveillance/Monitoring

During the screening period (Visit 1) subjects underwent informed consent, a medical history and physical exam with vital signs, pulmonary function test (PFT), concomitant medication review, and urine pregnancy test and were given an electronic diary for a 15 day baseline symptom and medication assessment. A randomization (Visit 2), subject eligibility was reviewed, vital signs obtained, pulmonary function tested, and the first intake of the study medication was completed under medical supervision. During the treatment maintenance period (Visits 3, 4 weeks after Visit 2, and Visits 4 through 6 occurring every 10 weeks) subjects filled out symptom and medication diaries for 7 days after each visit. Concomitant medications were recorded, and AEs were assessed. At Visit 7 subjects AEs were assessed, concomitant medications were recorded, and subjects were given electronic diaries for the 8 week efficacy assessment period. At the

end of the trial (Visit 8), a physical exam with vital signs was performed, along with spirometry and a possible urine pregnancy test, electronic diaries were collected, concomitant medications were recorded and adverse events assessed. Follow-up telephone calls were made 1 week after Visit 8. Study P015 did not solicit for specific adverse events with a diary or side effect report card.

Adverse events of special interest included asthma and acute asthma-related events, systemic allergic reactions, and adverse events leading to discontinuation.

6.2.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

1. The primary endpoint was the percent treatment difference compared to placebo of the average TCRS during the last 8 weeks of treatment. The TCRS is the sum of the allergic rhinitis DSS and the allergic rhinitis DMS
2. allergic rhinitis DSS and the allergic rhinitis DMS

Key Secondary Efficacy Endpoints

1. The average total allergic rhinitis DSS during the efficacy evaluation period
2. The average total allergic rhinitis DMS during the efficacy evaluation period
3. The average overall Rhinoconjunctivitis Quality of Life Questionnaire RQLQ(S) score during the efficacy evaluation period
4. The average total combined allergic rhinoconjunctivitis score during the efficacy evaluation period

Secondary Efficacy Endpoints

1. The average total allergic rhinoconjunctivitis DSS during the efficacy evaluation period
2. The average total allergic rhinoconjunctivitis DMS10 during the efficacy evaluation period
3. The average total combined conjunctivitis score10 during the efficacy evaluation period
4. The average total allergic conjunctivitis DSS during the efficacy evaluation period
5. The average total allergic conjunctivitis DMS10 during the efficacy evaluation period
6. The average total allergic rhinitis DSS, average total allergic rhinitis DMS and average TCRS during one week diary periods at visit 3, 4, 5 and 6
7. The average individual allergic rhinoconjunctivitis DSS during the efficacy evaluation period
8. Frequency (number/percentage) of symptom-free days
9. Global evaluation for efficacy
10. The average overall RQLQ score at visit 3, 4, 5 and 6
11. The change from baseline of overall RQLQ during the efficacy evaluation period and at visit 3, 4, 5 and 6
12. Average individual domains in the RQLQ score (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, emotional) during the efficacy evaluation period
13. The change from baseline of individual domains in the RQLQ score (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, emotional) during the efficacy evaluation period

Post-hoc Efficacy Endpoints

- Days with rhinitis exacerbations

Safety Endpoints

1. Adverse events
2. Investigational product related adverse events
3. Serious adverse events
4. Adverse event discontinuations
5. Local reactions related to the application site including oral pruritus, ear pruritus, throat irritation and mouth edema
6. Vital signs (resting blood pressure, heart rate).
7. Safety laboratory assessments (hematology, blood chemistry, urinalysis)
8. Forced Expiratory Volume in one second (FEV1)
9. Physical examination

6.2.9 Statistical Considerations & Statistical Analysis Plan

The study endpoints are found above in Section 6.2.8.

The total target sample size was 900 subjects randomized 1:1:1 to receive one of two doses of the study treatment (either 12DU or 6DU) or placebo for approximately 12 months. The minimal clinically relevant difference between active and placebo of the TCRS during the last 8 weeks of treatment was predefined to be 20% by the Applicant. There were no pre-specified upper or lower bound criteria of the 95% confidence interval. All statistical tests were performed with a 5% significance level, and all tests and CIs (95%) were two-sided unless otherwise mentioned.

Please see the statistical review for a detailed description of the statistical analysis by Dr. Gao.

Clinical Reviewer comment: This study was conducted in Europe under ALK. The Applicant indicated that the minimal clinically relevant difference between active and placebo of the TCRS was predefined to be 20%, however there was no pre-specified upper or lower bound criteria of the 95% confidence interval as was pre-specified in study P001. Per Dr. Gao, the Applicant estimated that 300 randomized subjects per treatment group (i.e., a total of 900 subjects) would provide about 90% power to reject the global hypothesis of no difference between any of the treatment groups with an F-test at 5% level of significance.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Below are the definitions of each population that was defined in the protocol and analyzed in the statistical analysis plan.

Total Analysis Set

This population included all subjects who entered the trial (i.e. signed an informed consent). This analysis set included screening failures. This set was used for listing reasons for screening failures and AEs before randomization.

Full Analysis Set (FAS)

This population included all randomized subjects in accordance with the ICH intent-to-

treat principle. This analysis set was the primary set for all efficacy analyses. It was also used for all baseline/demography tables, efficacy tables, safety tables and subject listings. This population was also used for the safety analysis, referred to as the Safety Set (SS)

Per Protocol (PP)

This population included all subjects who did not have major protocol deviations that would affect the primary endpoint. Subjects in the FAS who met one or more of the following criteria were excluded from the PP:

- Violated the inclusion/exclusion criteria significantly.
- Took prohibited medication too close to or during the efficacy evaluation period that may influence the primary endpoint.
- Had IMP compliance in the entire trial below 75%.
- Had IMP compliance in the efficacy evaluation period complying with the treatment stop date being less than a month (i.e. 30 days) prior to the last diary record in the efficacy evaluation period.
- Provided insufficient diary data defined as below 21 daily diary records in the efficacy evaluation period.
- Had any other significant protocol deviations influencing the primary efficacy endpoint.

6.2.10.1.1 Demographics

Subjects in this study were a European population. The trial population consisted of similar numbers of males and females (50% of each). The majority of the subjects were Caucasian (98%). The countries recruiting most subjects for the trial were Poland, Germany, Romania, and Czech with 25%, 14%, 12%, and 11%, respectively.

Table 21. Demographic Characteristics for Study P015

	Odactra 12 DU N (%)	Placebo N (%)	Total N (%)
Number of subjects	318	338	656
Gender:			
Male	163 (51.3)	166 (49.1)	329 (50.2)
Female	155 (48.7)	172 (50.9)	327 (49.8)
Age (years):			
Mean (SD)	32.1 (10.6)	32.2 (10.9)	--
Median	30.0	29.0	--
Race:			
White	314 (98.7)	331 (97.9)	645
Asian	1	1	2
African	--	1	1
Other	2	4	6
Ethnicity:			
Hispanic/Latino	1	1	2

Adapted from 125592/0: Clinical Study Report Panel 7-4

Clinical Reviewer comment: The majority of this population is White which may limit generalizability to non-White populations although there are no known differences in response to immunotherapy by race or ethnicity.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The mean number of years that all randomized subjects had been diagnosed with allergic rhinitis was about 10 years. In the 12 DU treatment group, 152 (48%) of subjects had asthma while 152 (45%) of the placebo group did. A total of 313 (32%) subjects (including those in all three cohorts) were mono-sensitized to HDM and of the remaining subjects most had 1 (20%), 2 (18%) or 3 (12%) additional aeroallergen sensitivities.

Clinical reviewer comment: Both house dust mite species contained in Odactra are present in the US and continental Europe. Both are the most abundant species of dust mite found in either locality. More subjects in study P015 were monosensitized than study P001 (32% versus 24%). Subjects in study P015 may have had less interference with symptom scores from other environmental allergens because of the higher rate of monosensitization compared to study P001, however, the efficacy results appear to be very similar between the 2 studies (please see Section 6.2.11 for Efficacy Analysis).

6.2.10.1.3 Subject Disposition

The table below outlines subject disposition.

Table 22. Subject Disposition for Study P015

Disposition	Odactra 12DU N (%)	Placebo N (%)	Total N (%)
Number of subjects	318	338	656
Study Disposition:			
FAS	318 (48.5)	338 (51.5)	656 (100)
PP	264 (83.0)	272	536 (81.7)
Completed	284 (89.3)	296	580 (88.4)
Discontinued:	34 (10.7)	42 (12.4)	76 (11.6)
Adverse event	13 (4.1)	7 (2.1)	20 (3.0)
Lack of Efficacy	0 (0)	2 (0.6)	2 (0.3)
Lost to follow-up	1 (0.3)	5 (1.5)	6 (0.9)
Non-compliance	4 (1.3)	6 (1.8)	10 (1.5)
Other	6 (1.9)	6 (1.8)	12 (1.8)
Pregnancy	1 (0.3)	4 (1.2)	5 (0.8)
Withdrawal by subject	9 (2.8)	12 (3.6)	21 (3.2)

Adapted from 125592/0: Clinical Study Report Panel 7-1

DU: development unit

FAS: full analysis set

PP: per protocol

Clinical reviewer comment: More subjects discontinued the study in P001 than in study P015 (24.2% versus 10.7%). More subjects discontinued due to an adverse event in study P001 than P015 (9.9% versus 4.1%). It is not clear why subjects discontinued at a higher rate in study P001. These subjects may have had more sensitivity to HDM and therefore increased local adverse reactions to Odactra.

6.2.11 Efficacy Analyses

The primary and secondary endpoints are described in Section 6.2.8. The primary efficacy analysis was the average TCRS during the period of interest (baseline, efficacy evaluation period or weekly after visit 3, 4, 5 and 6) was calculated as the average of all non-missing TCRS during the period of interest. Of note, no total combined conjunctivitis scores or total combined rhinoconjunctivitis scores were calculated for subjects in

Croatia and Serbia due to lack of scoring in Croatia and non-availability of eye drops in Serbia.

6.2.11.1 Analyses of Primary Endpoint(s)

The primary efficacy endpoint was the average Total Combined Rhinitis Score (TCRS) during the efficacy evaluation period and performed on the FAS using a multiple imputation strategy. This was calculated as the treatment difference using the treatment difference relative to placebo with the equation $[(\text{placebo} - \text{treatment})/\text{placebo} * 100]$. Study success was pre-specified as the minimally clinically relevant difference between treatment and placebo in the TCRS defined to be 20% in the FAS-MI population during the last 8 weeks of treatment.

*Clinical Reviewer note: The criteria for success were not agreed upon by CBER. This calculation is slightly different from that used in study P001, which was $[(\text{treatment} - \text{placebo})/\text{placebo} * 100]$. This equation calculates the percentages as negative numbers (versus positive in study P015). Additionally, the point estimate with the corresponding 95% CI is not provided for the primary endpoint. The statistical reviewer obtained similar results to those presented in study P015 when performing a multiple imputation analysis on the FAS population for the primary endpoint.*

Missing data in all treatment groups were sampled from the observed data in the placebo group using the method of unrestricted random sampling with replacement. All subjects with missing data were included in the analysis as if no treatment effect was present. The difference in (the back-transformed) adjusted means was calculated together with the associated p-value and 95% CIs. Multiplicity for the primary endpoint was controlled for by a 2-step testing procedure for pairwise comparisons of several treatment groups. The first step was to test if the means of each of the 3 treatment groups are equal. If the null hypothesis in step 1 could be rejected ($p < 0.05$), then the Applicant moved onto the second step, to test all pairwise comparisons at the same level of significance (5%). The 12 DU dose is of primary interest in this study.

The table below shows the primary endpoint calculations for a number of analyses.

Table 23. Primary Endpoint Calculations for Study P015: TCRS during the last 8 weeks of treatment

Analysis set	Treatment group	N	Adjusted mean TCRS [95% CI]	Absolute difference [95% CI]	Relative difference [95% CI]
FAS-MI (N=992)	Global*	992	-	-	-
FAS-MI (N=992)	Placebo	338	6.81 [6.48;7.13]	-	-
FAS-MI (N=992)	12 DU	318	5.71 [5.40;6.02]	1.09 [0.35;1.84]	-
FAS with observations	Placebo	298	6.76 [5.94;7.63]	-	-
FAS with observations	12 DU	284	5.53 [4.77;6.35]	1.22 [0.49;1.96]	18.1% [7.7%;27.6%]
PP (N=805)	Placebo	272	6.74 [5.86;7.67]	-	-
PP (N=805)	12 DU	264	5.38 [4.58;6.24]	1.36 [0.60;2.12]	20.2% [9.4%;29.8%]
FAS-LOCF (N=950)	Placebo	326	6.87 [6.12;7.66]	-	-

Analysis set	Treatment group	N	Adjusted mean TCRS [95% CI]	Absolute difference [95% CI]	Relative difference [95% CI]
FAS-LOCF (N=950)	12 DU	301	5.69 [4.99;6.43]	1.18 [0.46;1.90]	17.2% [7.1%;26.4%]

FAS: full analysis set

FAS-MI: FAS with imputation

FAS-LOCF: FAS with imputation of missing data using the method of LOCF

LOCF: last observation carried forward

PP: per protocol

CI = confidence interval.

Absolute treatment difference was calculated by Placebo – Treatment; percent treatment difference relative to placebo was calculated by (Placebo – Treatment)/Placebo × 100%.

Clinical Reviewer comment: The Applicant provided the relative difference between 12 DU Odactra and placebo for the FAS-MI analysis. This value, when using the equation for study P001 is -16.1% (95%CI: -25.8%, -5.7%) which is similar to the findings in Phase 3 field study P001. The study did not meet the pre-specified criteria of -20% in the FAS-MI population (the population pre-specified for the primary efficacy endpoint). However, the PP population did meet -20%. This may be because the PP population is defined as subjects who did not have a major protocol violation and therefore were the most compliant with treatment.

6.2.11.2 Analyses of Secondary Endpoints

Key secondary analyses include the rhinitis daily symptom score (DSS) and rhinitis daily medication score (DMS), and the combined rhinoconjunctivitis score. These scores are presented in the table below.

Table 24. Key Secondary Endpoints for Study P015

Key Secondary Endpoints	Analysis Set	Treatment Group	N	Adjusted Mean Estimate [95% CI]	Relative Difference [95% CI]
Rhinitis DSS	FAS-MI	Placebo	338	3.31 [3.20;3.43]	--
Rhinitis DSS	FAS-MI	12 DU	318	2.84 [2.73;2.96]	--
Rhinitis DSS	FAS with observations	Placebo	338	3.30 [2.84;3.80]	--
Rhinitis DSS	FAS with observations	12 DU	318	2.76 [2.34;3.22]	16.2% [5.8%;25.7%]
Rhinitis DMS	FAS-MI	Placebo	338	2.86 [2.68;3.05]	--
Rhinitis DMS	FAS-MI	12 DU	318	2.32 [2.17;2.48]	--
Rhinitis DMS	FAS with observations	Placebo	298	2.83 [2.27;3.44]	--
Rhinitis DMS	FAS with observations	12 DU	284	2.22 [1.73;2.78]	21.4% [3.2%;36.6%]
Combined rhinoconjunctivitis score*	FAS (excluding 2 countries)	Placebo	257	9.12 [7.87;10.47]	--
Combined rhinoconjunctivitis score*	FAS (excluding 2 countries)	12 DU	241	7.91 [6.72;9.21]	13.2% [1.5%;23.7%]

DSS: daily symptom score

DMS: daily medication score

FAS: full analysis set

FAS-MI: FAS with imputation

*For the analysis of the combined rhinoconjunctivitis score, subjects from Serbia and Croatia were excluded from the FAS. This was due to the fact that no antihistamine eye drops were available in Serbia and that the only antihistamine eye drops being available in Croatia were lodoxamide tromethamine.

6.2.11.3 Subpopulation Analyses

Subgroup analyses of the primary endpoint included information regarding sex, asthma status, age less than or greater than 30 years, and other allergic sensitizations. Study P015 was not powered to show efficacy in specific subgroups. Data showing gender subgroups is presented below.

Table 25. Subpopulation Analyses of the Primary Endpoint of the TCRS in Adults Ages 18 to 65 Years: Study P015

Treatment	N	Mean TCRS (SD)	Median TCRS (Lower Quartile, Upper Quartile)	Placebo – Odactra 12 DU Adjusted Mean TCRS (95% CI)
Male				
Odactra 12 DU	151	6.69 (4.53)	5.91 (3.18, 10.33)	1.39 [0.33, 2.44]
Placebo	152	8.08 (4.82)	7.18 (4.52, 11.18)	
Female				
Odactra 12 DU	133	6.66 (4.49)	5.85 (3.13, 9.79)	0.88 [-0.17, 1.93]
Placebo	146	7.54 (4.42)	7.90 (3.64, 10.52)	
Asthma				
Odactra 12 DU	137	6.80 (4.60)	6.07 (3.39, 0.14)	0.97 (-0.18, 2.12)
Placebo	137	7.77 (5.08)	6.74 (4.08, 10.79)	
Without Asthma				
Odactra 12 DU	147	6.56 (4.42)	5.85 (3.13, 9.73)	1.29 (0.32, 2.26)
Placebo	161	7.85 (4.23)	8.07 (4.75, 10.82)	
Monosensitized to HDM				
Odactra 12 DU	99	7.09 (5.04)	6.07 (3.02, 11.41)	1.21 (-0.15, 2.58)
Placebo	90	8.30 (4.47)	8.29 (5.26, 11.18)	

CI: confidence interval

DSS: daily symptom score

DU: development unit

SD: standard deviation

Placebo-Active is the absolute difference in means between each active group and placebo

Clinical reviewer comment: This study was not powered to demonstrate efficacy in subgroups. The percent treatment difference relative to placebo was not calculated for each subgroup.

6.2.11.4 Dropouts and/or Discontinuations

Section 6.2.10.1.3 provides a table detailing dropouts and discontinuations for trial P015. The number of dropouts overall was similar in the treatment group, 34 (10.7%), as compared with the placebo group 42 (12.4%). A higher number of dropouts due to adverse events occurred in the treatment group, 13 (4.1%) versus 7 (2.1%) placebo subjects.

6.2.11.5 Exploratory and Post Hoc Analyses

N/A

6.2.12 Safety Analyses

6.2.12.1 Methods

For trial P015, 922 subjects were eligible for randomization into 1 of 3 groups, placebo, 12DU, or 6DU. Of this group, 877 (88%) of these subjects completed the trial. The FAS population was used for safety evaluations.

Safety assessments included recording of all AEs, SAEs, AESIs, findings from physical exams, vital signs, lung function measurements, and safety laboratory assessments

(including pregnancy testing) throughout the trial. Adverse events were defined by the ICH Harmonized Tripartite Guideline E2A.

6.2.12.2 Overview of Adverse Events

More adverse events occurred the treatment groups, 213 (67%) in 12 DU and 212 (63%) in 6 DU, than in the placebo group 154 (46%). Out of these, 50 (15%) in the placebo group were considered possibly related to the study drug, while 167 (53%) in 12 DU group and 161 (48%) in the 6DU group were considered possibly related. The majority of all reported AEs were mild or moderate in severity. There were no severe AEs related to the study drug in the placebo group while there were 3 subjects in the 6DU group and 5 in the 12DU group that experienced severe AEs. These events included asthma, lip swelling, cough, oral pruritus, throat irritation, lip edema, mouth edema, and oral pain. All of these events resolved. Eight subjects in the placebo group experienced SAEs, while 4 did in the 6DU group. None in the 12DU group had an SAE. The SAEs were assessed as unlikely related to the study drug.

The most frequently reported drug-related AEs were: oral pruritus (19% in 6 DU, 21% in 12 DU, and 2% in placebo), throat irritation (14% in 6 DU, 15% in 12 DU, and 4% in placebo), nasopharyngitis (11% in 6 DU, 10% in 12 DU, and 11% in placebo), and edema of the mouth (reported by 6% of all subjects; 7% in 6 DU, 9% in 12 DU, and <1% in placebo). Most of these AEs had an onset within 1-2 days of the first drug intake and had a median onset within 1-15 minutes after the first drug intake in the active groups.

6.2.12.3 Deaths

No deaths occurred during the trial.

6.2.12.4 Nonfatal Serious Adverse Events

A total of 12 SAEs were reported by 12 subjects during the trial; 8 subjects from the placebo group and 4 subjects from the 6 DU group. No SAEs were reported in the 12 DU group. None of the SAEs were assessed as treatment related. The SAEs reported in the 6DU group were as follows: chronic tonsillitis, cholelithiasis, infection, and tachycardia. In the placebo group: epilepsy, depression, retinal artery occlusion, Non-Hodgkin's lymphoma, limb crushing injury, lower limb fracture, myocardial infarction, and esophageal injury.

Clinical reviewer comment: This reviewer agrees with the assessment that these SAEs are not related to the study treatment.

6.2.12.5 Adverse Events of Special Interest (AESI)

The AESIs in this trial included asthma and/or acute asthma-related events, systemic allergic reactions and AEs leading to discontinuation. AEs leading to discontinuation are discussed in section 6.2.12.7. One asthma exacerbation considered to be a severe AE occurred in the 6DU group. The subject took Odactra 6DU for 4 days. The subject discontinued the study drug and was treated with inhaled corticosteroids, antihistamine and inhaled beta 2 agonist. The subject was reported as recovered from the asthma exacerbation on the same day treatment was initiated.

One subject received epinephrine during the trial for treatment of a systemic reaction. The subject was in the 12DU group and experienced oropharyngeal pruritus followed by dysphonia and throat irritation, dry cough within the first 5 minutes of drug intake. The

subject was treated with epinephrine, oral steroids and an oral antihistamine. The symptoms resolved after 30 minutes. The subject continued the trial and completed the trial without other AEs except for mild oral pruritus.

6.2.12.6 Clinical Test Results

In a subset of 74 subjects in Germany, IgE and IgG₄ to *D. pteronyssinus* and *D. farinae* respectively, were assessed at visit 1 (week 0), 3 (week 4), 4 (week 14), 5 (week 24) and 8 (week 52). These endpoints were analyzed as the change from baseline to the end of treatment of Log₁₀ for both species.

After initiation of treatment, IgE increased in both treatment groups reaching a peak 4 weeks after treatment start after which the level slightly decreased. The increase of IgE in the 12 DU group was higher compared to the 6 DU group. No changes were observed for the placebo group.

The level of specific IgG₄ increased in both active groups beginning at week 4. The increase in the 12 DU group was numerically higher compared to the 6 DU group for the 2 active groups. In the 6 DU group, the level of IgG₄ reached a plateau after 14 weeks of treatment followed by an overall stable level during the rest of the trial. In the 12 DU group, the IgG₄ level followed a steady increase during the entire trial. No changes over time in the level of specific IgG₄ were observed for the placebo group.

Clinical Reviewer comment: The trends in IgE and IgG₄ in the Odactra 12DU group are consistent with documented trends in both biomarkers during allergen immunotherapy (2). It is not yet clear these biomarkers can reliably predict treatment efficacy, however the greater increase in IgG₄ and IgE in the 12DU group compared to the 6DU group may indicate a higher dose of Odactra is more effective in modulating the immune system and inducing tolerance to HDM allergens. These trends are similar to those seen in the Odactra 12DU group in study P001.

6.2.12.7 Dropouts and/or Discontinuations

A total of 30 subjects (3%) discontinued the trial due to 50 AEs; 10 (3%) subjects from the 6 DU group, 13 (4%) subjects from the 12 DU group, and 7 (2%) subjects from the placebo group. Out of the total number of AEs, 43 were considered drug related in 22 subjects. The AEs leading to discontinuation included oral discomfort, swollen tongue, pruritus, mouth edema, and throat irritation.

Clinical reviewer comment: The total numbers of drops out were small and similar across the treatment groups. The most common AEs leading to discontinuation were expected from a SLIT product and similar to those reported in study P001. None of drug-related AEs leading to discontinuation were serious.

6.2.13 Study Summary and Conclusions

Trial P015 was a Phase 3 one-year randomized, double-blind, placebo-controlled, parallel assignment trial evaluating the efficacy and safety of the house dust mite sublingual immunotherapy tablet in adult subjects with house dust mite-induced allergic rhinitis with or without asthma. The study evaluated 2 different doses of the study drug, Odactra, 6DU and 12DU compared to placebo. The study enrolled 338 subjects in the placebo group and 318 in the 12 DU group. An even number of males and females were recruited. The majority of the population was Caucasian.

The primary endpoint was the percent treatment difference compared to placebo of the average TCRS during the last 8 weeks of treatment in the FAS-MI population. The minimal clinically relevant difference between active and placebo of the TCRS during the last 8 weeks of treatment was predefined to be 20%. The primary endpoint was calculated as -16.1% (-25.8%, -5.7%). Study P015 did not meet the primary endpoint. All statistical tests were performed with a 5% significance level, and all tests and 95% confidence intervals (CIs) were two-sided unless otherwise mentioned. Sensitivity analyses including the FAS with observations, PP, and FAS-LOCF support the results of the primary efficacy analysis in the FAS-MI population, showing that there is mild to moderate improvement in symptom and medication use in subjects using the 12DU dose of the study drug. Analyses of key secondary endpoints points to a trend in improvement of rhinitis symptoms with less improvement in combined rhinoconjunctivitis measures.

In terms of safety, more adverse events related to the study treatment occurred in the treatment groups (12DU and 6DU) than in the placebo groups. The majority of these AEs were mild to moderate, however, 3 subjects in the 6DU group and 5 subjects in the DU group experienced severe AEs related to the study treatment. The AEs experienced in this study generally occurred within the first few days of drug initiation, soon after intake. One subject received epinephrine for a moderate systemic allergic reaction related to the study drug in the 12DU group. These AEs were expected and comparable to those reported in studies of licensed sublingual immunotherapy (SLIT) products. There were no study deaths and no SAEs related to the study treatment.

Overall, the primary and secondary efficacy analyses demonstrate a trend in improvement in rhinitis symptom control and medication use in adults who took the 12DU dose of the study treatment over the placebo control. This study supports the findings from the pivotal Phase 3 trial, P001. The safety findings in this study are similar to the findings from studies of other licensed SLIT products as well as study P001.

6.3 Trial #3 Protocol P003

Trial P003 was a Phase 2, randomized, placebo-controlled, parallel-assignment, dose-finding challenge study to evaluate the safety and efficacy of Odactra using an Environmental Exposure Chamber (EEC) in subjects with house dust induced allergic rhinitis with or without conjunctivitis. The study enrolled 124 subjects randomized 1:1:1 to receive either Odactra 12DU (N=42), 6DU (N=41), or placebo (N=41) for 24 weeks.

6.3.1 Objectives (Primary, Secondary)

The primary objective of this study was to evaluate the dose-related efficacy of Odactra compared to placebo in the treatment of HDM-induced rhinitis based on the average total nasal symptom score (TNSS) determined during the chamber challenge session at Week 24.

Secondary objectives were to evaluate the onset of action and dose response of Odactra versus placebo in the treatment of HDM-induced rhinitis based on the average TNSS during chamber sessions at Week 8, 16, and 24. Other secondary objectives included the evaluation of the efficacy of Odactra versus placebo in the treatment of HDM-induced rhinoconjunctivitis based on the average total symptom score (TSS) which is the sum of TNSS and TOSS (total ocular symptom score) during the chamber session

at Week 8, 16, and 24, the TOSS at Week 8, 16, and 24, and change in specific IgE and IgG₄ during the study period.

The safety objective of this study was to evaluate the safety and tolerability of Odactra I two doses (6 and 12 DU) dosed daily over a 6-month (26 weeks) treatment period in adults with HDM-induced allergic rhinitis/rhinoconjunctivitis. The safety variables assessed were Tier 1, 2, and 3 safety endpoints which include AEs, vital signs, and safety laboratory assessments.

6.3.2 Design Overview

The study design consisted of 10 study visits for screening, randomization, 4 challenge sessions (Weeks 0, 8, 16, and 24), and 4 monthly visits over 26 weeks (Week 4, 6, 8, and 10). Subjects began daily intake of the study treatment or placebo at Day 1 (randomization) first dose given on site to monitor for allergic reactions and continued the treatment daily for 24 weeks if the first dose was tolerated. The last study visit took place 2 weeks after the EEC challenge scheduled at 24 weeks for follow up.

Each challenge session was 6 hours in duration. Prior to the challenge sessions, subjects were required to stop their medications to treat allergic rhinitis and conjunctivitis symptoms. Subjects were allowed to use rescue medications while in the chamber. Each session was monitored and subjects were provided medical treatment if warranted. Subjects recorded symptoms every 15 minutes in electronic diaries. Data from the last 4 hours of the session was used for analysis. Four nasal symptoms (itchy nose, blocked nose, runny nose, and sneezing) were evaluated every 15 minutes on a 4-point rating scale (0=none to 3=severe) for the TNSS. Two ocular symptoms (gritty feeling/red/itchy eyes and watery eyes) and 3 asthma symptoms (cough, wheeze, chest tightness/shortness of breath) were scored but did not contribute to the primary efficacy endpoint.

The EEC used in the study was the (b) (4) Chamber. The ECC is a (b) (4) meter cubic meter room that is a stable environment which controls factors such as humidity, temperature, airborne irritants, barometric pressure, and air flow. The HDM particles (approximately 0.3 g material per hour) were dispensed into a constant turbulent flow of air. The chamber was charged with 100% fresh air which was cleaned, cooled, dried, and then loaded with qualitatively and quantitatively determined HDM allergen load. The material used was a mixture of the 2 HDM species obtained from cultures (provided by (b) (4)). The mixture was a 10:10:1 mixture of whole bodies and feces from both species, which reflects the composition of mite material during natural exposure. The HDM batch used in the study demonstrated *in vitro* characteristics comparable to previous batches used in clinical trials.

Clinical reviewer comment: Detectable house dust mite allergen is found in beds in most homes (84.2%) in the US. One half of these homes had concentrations over 2µg per gram of dust, the proposed threshold of exposure for allergic sensitization to house dust mite (14). Subjects are exposed to 0.3 grams of material during the EEC challenge. This dose should be more than enough to elicit symptoms in allergic individuals during a challenge. The rate of symptoms in the placebo group supports the chosen dose for exposure in the challenge.

6.3.3 Population

The study enrolled adult subjects 18 years of age and older with or without asthma who had a clinical history of house dust mite-induced allergic rhinitis/rhinoconjunctivitis for at least 1 year, Eligibility criteria stated that subjects demonstrated a positive skin prick test response at least 3mm and specific IgE at least 0.7kU/L to house dust mite (*D. pteronyssinus* and/or *D. farinae*), forced expiratory volume in 1 second (FEV1) $\geq 70\%$ of predicted at screening and randomization, and a total nasal symptom score ≥ 6 of 12 within the first 2 hours of the screening environmental exposure chamber session.

Females of childbearing age were required to negative urine pregnancy test at screening and randomization visits and agree to acceptable methods of birth control.

Inclusion criteria

1. Subject is male or female and ≥ 18 years of age, on the day of signing informed consent.
2. Subject has a clinical history of allergic rhinitis/rhinoconjunctivitis to house dust mite of 1 year duration or more (with or without asthma).
3. Subject has a total nasal symptom score of at least 6 of 12 within the first two hours of the screening EEC session prior to randomization.
4. Subject has a positive skin prick test (SPT) response (average wheal diameter of two tests must be at least 3 mm larger than the saline control after 15 to 20 minutes) to *D. pteronyssinus* ((b) (4)) and/or *D. farinae* ((b) (4)) at the Screening Visit.
5. Subject has a serum specific IgE to *D. pteronyssinus* and/or *D. farinae* at the Screening Visit of at least 0.7 kU/L.
6. Subject has a forced expiratory volume in 1 second (FEV1) of at least 70% of predicted value at the Screening and Randomization Visits.
7. Female subject of childbearing potential has a negative urine pregnancy test at screening and randomization visits. Female subject who are of reproductive potential must agree to remain abstinent or use (or have their partner use) 2 acceptable methods of birth control within the projected duration of the study. Acceptable methods of birth control are: intrauterine device (IUD), diaphragm with spermicide, contraception via pills/patches/depo, condom, vasectomy. Note: A female subject who is not of reproductive potential is eligible without requiring the use of contraception. A female subject who is not of reproductive potential is defined as: one who has either 1) reached natural menopause (defined as 6 months of spontaneous amenorrhea with serum follicle stimulating hormone (FSH) levels in the postmenopausal range as determined by the laboratory, or 12 months of spontaneous amenorrhea), 2) 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, or 3) bilateral tubal ligation.
8. Subject, understands the study procedures, alternative treatments available, and risks involved with the study, and voluntarily agrees to participate by giving written informed consent.
9. Subject is able to adhere to dose and visit schedules.
10. Subject is able to read, understand and complete questionnaires and diaries.
11. Subject must be willing to give written informed consent for pharmacogenomic testing (messenger ribonucleic acid (mRNA), and able to adhere to dose and visit schedules. Note: Subjects who are unwilling to sign the informed consent for pharmacogenomic testing may be included into the trial, however, pharmacogenomic samples must not be obtained.

Exclusion criteria

1. Subject is sensitized and regularly exposed to animal dander and molds, (e.g., present in the home, job, etc.) which could potentially interfere with EEC sessions.
2. Subject is sensitized and regularly exposed to seasonal allergens (i.e., Birch or grass pollen) which could potentially interfere with EEC sessions.
3. Subject who has received an immunosuppressive treatment within 3 months prior to the Screening Visit (except steroids for allergic and asthma symptoms).
4. Subject has a history of chronic urticaria and/or angioedema within the last 2 years prior to Screening.
5. Subject has had previous immunotherapy treatment with any HDM allergen for more than 1 month within the 3 years prior to the Randomization Visit.
6. Subject is receiving ongoing treatment with any specific immunotherapy at the time of the Screening Visit.
7. Subject has a history of anaphylaxis with cardiorespiratory symptoms with prior immunotherapy, due to an unknown cause or to an inhalant allergen.
8. Subject has unstable uncontrolled/partially controlled or severe asthma, as judged by the clinical investigator, or a subject who has experienced a life-threatening asthma attack or an occurrence of any clinical deterioration of asthma that resulted in emergency treatment, hospitalization due to asthma, or treatment with systemic corticosteroids (but allowing short-acting beta-agonists [SABA]) at any time within the last 3 months prior to Screening.
9. Subject has asthma requiring medium or high-dose inhaled corticosteroid (ICS) within the last 12 months prior to Screening.
10. Subject who is unable to meet medication washout requirements prior to screening EEC (Note: Subject must agree to remain off of the listed medications for the remainder of the study): oral, topical or nasal antihistamines; nasal or ocular decongestants (3 days), oral corticosteroids (12 weeks), nasal corticosteroids (14 days), long-acting parenteral (intramuscular, intra-articular) corticosteroids (90 days), short-acting parenteral corticosteroids (30 days), long-acting inhaled Beta agonists (30 days), leukotriene antagonists/synthase inhibitors (30 days), corticosteroid eye drops (7 days), medium or high dose inhaled corticosteroids (12 months), inhaled, topical, or oral nedocromil or cromolyn sodium (14 days)
11. Subject who is unable to meet medication washout requirements prior to Randomization: immunosuppressive therapy (except steroids for allergic and asthma symptoms) (90 days), beta blockers, regardless of route of administration (7 days), anti-IgE treatment (e.g., Xolair) at any time, immunotherapy to any house dust mite (3 years), tricyclic antidepressant medications with antihistaminic effects (e.g., doxepin, mianserin) (14 days), monoamine oxidase inhibitors (14 days), antipsychotic medications with antihistaminic effects (e.g., chlorpromazine, levomepromazine, clozapine, olanzapine, thioridazine) (7 days), investigational drugs (30 days), oral or topical antihistamines; nasal or ocular decongestants (3 days)
12. Subject with a history of clinically significant conditions that could potentially interfere with the trial, trial conduct or trial procedures
13. Subject has a clinical history of chronic sinusitis during the past 2 years prior to the Randomization Visit.
14. Subject has any nasal condition that could confound the efficacy or safety assessments (e.g., nasal polyposis).

15. Subject is pregnant or breast-feeding, or expecting to conceive within the projected duration of the study.
16. Subject has a known history of allergy, hypersensitivity or intolerance to investigational medicinal products (except for *D. pteronyssinus* and/or *D. farinae*).
17. Subjects who cannot cooperate or complete trial procedures/maneuvers.
18. Subject who is experiencing upper or lower airways symptoms from an upper or lower respiratory tract infection (viral or bacterial) or allergic rhinoconjunctivitis exacerbation at Screening Chamber Challenge Visit. Note: The Screening Chamber Challenge Visit could be rescheduled up to 1-2 weeks after complete resolution of the event to re-assess eligibility and participation in the EEC challenges and trial.
19. Subject must have an FEV1 of at least 70% of predicted value prior to entering the Chamber Challenge (Visit 2, 5, 7, 9). Visits can be rescheduled up to 1-2 weeks after complete resolution of the event (leading to reduced lung function) to re-assess eligibility and participation in the EEC challenges.
20. A subject cannot participate in a different investigational study at any site, during the same timeframe of this study.
21. No person directly associated with the administration of the study may participate as a study subject. No family member of the investigational study staff may participate in the study.

Clinical Reviewer comment: These criteria are acceptable to appropriately define a house dust mite allergic population. Severe or unstable asthmatics could not enroll in study P003, limiting generalizability of safety and efficacy results to this population (i.e. recent use of oral steroids, recent hospitalization, or history of severe exacerbation).

6.3.4 Study Treatments or Agents Mandated by the Protocol

The study treatment consisted of a placebo tablet or Odactra. The placebo tablet contained only excipients; gelatin, mannitol, and sodium hydroxide. Odactra and placebo were matched in appearance and were packaged identically so that treatment blind was maintained. In addition to excipients, Odactra contains house dust mite extract. Odactra is measured in 12 DU of standardized allergen extract of two species of cultivated house dust mite, *Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae* (Der f) (b) (4)

The major allergen content in Der p and Der f of the group 1 and group 2 major allergens (Der p 1, Der p 2, Der f 1 and Der f 2) is measured in relation to the in-house reference standard.

A computer-generated schedule was used for randomization. The Biostatistics and Research Decision Sciences (BARDS) department generated the randomized allocation schedule for treatment assignment.

6.3.5 Directions for Use

Subjects took the first dose of the study treatment at the study site and observed for allergic reactions for 30 minutes. If subjects tolerated the dose in clinic, subjects were directed to take one sublingual tablet daily at home. Subjects were advised not to swallow during the first minute and not to eat or drink for 5 minutes after tablet administration.

6.3.6 Sites and Centers

The trial was conducted at a single center located in Vienna, Austria (EU).

6.3.7 Surveillance/Monitoring

During the screening period (6 weeks prior to randomization), subjects underwent informed consent, a medical history and physical exam with vital signs, spirometry, concomitant medication review, baseline EEC challenge, and pregnancy test. Subjects were required to meet a pre-specified threshold of 6 out of 12 points for the total nasal symptom score during the first 2 hours of the screening challenge.

On Day 1 (randomization), subjects underwent medication review, a physical with vital signs, oropharyngeal exam, pregnancy testing, and spirometry for asthmatic subjects. Asthmatic subjects were given an asthma action plan. Subjects were observed for 30 minutes after taking the first tablet of the study drug. During treatment phase, there were 7 visits total. Subjects underwent a physical exam, medication compliance check, vital signs, and pregnancy testing these visits. In addition, prior to each EEC session, subjects underwent a physical exam with vital signs and spirometry (for asthmatics). During the chamber session, subjects measure peak expiratory flow every 30 minutes and are monitored by study observers. A follow up visit was completed 2 weeks after the last chamber session.

Assessment of adverse events took place throughout the study beginning after the screening visit (Visit 1). In this study, an adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment AEs were evaluated by their relation. No pre-specified adverse events were solicited or recorded. Subjects were advised to monitor for adverse events and record any concomitant medications used. Information on adverse events was collected throughout the study and for 2 weeks after the last dose of study drug was taken.

Events of clinic interest included an overdose of the study drug, elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) laboratory values, systemic allergic reactions such as anaphylaxis, anaphylactic reactions, anaphylaxis, and/or systemic, adverse events treated with epinephrine, and severe local swelling or edema of the mouth and/or throat.

6.3.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

1. The average total nasal symptom score (TNSS) over the last 4 hours of the EEC challenge at Week 24 in the Full Analysis Set (FAS) population.

Secondary Efficacy Endpoints (analyzed using the FAS population)

1. Average TNSS over the last 4 hours of the chamber challenge at Week 16
2. Average TNSS over the last 4 hours of the chamber challenge at Week 8
3. Average TSS over the last 4 hours of the chamber challenge at Week 24
4. Average TSS over the last 4 hours of the chamber challenge at Weeks 8 and 16
5. Average TOSS over the last 4 hours of the chamber challenge at Weeks 8, 16, and 24

6. Immunologic parameters including HDM specific IgE and IgG4, collected at Screening and Week 8.

Safety Endpoints (analyzed using the All Subjects as Treated population)

Tier 1

1. Proportion of subjects reporting pre-specified local application site reactions of oral pruritus, ear pruritus, throat irritation, and edema mouth;
2. Proportion of subjects reporting systemic allergic reactions
3. Events treated with epinephrine.

Tier 2

4. Proportion of subjects with any serious AE
5. Proportion of subjects with any drug-related AE
6. Proportion of subjects with any serious and drug-related AE
7. Proportion of subjects with specific AEs or system organ classes (SOCs) (incidence ≥ 4 subjects in one of the treatment groups).

Tier 3

8. Adverse events, vital signs, and safety laboratory assessments (hematology, blood chemistry, and urine analyses) which were not classified as Tier 1 or Tier 2 safety endpoints.

6.3.9 Statistical Considerations & Statistical Analysis Plan

The total target sample size was about 132 assuming a 20% drop out rate. The study enrolled 124 subjects randomized to one of three treatment arms 1:1:1 to receive Odactra 12DU, 6DU, or placebo treatment.

The primary efficacy endpoint was analyzed using the analysis of covariance (ANCOVA) model with treatment and baseline TNSS as covariates. Baseline score was computed based on the data obtained during the last 4 hours (out of total 6) of the chamber session during the screening challenge prior to randomization. A 2-sided 95% confidence interval of the difference in adjusted means between an active treatment group and placebo group was used. The difference in adjusted means between the two treatment groups relative to the adjusted mean of the placebo group was presented as a percentage with corresponding confidence interval.

The secondary endpoints were analyzed on the FAS in a similar fashion using the ANCOVA model, with treatment and baseline score of the endpoint being analyzed as covariates.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

Below are the definitions of each population to be analyzed

Full Analysis Set (FAS)

This population served as the primary population for the efficacy analysis. The FAS population consists of all randomized subjects who received at least one dose of study treatment and had at least one post-randomization observation for the analysis endpoint.

Per Protocol (PP)

This population was used for supportive analysis of the primary efficacy endpoint. The PP population excludes subjects that had deviations from the protocol that may have substantially affected the results of the primary efficacy endpoint. These include negative skin prick testing, negative HDM specific IgE, or subjects who took a prohibited medication.

Clinical Reviewer Comment: The study eligibility criteria indicated that subjects who were negative for SPT and HDM specific IgE were to be excluded from the study. Despite this, 1 subject who was negative for HDM specific IgE, but positive by SPT was included. In total, 4/124 (3.2%) protocol violations occurred in the study.

All Subjects as Treated (ASaT)

This population was used for the safety analysis. The ASaT population consisted of all randomized subjects who received at least one dose of study treatment. Subjects were included in the treatment group corresponding to the study treatment they actually received. For most subjects this was the treatment group to which they are randomized. Subjects who took incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

6.3.10.1.1 Demographics

Subjects in this population were European based population. Overall, 66 (53.2%) participants were female, 121 (97.6%) were ages 18 to 50 while only 3 (0.3%) were ages 50 to 65 years. The racial and ethnic makeup of the population was 91.1% White. Asthmatics made up 24.2% of the study population.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The mean duration of the diagnosis of allergic rhinitis/rhinoconjunctivitis in all randomized subjects was 16.3 years. The percentage of subjects who were only sensitized to HDM was 12.9% while the remaining subjects had sensitivity to HDM as well as other environmental aeroallergens. 31% of subjects had asthma (23.8% in the treatment group and 22% in the placebo group).

6.3.10.1.3 Subject Disposition

The table below outlines subject disposition.

Table 26. Study P003: Subject Disposition

Disposition	Odactra 12DU N (%)	Placebo N (%)	Total N (%)
Number of subjects (N)	42	41	124
Study Disposition:			
Completed	36 (85.7)	34 (82.9)	106 (85.5)
Treated	42 (100)	41 (100)	124 (100)
FAS¹	40 (95.2)	40 (97.6)	119 (96)
PP²	39 (92.9)	39 (95.1)	115 (92.7)
Included in analysis at Week 24	36 (85.7)	34 (82.9)	106 (85.5)
Included in analysis at Week 16	39 (92.9)	38 (92.7)	113 (91.1)
Included in analysis at Week 8	40 (95.2)	39 (95.1)	118 (95.2)
Discontinued:	6 (14.3)	7 (17.1)	18 (14.5)
Adverse event	3 (7.1)	6 (14.6)	9 (7.3)
Lost to follow-up	0	0	1 (0.8)
Withdrawal by subject	3 (7.1)	1 (2.4)	8 (6.5)

Adapted from 125592/0: Clinical Study Report P003 Table 10-2

DU: development unit

¹FAS: full analysis set

²PP: per protocol

6.3.11 Efficacy Analyses

The primary and secondary endpoints are described in Section 6.3.8. There were no pre-specified criteria for study success.

6.3.11.1 Analyses of Primary Endpoint(s)

The primary efficacy analysis was the total nasal symptom score (TNSS) in the EEC at Week 24 in the FAS population. This score was calculated as the treatment difference relative to placebo by the following equation: $[(\text{Odactra} - \text{Placebo}) / \text{Placebo} * 100]$.

The table below shows the results for the primary endpoint in the FAS and PP populations.

Table 27. Efficacy Analysis of the Primary Endpoint of the TNSS in the Full Analysis Set Population and Per Protocol Population: Study P003

Treatment	N	Baseline Mean TNSS (SD)	Mean TNSS (SD)	% Treatment Difference Relative to Placebo (95% CI)
FAS				
Odactra 12 DU	36	7.74 (1.98)	3.83 (2.67)	-48.6 (-60.2, -35.3)
Placebo	34	7.32 (1.61)	7.31 (2.69)	---
PP				
Odactra 12 DU	35	7.81 (1.96)	3.91 (2.66)	-47.9 (-60.2, -35.3)
Placebo	34	7.32 (1.61)	7.31 (2.69)	---

Adapted from 125592/0 Clinical Study Report Table P003 11-2 and Table 14-10

CI: confidence interval

FAS: full analysis set

PP: per protocol

SD: standard deviation

TNSS: total nasal symptom score

Treatment difference relative to Placebo was calculated by $(\text{Odactra} - \text{Placebo}) / \text{Placebo} * 100\%$

6.3.11.2 Analyses of Secondary Endpoints

Key secondary analyses include the treatment difference relative to placebo at Weeks 8 and 16 in the FAS population which includes ocular symptoms in the analysis. These results are shown below.

Table 28. Efficacy Analysis of Key Secondary Endpoints of the TNSS in the Full Analysis Set Population at Weeks 16 and 8: Study P003

Treatment	N	Baseline Mean TNSS (SD)	Mean TNSS (SD)	% Treatment Difference Relative to Placebo (95% CI)
TNSS Week 16				
Odactra 12 DU	39	7.76 (1.91)	4.83 (2.47)	-30.1 (-42.3, -16.8)
Placebo	38	7.42 (1.61)	6.76 (2.40)	---
TNSS Week 8				
Odactra 12 DU	40	7.82 (1.92)	5.37 (2.57)	-20.4 (-33.3, -6.8)
Placebo	39	7.38 (1.59)	7.31 (2.69)	---

Adapted from 125592/0 Clinical Study Report Table P003 11-3 and Table 11-4

CI: confidence interval

FAS: full analysis set

PP: per protocol

SD: standard deviation

TNSS: total nasal symptom score

Treatment difference relative to Placebo was calculated by (Odactra – Placebo)/ Placebo*100%

6.3.11.3 Subpopulation Analyses

Study P003 was not powered to show efficacy in specific subgroups. At Week 24 the mean TNSS in female subjects in the Odactra12DU (N= 16) group was 3.21 (placebo (N = 15) was 7.28) and 4.33 in male subjects who received Odactra 12DU (N=20) (placebo (N=19) was 7.37).

Clinical reviewer comment: This trend suggests that SLIT may have improved efficacy in females and is consistent with the subgroup findings in study P001.

6.3.11.4 Dropouts and/or Discontinuations

In study P003, 18 (14.5%) discontinued the study early. Nine subjects (7.3%) discontinued due to an AE (3 in the 12DU group and 6 in placebo). Eight subjects withdrew consent. One subject was lost to follow-up.

6.3.11.5 Exploratory and Post Hoc Analyses

N/A

6.3.12 Safety Analyses

6.3.12.1 Methods

A total of 124 subjects were included in the safety analysis. The All Subjects as Treat (ASaT) population was used for safety analysis and defined as all randomized subjects who took at least one dose of study medication. Adverse events were assessed throughout the trial and 2 weeks after the last chamber session. There were no pre-specified solicited adverse events. The mean duration of treatment was 157.4 days with 116 (93.5%) of subjects receiving treatment for at least 16 weeks and 89 subjects (71.7%) receiving treatment for at least 23 weeks. The range was 29 to 180 days. There was no notable difference in treatment exposure across treatment groups.

6.3.12.2 Overview of Adverse Events

Overall, 85.5% of subjects experienced at least one AE during the trial with similar events in the 2 treatment groups. More AEs occurred in the treatment groups. In the 12DU group, 32 (76.2%) drug-related adverse events occurred versus 2 (4.9%) in the placebo. The most frequently reported AEs that occurred with an incidence of $\geq 2\%$ were throat irritation, oral edema (23.8% 12DU versus 0% placebo), oral pruritus (14.3% 12DU versus 0% placebo), ear pruritus (7.1% 12DU versus 0% placebo) and lip swelling (19% 12DU versus 2.4% placebo). One serious adverse event occurred in the placebo group (vertigo), none in the treatment groups. No subjects discontinued due to a drug-related adverse event. Of note, 8 discontinuations (3 in the 12 DU group and 5 placebo subjects) were related a decrease of 25% in PEF or 20% in FEV1 during a chamber provocation session which were pre-specified criteria in the protocol requiring study discontinuation as a safety precaution. These events were assessed as unrelated to the study drug. The most frequently reported AEs were throat irritation, nasopharyngitis, and dyspnea.

More subjects in the Odactra groups reported local allergic reactions including oral edema, oral pruritus, and throat irritation compared with placebo subjects. Subjects who received Odactra 12DU reported increased lip swelling/edema in the 12 DU group compared with placebo. One event of oral pruritus (6 DU) was assessed by the investigator as severe in intensity, one event each of oral edema and lip swelling (both 12 DU) were assessed as moderate, and all other local reactions were assessed as mild in intensity. The median time to onset of the local reactions in the Odactra12 DU group was from 1 to 7 days.

No systemic allergic reactions or cases of anaphylaxis were reported during the study. However, one subject (12 DU group) reported rhinorrhea, swollen tongue, pharyngeal edema, and throat irritation, all with a duration of 25 minutes on Day 13. The subject was treated with an oral antihistamine and completed the study. There were no reports of use of epinephrine during the study. There were no reports of severe local swelling or edema of the mouth and/or throat during the study.

Clinical reviewer comment: The subject discussed above did not qualify for a diagnosis of anaphylaxis because this subject met only one of the required criteria (skin-mucosal tissue involvement after exposure to a likely allergen (in this case house dust mite)), not two or more which would include the following: respiratory compromise, reduced blood pressure, or persistent gastrointestinal symptoms (15).

6.3.12.3 Deaths

No deaths occurred during study P003.

6.3.12.4 Nonfatal Serious Adverse Events

One serious adverse event of vertigo occurred in the placebo group outside of the EEC setting on Day 148. The subject was discontinued from the study.

Clinical reviewer comment: The SAE of vertigo was not related to Odactra because the study subject received the placebo treatment.

6.3.12.5 Adverse Events of Special Interest (AESI)

There were no reports of systemic allergic reactions or epinephrine use. No cases of eosinophilic esophagitis were reported.

6.3.12.6 Clinical Test Results

Analyses of a subset of the study population suggested a trend towards decreased IgE levels at both doses of Odactra for both species of HDM at Week 24 compared to Week 8. In addition, IgG4 levels were increased for both doses and species at Week 24 compared to Week 8.

6.3.12.7 Dropouts and/or Discontinuations

No subject discontinued due to a drug-related adverse event. However, 8 discontinuations were the result of a decrease in peak expiratory flow (by 25%) or FEV1 (by 20%) during the chamber session. Three subjects (7.1%) in the 12 DU group and 5 subjects (12.2%) in the placebo group discontinued the study due to these protocol discontinuation criteria. The events were assessed as moderate in intensity and resolved within hours or a few days of the chamber session allergen exposure. There were no AEs of asthma reported for these 8 subjects (3 of which had concomitant asthma at baseline), and these subjects did not develop delayed exacerbations of asthma following the EEC sessions.

6.3.13 Study Summary and Conclusions

The exposure to HDM allergen in a field trial (i.e. a natural environment) is not consistent unlike the EEC which exposes subjects to a stable, controlled, and constant allergen load. The efficacy data from study P003 demonstrate that Odactra is effective in relieving HDM-induced rhinitis.

The safety data are supportive, with no SAEs related to Odactra or epinephrine use reported. One subject in the 12 DU dose group reported swollen tongue and pharyngeal edema. Epinephrine was not used in this case, although it is important to note, in this circumstance some providers may have elected to use epinephrine. Overall, this study offers strong supportive evidence for use of Odactra for the treatment of HDM-induced allergic rhinitis with or without conjunctivitis.

7. INTEGRATED OVERVIEW OF EFFICACY

Odactra is a SLIT product comprised of an extract of two house dust mite species. It is indicated as immunotherapy for the treatment of house dust mite-induced allergic rhinitis, with or without conjunctivitis confirmed by positive skin test or in vitro testing for *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* IgE antibodies in persons 18 through 65 years of age.

The Applicant provided 3 studies; 2 phase 3 field trials (P001, P015) and a Phase 2, single-center EEC study, P003, to support efficacy.

Study P001 was a Phase 3 pivotal field study that included 1482 subjects in North America ages ≥ 12 years randomized 1:1 to Odactra 12DU (N=741) or placebo (N=741). Subjects took the study treatment for 12 months. The study missed the pre-specified primary endpoint of the percent treatment difference relative to placebo of the average TCRS during the last 8 weeks of treatment in the FAS population. This analysis was -

17.2% 95%CI (-25.0%, -9.7%). Post hoc analysis of the primary efficacy endpoint in adults ages 18 to 65 years in the FAS population was -16.0% 95% CI (-23.2%, -5.3%).

Clinical reviewer comment: In study P001 the adolescent subgroup, while not powered to demonstrate efficacy, appeared to have improved symptom control with Odactra as compared to adult subjects. The dropout rate in both studies was higher in the Odactra group due to adverse reactions, particularly in study P001. Subjects in the Odactra group who dropped out may have done so because these subjects had more severe symptoms related to HDM sensitivity and increased adverse reactions to the product. These subjects may have benefited from treatment. Those who stayed in the study may not have been as sensitive and may not have experienced as much symptom improvement with Odactra. This may explain why the Applicant missed the pre-specified endpoint

Study P015 was a supportive phase 3 field study that included subjects in Europe ages 18 to 65 years randomized 1:1:1 to Odactra 12DU (N=318), 6DU, or placebo (N=338). Subjects took the study treatment for 12 months. The same primary endpoint as P001 was used in study P015, however, there was no pre-specified upper bound criterion. Study success was pre-specified as the minimally clinically relevant difference between treatment and placebo of the TCRS which was defined to be 20% in the FAS-MI population during the last 8 weeks of treatment. This study missed the pre-specified endpoint with -16.1% 95% CI (-25.8%, -5.7%) in the Odactra 12DU group.

A post-hoc pooled analysis of the primary endpoint of the percent treatment difference relative to placebo of the average TCRS during the last 8 weeks of treatment in the FAS population of studies P001 and P015 are shown below. This analysis included all subjects who received at least one dose of the study treatment.

Table 29: Pooled Analysis for the Primary Efficacy Endpoint Percent Treatment Difference Relative to Placebo of the Average TCRS: Studies P001 and P015

Treatment	N	Baseline Mean DSS (SD)	Mean TCRS (SD)	% Treatment Difference Relative to Placebo (95% CI)
FAS				
Odactra 12 DU	850	7.94 (1.71)	5.34 (4.01)	-17.4 (-23.4, -10.9)
Placebo	918	7.96 (1.72)	6.24 (4.24)	---
FAS-MI				
Odactra 12 DU	1058	7.94 (1.72)	5.34 (4.01)	-13.2 (-19.5, -7.0)
Placebo	1079	7.93 (1.74)	5.29 (4.24)	---

Adapted from 125592/0 Summary of Clinical Efficacy Table 2.7.3

CI: confidence interval

DS: daily symptom score

FAS: full analysis set

MI: multiple imputation

PP: per protocol

SD: standard deviation

Treatment difference relative to Placebo based on medians was calculated by (Odactra – Placebo)/ Placebo*100%

Missing data in both treatment groups were imputed by sampling from the observed data of the endpoint in the placebo group using unrestricted random sampling with replacement.

Clinical reviewer comment: Although the studies were generally designed similarly with respect to the efficacy endpoints, the interpretation of this pooled analysis is limited

because the studies were conducted by different investigators, and the study populations of P001 and P015 differ by age, racial makeup and geographic location. In addition, the discontinuation rates differed between the two studies. Hence, these analyses are supportive, not pivotal for establishing effectiveness. The EEC study was not pooled because this study design was completely different.

Pooled analysis of the primary efficacy endpoint in studies P001 and P015 does meet the pre-specified upper bound described for study P001 in the pooled FAS population. It does not meet this upper bound for the FAS-MI population. The FAS-MI is likely the more conservative estimate because it uses imputed data from the placebo group. Despite this, these data continue to show a consistent treatment effect.

Study P003 enrolled adults 18 years of age and older for treatment with Odactra 12 DU (N=42), 6DU (N=41), or placebo (N=41) for 24 weeks. Efficacy was assessed at 24 weeks during an EEC challenge. Subjects only recorded symptoms during these challenges in contrast with study P001 and P015 who combined symptom and medication scores for the primary endpoint. The primary endpoint was the percent treatment difference relative to placebo of the average TNSS at the end of 24 weeks. The primary endpoint was calculated to be -48.6% 95% CI (-60.2%, -35.3%) in the 12 DU group.

Study P003 supported the findings of studies P001 and P015 by demonstrating reduction in symptoms in a controlled environment that delivers a specific, predictable concentration of allergen to study subjects. Since field efficacy studies may be less apt to demonstrate a substantial change in response to immunotherapy for perennial allergens because there is no comparison between pre-season and post-season effects, the results of the study P003 conducted in adults 18 years of age and older, provided additional supportive data regarding the efficacy of Odactra in reduction of average TNSS as early as 24 weeks after initiation of treatment. Allergen exposure in the field can vary based on many environmental factors such as humidity, temperature, cleanliness, and the types of flooring, curtains, or upholstery present indoors. Subjects sensitized to HDM are generally sensitized to other allergens. Only 24% of subjects in P001 were monosensitized. Subjects sensitized to other perennial allergens such as cockroach, cat, dog, or some fungi may have experienced symptoms due to exposure to these allergens during the field studies, interfering with the symptom control provided by treatment with Odactra.

Taken together, these data support the efficacy of Odactra for the treatment of house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis in persons with confirmed allergy to house dust mites.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety evaluations included solicited adverse reactions, unsolicited adverse events, SAEs, and deaths. All summaries of adverse events were based on the safety population defined as randomized subjects who received at least one dose of the study treatment.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety of Odactra was evaluated in 8 clinical studies submitted to the BLA. These studies were conducted in both North America and Europe. Please see Section 5.3 for a summary of these studies. The 5 studies summarized in this section are Phase 2 and 3 studies (P012/MT-02, P014/MT-04, P003, MT-06/P015, and P001) that evaluated the final dose and formulation, Odactra 12DU that included the age group (adults ages 18 to 65 years) for which the Applicant seeks licensure.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

A total of 1383 subjects were exposed to at least one dose of 12 DU Odactra in studies for allergic rhinitis with or without conjunctivitis, with or without asthma and studies evaluating allergic asthma with or without rhinitis. A total of 1540 subjects were in the pooled placebo group for the 12DU dose. The mean number of days exposed to treatment was 281.4 with a range of 0 to 550 days. A total of 1101 subjects participated in the trials for allergic rhinitis/rhinoconjunctivitis. The mean exposure time for that group was 253.5 days. The age range of subjects in these studies was 12 to 85 years of age.

A total of 629 (45.5%) males versus 754 (54.5%) females participated in the 12DU group. The mean age was 33.8 years in the treatment groups and 33.6 in the placebo groups. In the 12DU pooled group, 86.4% were white, 5.9% black, 4% Asian, 2.8% multi-racial, 0.4% American Indian or Alaskan Native, 0.1% other, and 0.2% unknown, by ethnicity, 5.1% were Hispanic or Latino. In the placebo group, 87.5% were white, 5.1% black, 3.6% Asian, 3% multi-racial, 0.3% American Indian or Alaskan Native, 0.4% other, and 0.3% unknown, by ethnicity, 4.4% were Hispanic or Latino.

8.2.3 Categorization of Adverse Events

See Section 8.1.

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

Pooled safety data should be interpreted with caution. Study P001 is the only study that utilized a Side Effect Report Card to solicit adverse reactions for the first 28 days. Unsolicited events were recorded for the entire study period. All other studies recorded unsolicited adverse events.

8.4 Safety Results

A table summarizing adverse events, severe adverse events, and SAEs in subjects who received Odactra 12DU compared with placebo is below.

Table 30. Summary of Adverse Events in Studies P012, P014, P15, P003, and P001 in All Randomized Subjects

	Odactra 12 DU N (%)	Placebo N (%)
Subjects in population	1383	1540
With one or more adverse event	1146 (82.9)	979 (63.6)
Intensity		
Mild	589 (42.6)	492 (31.9)
Moderate	466 (33.7)	404 (26.2)
Severe	86 (6.2)	81 (5.3)
Unknown	5 (0.4)	2 (0.1)
No adverse event	237 (17.1)	561 (27.5)
With drug-related adverse event	951 (68.8)	423 (27.5)
With serious adverse events	17 (1.2)	31 (2)
With serious drug-related adverse events	3 (0.2)	2 (0.1)
Discontinued due to an adverse event	113 (8.2)	41 (2.7)
Discontinued due to a drug-related adverse event	91 (6.6)	12 (0.8)
Discontinued due to a serious adverse event*	5 (0.4)	10 (0.6)
Discontinued due to a serious drug-related adverse event*	1 (0.1)	2 (0.1)
Deaths	0	0

Adapted from 125592/0 Summary of Clinical Safety Table 2.7.4:12 and 2.7.4:23

DU: development unit

*See Section 8.4.2

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 occurred in the 8 studies submitted.

8.4.2 Nonfatal Serious Adverse Events

Overall, 37 treatment recipients (17 on 12DU and 20 on 6DU) reported a SAE compared with 31 of placebo recipients. Five SAEs met the ICH definition of seriousness and were assessed by the investigator as drug related. The Applicant also reported any overdose event as an SAE. An overdose event was defined as any subject who took more than one dose in a day that resulted in an adverse reaction even if no other serious criteria were met. Two subjects had accidental overdoses (total dose of 24DU each) resulting in mild throat pruritus, irritation, and pain. No subject experienced a severe or serious reaction after an overdose of Odactra. All of these occurred in the MT-04 trial 12DU (1), 6DU (2), and placebo (2). Please see the narratives below. Two adverse events were upgraded to SAEs after database lock. In the MT-04 trial, a subject in the placebo group had placenta previa hemorrhage assessed as unrelated. In MT-06, one subject in the 6DU group had idiopathic thrombocytopenic purpura that was assessed as mild and drug-related.

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

1. One subject taking Odactra 12DU experienced moderate worsening asthma after recent pneumonia and viral infection. This event began before the first day of study drug administration. The subject took Odactra for 6 days. The subject was hospitalized for 2 days and discontinued from study P014.

2. One subject taking Odactra 6 DU experienced mild arthralgia in study P014
3. One subject taking Odactra 6DU experienced moderate laryngeal edema immediately after using chlorhexidine mouth wash. Direct laryngoscopy was conducted and edema of the left arytenoid was visualized; no edema of the epiglottis or oropharynx was observed. The subject continued in study P014.
4. One subject taking Odactra 6DU was diagnosed with idiopathic thrombocytopenic purpura.

Placebo

1. One subject was diagnosed with hepatocellular injury on Day 365 and was discontinued from study P014
2. One subject was diagnosed with erosive esophagitis on Day 239 after reportedly drinking a fluid with an acid taste. The subject was discontinued from the trial and recovered.

Clinical reviewer comment: This reviewer does not consider these clinical events to be related to the study treatment.

8.4.3 Study Dropouts/Discontinuations

In the 12DU recipients, 21.4 % discontinued the study, 8.2% discontinued the study due to an adverse event, and 6.6% discontinued due to a drug-related adverse event. One subject discontinued due to an SAE. In placebo recipients, 17% discontinued the study, 2.7% discontinued due to an adverse event and 0.8% discontinued due to drug-related adverse event. The most common reason was withdrawal by subject (6%). Two subjects discontinued due to an SAE.

8.4.4 Common Adverse Events

The most common solicited adverse reactions reported in study P001 of $\geq 10\%$ of subjects taking Odactra were throat irritation/tickle, itching in the mouth, itching in the ear, swelling of the uvula/back of the mouth, swelling of the lips, and swelling of the tongue, throat swelling, nausea, tongue pain, tongue ulcer/sore on the tongue, stomach pain, mouth ulcer/sore on the mouth, and taste alteration. Adverse events that were frequently reported across safety data from Phase 2 and 3 studies were oral pruritus, ear pruritus, eye pruritus, throat irritation, swollen tongue, lip swelling, and upper abdominal pain which were also more common in the 12DU recipients. In the placebo group, oral pruritus, ear pruritus, and throat irritation were the adverse events with the highest reported frequency. A table summarizing unsolicited adverse events is below.

Table 31. Summary of Adverse Events by System Organ Class with Incidence $\geq 2\%$ in One or More Treatment Groups in Phase 2 and 3 Studies P012, P014, P003, P015, and P001. All Randomized Subjects

	Odactra 12 DU N (%)	Placebo N (%)
Subjects in population	1383	1540
Ear pruritus	413 (29.9)	95(6.2)
Eye pruritus	28 (2.0)	22 (1.4)
Upper abdominal pain	110 (7.2)	48 (3.1)
Dyspepsia	34 (2.5)	0
Lip edema	28 (2.0)	4 (0.3)
Lip swelling	161 (11.6)	20 (1.3)
Mouth swelling	83 (6.0)	12 (0.8)
Oral pruritus	594 (43.0)	131 (8.5)
Swollen tongue	137 (9.9)	18 (1.2)
Tongue pruritus	67 (4.8)	14 (0.9)
Dysgeusia	76 (5.5)	29 (1.9)
Asthma	40 (2.9)	57 (3.7)
Oropharyngeal pain	39 (2.8)	29 (1.9)
Throat irritation	603 (43.6)	192 (12.5)

Adapted from STN 125592/0: Summary of Clinical Safety Table 2.7.4: 16

DU: development unit

Data on solicited adverse reactions were not solicited consistently in all studies. This table contains both sets of data.

Table 32. Solicited Adverse Reactions Within the First 28 Days of Treatment in Subjects Ages 18 through 65 years: Study P001

Adverse Reaction (Patient-Friendly Term)	Study Population: Study 1 Adverse Reactions of Any Intensity	Study Population: Study 1 Adverse Reactions of Any Intensity	Study Population: Study 1 Adverse Reactions That Were Severe [†]	Study Population: Study 1 Adverse Reactions That Were Severe [†]
	Odactra (N=640)	Placebo (N=631)	Odactra (N=640)	Placebo (N=631)
Ear and labyrinth disorders				
Itching in the ear	51.7%	11.7%	0.3%	-
Gastrointestinal disorders				
Itching in the mouth	61.3%	14.1%	0.2%	-
Swelling of the uvula/back of the mouth [†]	19.8%	2.4%	-	-
Swelling of the lips	18.0%	2.7%	-	-
Swelling of the tongue	15.8%	2.1%	-	-
Nausea	14.2%	7.1%	-	-
Tongue pain	14.2%	3.0%	-	-
Tongue ulcer/sore on the tongue	11.6%	2.1%	-	-
Stomach pain	11.3%	5.2%	0.2%	-
Mouth ulcer/sore in the mouth	10.3%	2.9%	-	-
Diarrhea	6.9%	3.6%	-	-
Vomiting	2.5%	1.4%	-	-
Nervous system disorders				
Taste alteration/food tastes different	10.0%	3.6%	-	-
Respiratory, thoracic and mediastinal disorders				
Throat irritation/tickle	67.0%	20.8%	0.3%	-
Throat swelling	13.6%	2.4%	0.2%	-

Adapted STN: 125592/0: Package Insert

Clinical Reviewer Comment: The data on solicited adverse reactions shown here indicate that the majority of these adverse reactions were not severe. The rates for these reactions are higher than those reported for other approved SLIT products because this study actively solicited information on the occurrence of these reactions from subjects.

8.4.5 Clinical Test Results

Not applicable.

8.4.6 Systemic Adverse Events

No systemic allergic reactions were reported in phase 1 trials. In all combined phase 2 and 3 trials, 7 subjects reported systemic allergic reactions in the 12 DU group and 3 subjects in the placebo group. One of these was considered related to the study drug (narrative 1 under Systemic Allergic Reactions). Eight events of epinephrine use were reported. Four events of epinephrine use were related to the study drug out of subjects taking Odactra 12DU or 6DU. Only one of these was considered an anaphylactic

reaction (narrative 1 under Systemic Allergic Reactions). These events are summarized below.

Systemic Allergic Reactions

Events related to study drug

1. One subject in study P001 taking Odactra 12 DU had a systemic allergic reaction that included facial flushing, itchy palms and swollen throat. This reaction occurred on Day 1 in the investigator's office after 10 minutes of dosing. The subject was treated with intramuscular epinephrine. The reaction was assessed as moderate. The subject recovered and was discontinued from the trial.

Events unrelated to study drug

2. One subject experienced an anaphylactic reaction after consuming a food containing peanuts on Day 18, 2 days after the last dose of Odactra 12 DU. The subject was treated with an antihistamine. The subject was discontinued from the study on Day 16 due to mouth ulceration.
3. One subject taking Odactra 12DU in study P001 experienced an allergy flare reported as a hypersensitivity reaction from a dust exposure on Day 245 and was treated with an oral antihistamine. The event was assessed as moderate.
4. One subject on placebo in study P001 had a drug hypersensitivity reaction (hives) to Bactrim on Day 147.
5. One subject on placebo in study P001 had throat tightness, difficulty swallowing, and an itchy face. The subject was treated with epinephrine and continued in the study. The event was assessed as mild.
6. One subject on placebo in study P001 had an anaphylactic reaction 24 hours after the last dose of study drug. The subject self-administered epinephrine. This event was classified as a serious adverse event. The subject had a history of food allergy, however the exact trigger was not identified.
7. One subject taking Odactra 12 DU in study P014 experienced 2 non-serious adverse events: dyspnea and pruritus. These events were related to a reaction to amoxicillin on Day 392. This event was considered mild and the subject completed the study.

Epinephrine Use

Events related to study drug

1. One subject taking Odactra 12DU in study P001 had multiple local oral reactions including oral itching and throat irritation on Days 1 to 2 as well as severe throat tightness on Day 7, 30 minutes after Odactra administration and self-administered epinephrine. The subject recovered and was discontinued from the trial.
2. One subject taking Odactra 12DU in study P001 developed moderate throat and chest discomfort 30 minutes after drug intake on Day 128. The subject self-administered epinephrine and the event resolved. The subject continued in the study.
3. One subject taking Odactra 12DU in study P015 experienced oropharyngeal pruritus, dysphonia, throat irritation, and cough within 5

minutes of taking the study drug on Day 1. The subject was treated with epinephrine, antihistamines, and steroids. The symptoms were reported as mild and resolved after 30 minutes. The subject completed the study.

4. Please see narrative 1 under Systemic Allergic Reactions.

Events unrelated to study drug

5. One subject taking Odactra 12 DU in study P001 developed pharyngeal edema after an exposure to environmental dust. This occurred 1 day after her last dose of Odactra. The subject self-administered epinephrine and the event resolved. The subject was continued in the study.
6. One subject in the placebo group self-administered epinephrine due to moderate pharyngeal edema as a result of a food reaction.
7. Please see narratives 5 and 6 under Systemic Allergic Reactions.

Clinical reviewer comment: This reviewer agrees with the assessments of relatedness to the product. One subject qualifies for a systemic allergic reaction (narrative 1 under Systemic Allergic Reactions) related to the study product. The other reactions described as related to the product are considered local allergic reactions, but were reported as systemic reactions due to the Applicant's reporting criterion. Out of 1383 subjects who were exposed to Odactra 12DU, the incidence of epinephrine use for a reaction related to Odactra is (5/1383 (0.36%)).

8.4.7 Local Reactogenicity

Adverse events were solicited only in study P001. Please see section 6.1.12 for a review of local adverse reactions.

8.4.8 Adverse Events of Special Interest – Eosinophilic Esophagitis

Due to the concern for eosinophilic esophagitis in subjects taking SLIT products, selected upper GI tract AEs were reviewed. Three cases reporting a subject undergoing evaluation for eosinophilic esophagitis were identified. These cases occurred in 1 adult subject taking 6DU (P015), 1 adolescent taking 12 DU (P001), and 1 adolescent in the placebo group (P001). These events are summarized below.

1. One 13 year old subject taking Odactra 12 DU in study P001 was diagnosed with eosinophilic esophagitis. On Day 204 the subject was diagnosed with eosinophilic esophagitis 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 was evaluated for potential eosinophilic esophagitis in the placebo group of study P001. The subject underwent 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 eosinophilic in the mid or distal esophagus and only 2 per high powered field in the proximal esophagus. The subject was ultimately diagnosed with gastroesophageal reflux disease. This subject completed the trial.
3. One 34 year old subject in study P015 taking Odactra 6DU was evaluated for eosinophilic esophagitis due to difficulty swallowing meals reported on Day 99. The subject underwent an upper endoscopy with biopsies that demonstrated eosinophils (the number of eosinophils per high powered field was not reported).

The subject was diagnosed with eosinophilic esophagitis and underwent treatment with swallowed budesonide for 14 days. On Day 121 the subject was diagnosed with mild gastroesophageal reflux disease and subsequently started on lansoprazole. The subject was reported as not recovered from eosinophilic esophagitis or acid reflux disease at the time of study completion.

Clinical reviewer comment: Two subjects were diagnosed with eosinophilic esophagitis, and only one taking the 12 DU dose of Odactra. One subject (narrative #2) had an unclear diagnosis. There was no esophageal biopsy (required for diagnosis of eosinophilic esophagitis) prior to treatment with lansoprazole. This case was reported as a diagnosis of gastroesophageal reflux, however the subject's symptoms may have been related to concomitant eosinophilic esophagitis.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Please see Section 8.5.7 for a discussion on overdose events.

8.5.2 Time Dependency for Adverse Events

After the first dose of study drug, the median time to onset of any local adverse reaction was 1 to 7 days in the 12 DU group. The majority of local adverse reactions in the treatment groups occurred with a median time to onset of 1 day, while a few occurred with a median time to onset of 2 to 7 days. For the 2 most frequently reported adverse reactions with the treatment (oral pruritus and throat irritation), the median time to onset for both was within 1 day, and specifically, within 1 to 3 minutes of the first dose of study drug. For solicited adverse reactions in study P001, the median time to onset of these adverse reactions following initiation of treatment with ODACTRA varied from 1 to 7 days. The median duration of these adverse reactions that occurred on the first day of treatment initiation varied from 30 to 60 minutes. These adverse reactions recurred for a median of 2 to 12 days

For the onset of local adverse reactions when graded by intensity (as assessed by the investigator), the time to onset for the majority of mild and moderate local adverse reactions in treated subjects was within approximately 28 days of the first dose of study drug. Few local adverse reactions of severe intensity were reported and the majority of those occurred within 7 days of the first dose and resolved within 1 day.

The median duration of local adverse reactions ranged from 14.5 to 67 minutes for the 12 DU group. The median duration of most local adverse reactions was approximately 30 to 60 minutes. The median duration of recurrence of local adverse reactions ranged from 1 to 14 days for the 12 DU group. When evaluated by intensity (as assessed by the investigator), the majority of the moderate local adverse reactions resolved within several weeks. Of the few severe local adverse reactions reported, the majority resolved within 1 day.

For the 2 most frequently reported adverse events of abdominal pain upper and nausea, the median time to onset (in days) for subjects on 12 DU was 5.0 and 4.5 days and the median recurrence (in days) was 3.0 and 2.0 days, respectively.

For systemic allergic reactions or adverse reactions requiring epinephrine use related to Odactra (5 events total), the majority occurred within the first week of initiating Odactra (4/5).

8.5.3 Product-Product Interactions

The study treatment was not evaluated in combination with other sublingual or subcutaneous immunotherapy products.

Prohibited medications in the pivotal trial, P001, included beta blockers. Persons who take beta blockers may be at higher risk for complications from a systemic adverse reaction to the product because they may be unresponsive to epinephrine or inhaled bronchodilators used in the treatment of serious allergic reactions.

8.5.4 Human Carcinogenicity

Please see Section 4.3 for the toxicology assessment.

8.5.5 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

In clinical studies submitted to the BLA, 1 out of 9 subjects experienced severe vomiting 15 minutes after taking a dose of 32DU in a Phase 1 study. In a Phase 3 study, 2 out of 9 subjects reported reactions after taking 24DU. One subject experienced oral pruritus and throat irritation and a second experienced oral pain. Both of these reactions resolved and were mild in intensity.

8.6 Safety Conclusions

An integrated review of safety data finds that the Odactra safety profile is acceptable. Adverse reactions expectedly occurred in the treatment group more often than placebo. The most common solicited adverse reactions occurring in $\geq 10\%$ of subjects taking Odactra 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 (10%), and taste alteration (10%). Similar findings have been reported in licensed SLIT products including throat irritation, oral pruritus, ear pruritus, and lip swelling. The majority of these events were mild to moderate, occurred very early in treatment and resolved without complication.

No deaths occurred throughout the 8 clinical studies. None of the reported serious adverse events were related to Odactra and there were no serious unexpected adverse events. Across 8 clinical studies conducted with different doses of Odactra, eosinophilic esophagitis was reported in 2/2737 (0.07%) subjects who received Odactra compared to 0/1636 (0%) subjects who received placebo.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There are limited data in the submission regarding the use of Odactra during pregnancy.

Thirty pregnancies total occurred in the development program. Twelve occurred in the treatment groups including 6 in the 12 DU group. There were six complications reported as resolved. The complications included 4 spontaneous abortions (3 placebo, 1 on 12 DU), 1 induced abortion (12DU) and 1 instance of placenta previa in 1 subject on placebo. Twenty four of the 30 subjects had an exposure of ≤ 2 days to the study drug after pregnancy onset date. The pregnancy onset date was defined as the reported date of the positive serum or urine pregnancy test. Of subjects who took Odactra instead of placebo over 2 days (4), one subject took Odactra for 3 days and had an elective abortion. The other three were reported as taking the drug for 15 days (3DU dose), 32 days (1DU), and 42 (3DU) days. For these 3 subjects the treatment end date was based on the last dose of the study drug reported in the clinical database, however, based on the reports submitted, these subjects discontinued the study drug on the same day as the day the pregnancy was confirmed. The Applicant did not report the subject's last menstrual period or approximate gestational age of the fetus.

Clinical reviewer comment: No safety signals emerged based on this small amount of data, which included mostly very brief exposures after conception. No safety concerns have been identified in pregnant patients treated with subcutaneous immunotherapy. As a result, practice parameters for SCIT advise that pregnant patients may continue immunotherapy if the patient is already in the maintenance dosing phase (2, 12).

There are no data to suggest that SLIT would have an adverse impact on the fetus or result in a different safety profile in a pregnant woman. The manufacturers of previously licensed SLIT products have not been required to conduct a pregnancy registry. A pregnancy registry was not required for Odactra.

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

As specified by the Pediatric Research Equity Act (PREA), the submission of this original BLA required a Pediatric Study Plan. The safety and effectiveness of Odactra has not been established in persons 17 years of age and younger. The number of pediatric subjects was too low to support a pediatric indication. To comply with PREA, the Applicant is required to conduct 2 studies in pediatric subjects 5 through 17 years of age. Both of these studies are anticipated to begin in October of 2017.

A partial waiver was granted to the Applicant for subjects younger than 5 years of age since necessary studies are impossible or highly impracticable because the number of children younger than 5 years of age with allergic rhinitis/rhinoconjunctivitis diagnostically due to sensitivity to house dust mite is small (Federal Food, Drug, and Cosmetic Act (FD&C Act) Section 505B (a)(4)(B)(i)). A deferral was granted for subjects 5 to less than 18 years of age) because the drug or biological products ready for approval in adults before pediatric studies are complete (FD&C Act Section 505B (a)(3)(A)(i)).

Two pediatric studies are planned. Both are Phase 3 studies. The first will evaluate the efficacy and safety of Odactra in children and adolescent 5 through 17 years of age with house dust mite induced allergic rhinitis/rhinoconjunctivitis over 12 months. The second will evaluate the safety of Odactra in children and adolescents 5 through 17 years of age

with house dust mite induced allergic rhinitis/rhinoconjunctivitis over 28 days. Together, these studies would accrue a total of 1000 subjects.

Clinical reviewer comment: Only 189 subjects ages 12 to < 18 years took part in study P001. The size of the adolescent population evaluated in Phase 3 studies is inadequate to evaluate the safety and efficacy of Odactra. The Applicant presented safety and tolerability data during the EOP2 meeting that supported the inclusion of subjects ≥ 12 years of age in study P001. CBER anticipates the 2 proposed phase 3 studies will provide additional information to adequately evaluate the safety and efficacy of Odactra in the pediatric population 5-17 years of age.

9.1.4 Immunocompromised Patients

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

9.1.5 Geriatric Use

The safety of Odactra in the geriatric population has not been established. The number of subjects over 65 years of age evaluated in the Applicant's development program (N=25) is too small to establish safety and effectiveness of the product in this population.

10. CONCLUSIONS

The results from two Phase 3 field efficacy studies (P001 and P015) demonstrate a reduction in TCRS during the last 8 weeks of a 52 week treatment course. The results of the Phase 3 study (P001) conducted in adults and adolescents in the North America indicate that the point estimate difference between treatment and placebo for the difference in average TCRS exceeded the pre-specified criteria for success of -15% although the lower bound of the 95% CI for this difference was -9.7% (slightly less than the pre-specified success criteria of -10%). An additional field efficacy study, P015, conducted only in adults 18 years of age and older, provides additional support for the efficacy of Odactra in reducing the average TCRS by 16% in adults during the last 8 weeks of treatment (95% CI: -25.8%, -5.7%). The similarity of the results in large, geographically and ethnically diverse populations (North America and Europe) demonstrates that the treatment effect of Odactra is consistent.

Field efficacy studies may be less apt to demonstrate a substantial change in response to immunotherapy for perennial allergens because there is no comparison between pre-season and post-season effects. Only 24% of subjects were sensitized only to HDM in study P001 and 32% in study P015. Subjects sensitized to other perennial allergens such as cockroach, cat, dog, or some fungi may have experienced symptoms due to exposure to these allergens as well as seasonal allergens present in warmer climates in addition to HDM exposure, interfering with symptom control provided by Odactra. Additionally, daily exposure to the HDM allergen is not predictable (unlike seasonal allergens) or consistent and varies throughout the year based on many environmental factors including humidity, the presence of carpeting and upholstery, the use allergen-proof bedding covers, and general cleanliness.

The results of the Phase 2 EEC study (P003) conducted in adults 18 years of age and older provided additional supportive data regarding the efficacy of Odactra in reduction

of average TNSS as early as 24 weeks after initiation of treatment. The primary endpoint was calculated to be -48.6% 95% CI (-60.2%, -35.3%) in the 12 DU group. This robust supportive data demonstrates that Odactra improves symptom control in subjects exposed a controlled environment that delivers a specific, predictable concentration of allergen. Study P003 also studied the Odactra 6DU dose. The treatment effect of 6DU was not as substantial as 12 DU; -26.6% 95%CI (-39.6%, -11.2%). The robust efficacy at higher doses demonstrated a real treatment effect.

Taken together, these data support the effectiveness of Odactra for the treatment of house HDM-induced allergic rhinitis, with or without conjunctivitis in persons 18 through 65 years of age with confirmed allergy to house dust mites.

Subjects treated with Odactra including the 12DU dose had higher rates of local adverse reactions than those treated with placebo. However, these reactions were expected generally mild and were tolerated by most subjects. The risk of severe, systemic adverse reactions appears to be low; this risk will be further characterized in a post-licensure PMC. Overall, the benefit-risk profile of Odactra is acceptable for approval.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 33. Summary of Risk-Benefit Analysis for Odactra		
Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> House dust mite-associated allergic rhinitis with or without conjunctivitis is a common disease affecting 8% of adults in the U.S. Allergic rhinitis can cause significant impairment of daily function due to symptoms including decreased energy, productivity, and social functioning The total direct medical cost of allergic rhinitis is about \$3.4 billion including cost of medication and medical visits (14). 	<ul style="list-style-type: none"> Symptoms from house dust mite allergy cause significant disruption in daily activities and function
Unmet Medical Need	<ul style="list-style-type: none"> Over the counter (OTC) medications are available to treat the symptoms of allergic rhinitis/rhinoconjunctivitis. However, OTC medications have some side effects. And the cost of daily medications can be prohibitive. Subcutaneous immunotherapy (SCIT) for treatment of house dust mite allergy is offered by some health care practitioners (HCP). However, SCIT is more invasive and must be administered in a clinical setting with appropriately trained staff to monitor for acute anaphylactic reactions. No perennial sublingual immunotherapy (SLIT) product is licensed in the U.S. for the treatment of house dust mite induced allergic rhinitis with or without conjunctivitis. 	<ul style="list-style-type: none"> Sublingual immunotherapy is a non-invasive therapy. Sublingual immunotherapy can be administered at home with proper instruction. OTC medications treat symptoms, but not the underlying cause of rhinitis/rhinoconjunctivitis. There is an unmet medical need for safe and effective treatments of house dust mite associated rhinitis/rhinoconjunctivitis.
Clinical Benefit	<ul style="list-style-type: none"> Phase 3 study P001 was a double blind, randomized controlled field efficacy study that showed the relative treatment difference of the total combined rhinitis score compared to placebo was -17.2% (95% CI: -25.0%, -9.7%) in ages ≥ 12 years after 12 months Phase 3 study P015 was a double blind, randomized controlled field efficacy study in adults ages 18 through 65 provided to support study P001. Study P015 demonstrated a similar treatment effect in the relative treatment difference of the total combined rhinitis score compared to placebo as -16.1% (95%CI: -25.8%, -5.7%) after 12 months Phase 2 study P003 was an environmental chamber study submitted to support efficacy in the adult population ages 18 to 65 years. After 24 weeks of taking Odactra, the relative treatment difference of the total nasal symptom score compared to placebo was -48.6% (95% CI:-60.2%, -35.3%) 	<ul style="list-style-type: none"> Odactra consistently shows a therapeutic benefit over 12 months Field studies do not control for inconsistent exposure to house dust mite allergens Environmental chamber data demonstrates subjects experience robust symptom relief after 24 weeks during steady and continual exposure to house dust mite allergens The duration of effectiveness on therapy beyond one year and effectiveness after discontinuation Odactra have not been characterized.
Risk	<ul style="list-style-type: none"> The most serious risks of treatment with Odactra are systemic allergic reactions such as anaphylaxis or pharyngeal edema. These adverse reactions occurred at a rate of 0.36% (anaphylaxis), 13.6% (pharyngeal edema) and 0.2% (severe pharyngeal edema) The most common reactions 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%). Most reactions are mild to moderate in severity, and they resolve relatively quickly and without sequelae. Two subjects taking Odactra (12 DU and 6 DU) developed eosinophilic esophagitis. Across 8 clinical studies conducted with different doses of Odactra, eosinophilic esophagitis was reported in 2/2737 (0.07%) subjects who received Odactra compared to 0/1636 (0%) subjects who received placebo. 	<ul style="list-style-type: none"> The risk of serious allergic reaction with Odactra is small. Local reactions are common, but generally mild to moderate and self-limited. Further studies are needed to characterize the incidence of eosinophilic esophagitis in patients taking SLIT products
Risk Management	<ul style="list-style-type: none"> Odactra should be prescribed along with a prescription for injectable intramuscular epinephrine in case of systemic reactions. Patients should be warned about the potential risk of eosinophilic esophagitis and directly to contact a health care professional if any signs or symptoms of eosinophilic esophagitis occur 	<ul style="list-style-type: none"> The rate of systemic allergic reactions is low, and the risk can be mitigated effectively with auto-injectable epinephrine The package insert and the current pharmacovigilance plan are adequate to manage these risks.

11.2 Risk-Benefit Summary and Assessment

Allergic rhinitis is a common respiratory condition affecting 8% of adults in the US. This condition can affect quality of life including work or school performance and lead to or affect other clinical disorders such as asthma, rhinosinusitis, and sleep disorders. Sublingual immunotherapy can be taken at home after the first dose with appropriate patient counseling, decreasing the burden of clinic visits for patients. Odactra is the first perennial sublingual immunotherapy product.

Data submitted to the BLA demonstrates the benefit of Odactra for the treatment of house dust mite induced allergic rhinitis with or without conjunctivitis in adults ages 18 to 65 years of age. Both field efficacy studies and the environmental chamber challenge study all demonstrate a consistent treatment effect. 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 subject using Odactra reported a systemic allergic reaction related to the drug. Five subjects overall reported use of epinephrine or an allergic reaction requiring treatment out of 1383 subjects taking Odactra 12DU. One case of eosinophilic esophagitis was reported in a subject taking Odactra 12DU. The most common reactions were throat irritation, oral pruritus, ear pruritus, and lip swelling. 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. Subjects with mild to moderate asthma had a similar safety profile in pivotal study P001 to subjects without asthma.

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

11.3 Discussion of Regulatory Options

The approval of Odactra for the treatment of house dust mite induced allergic rhinitis in adults was based on the efficacy data from the studies P001, P015, P003. Adolescents down to the age of 12 years were included in study P001, but not P015. While Odactra demonstrated a favorable efficacy profile, the numbers were too small to reach conclusions regarding the efficacy and safety in this population. Therefore, the reviewer recommends against including the age group 12 through 17 years in the indication until additional studies are provided for CBER review (see Section 9.1.3).

11.4 Recommendations on Regulatory Actions

Both randomized, placebo controlled phase 3 field studies clearly showed a treatment effect, though the primary endpoint was not met. Multiple factors are responsible for the difficulties of showing specific treatment effects by a single allergen in a field study. Most subjects with allergic rhinitis are sensitized to other seasonal and perennial allergens. Exposure to these allergens during the efficacy assessment period interferes with the symptom control provided by Odactra. Field studies may not demonstrate a substantial

change in response to immunotherapy for perennial allergens because there is no comparison between pre-season and post-season effects as would be possible with a seasonal allergen. In addition, house dust mite allergen concentration often varies in each home environment due to environmental and human-controlled factors such as temperature, humidity, cleanliness, and the types of flooring, curtains, or upholstery present indoors. Thus, each study subject may be exposed to a very different level of allergen. Because of these factors, the data showing treatment effect from the phase 2 EEC study is compelling because of the nature of its single allergen challenge under controlled conditions. The EEC study provided clear supportive evidence that treatment with Odactra improves symptom control. Therefore, Odactra is recommended for approval in adult subjects ages 18 through 65 years as immunotherapy for house dust mite (HDM)-induced allergic rhinitis/rhinoconjunctivitis, confirmed by positive skin test or *in vitro* testing for *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* IgE antibodies.

11.5 Labeling Review and Recommendations

CBER recommended, and the Applicant agreed to, several revisions to the package insert intended to clarify and more clearly describe the clinical data. Section 6 Adverse Reactions was revised to separately display solicited adverse events (as opposed to unsolicited adverse events) for Study P001.

Since eosinophilic esophagitis is known risk associated with SLIT products, the package insert lists eosinophilic esophagitis under Section 5 Warnings and Precautions. Although the occurrence of anaphylaxis or systemic allergic reactions observed in clinical studies pre-licensure was not common, treatment with Odactra may require use of epinephrine. For this reason, the product labeling includes a Black Box warning and a medication guide, both of which emphasize the potential risk for severe allergic reactions and need for access to auto injectable epinephrine.

The package insert 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.

For the Pregnancy subsection (Section 8 Use in Specific Populations), CBER modified the label to remove language stating that Odactra is not systemically absorbed. According to the Final Rule for the Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling, biologic products are considered systemically absorbed when the absorption of the drug or biological product travels from its site of administration (in this case sublingually) into serum or other body tissues where the drug or biological product can reach its receptor or target cell and exert its pharmacological or immunological effect. In this case, SLIT is absorbed through the oral mucosa and interacts with the tissues and cells of the immune system to decrease responsiveness upon house dust mite exposure.

Clinical Reviewer comment: Few studies exist to clarify how sublingual allergen immunotherapy is absorbed. Two small studies evaluated sublingual absorption of a radiolabeled allergen and allergoid in humans and showed that absorption occurred in the oral mucosa and was detected in the plasma (free radioiodine and small radiolabeled

peptides) a period of time after sublingual administration (10, 11). This is consistent with the definition described above for the systemic absorption of a biologic product.

11.6 Recommendations on Postmarketing Actions

The Applicant will conduct one PMC to accrue 10,000 subjects over 5 years to assess rates of serious allergic reactions and eosinophilic esophagitis. The proposal was agreed upon between CBER and the Applicant. Please see Section 4.6.